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ORIGINAL PAPER

MONITORING SURFACE CONTAMINATION FOR THIRTY ANTINEOPLASTIC DRUGS: A NEW PROPOSAL FOR SURFACE EXPOSURE LEVELS (SELs)

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Abstract

Background: Chemotherapy drugs are widely used to treat cancer, but their active compounds represent a danger for workers who could be exposed to them. However, they aren't yet included in directive CE No. 1272/2008 and the European Biosafety Network has only recommended a limit value of 100 pg/cm^2 for surface contamination. Thus, it is crucial to assess surface contaminations in healthcare environments. Currently, the technique of choice is surface wipe test combined with liquid chromatography tandem mass spectrometry to achieve high sensibility. **Material and Methods:** A campaign involving Careggi University Hospital (Florence, Italy) was performed from January 2020 to December 2021, collecting 1449 wipe samples between administration units, preparation unit, and personnel gloves. From the obtained data, the 90th percentile was calculated for 30 antiblastic drugs and proposed as surface exposure levels (SELs); while from data concerning personnel glove contamination, weekly contamination was estimated. **Results:** In the 2-year period only 417 wipe samples were found positive (28.8%), the majority of which regard samples coming from administration unit bathrooms. The proposed SELs are almost all <100 pg/cm^2, except for few drugs which produce higher contamination on bathroom surfaces. Also, the estimation of pharmacy personnel's glove contamination highlighted very low results (ng/week). **Conclusions:** Deeply established protocols and procedures for safe handling of ADs allow for obtaining excellent cleaning results and thus a safer work environment, however, the risk of cytostatic contaminations cannot be avoided in healthcare workplaces, and thus a harmonization of classification and labeling of chemotherapy drugs throughout the European Union should be done. Med Pr. 2022;73(5):383–96

Key words: health risk assessment, antineoplastic drugs, wipe test, ultra-high performance liquid chromatography, surface exposure level, tandem mass spectrometry

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INTRODUCTION

In 2020, the Global Cancer Observatory of the International Agency for Research on Cancer (IARC) reported that >19 million cases of cancer were diagnosed worldwide, and it is estimated that in 2040 there will be 30 million new cases. Chemotherapy continues to be the highest drug therapeutic segment used to treat cancer for 2020 (about 50%) [1]. In Italy, the level of consumption of antineoplastic drugs (ADs) increased significantly from 12.6 daily defined dose (DDD) per 1000 inhabitants per day in 2011 to 16.9 DDD in 2020 [2]. Currently, about 80% of the 331 oncology wards surveyed in Italy by the Società Italiana di Farmacia Ospedaliera e dei Servizi Farmaceutici delle Aziende Sanitarie (SIFO), carry out on average about 20 000 administrations/year.

The IARC has classified some active components of ADs into diverse carcinogenicity groups – 12 into IARC group 1 "Carcinogenic to humans," 8 into IARC group 2A "Probably carcinogenic to humans," and 10 into IARC group 2B "Possibly carcinogenic to humans." Challenging for employers and occupational and environmental hygiene specialists is the necessity to get into a complex and ambiguous regulatory context which is not able to easily harmonize the communication of classification criteria between manufacturers and users [3]. A step ahead has been moved with the approval of the directive EU 2019/983 by the European Parliament, an amendment of the directive 2004/37/CE, which includes the risks related to exposure to cytotoxic drugs at the workplace. For example, methotrexate [4], 5-fluorouracil, and doxorubicin [5] are not classified as carcinogenic in the EU, while have been placed on the list of dangerous drugs used in chemotherapy by IARC, mainly due to their teratogenic and genotoxic effects. Recently, it has been shown by a study carried out on 2440 nurses, that negative health effects are associated between the handling of ADs and the percentage of spontaneous abortions, especially in those nurses who had not used personal protective equipment (PPE) and engineering systems for controlling exposure [6]. Dermal absorption is the major exposure route by direct contact with the drugs (manipulate vials producers and/or pharmacological solutions in intravenous bags), or indirect contact as a result of touching contaminated surfaces, which could be considered the main routes of dermal exposure.

Despite the first guidelines on hazardous drugs published in 1978 by Swedish National Social Welfare Board, the first indication concerning ADs of a recommended limit value for surface threshold contamination arises only in 2016, proposed in the European Policy Recommendations "Preventing Occupational Exposure to Cytotoxic and Other Hazardous Drugs" by the European Biosafety Network and equal to 100 pg/cm^2 [7]. Subsequently, multiple new recommendations and guidelines have been published or substituted [8] but even if this updating led to a decrease in occupational exposure, operators' risk has not been yet eradicated [9]. In addition, a new category of the limit value referred to surface contamination, the threshold limit value (TLV) – surface limit (SL), was introduced by the American Conference of Governmental Industrial Hygienists (ACGIH) in the published volume "Threshold Limit Values and Biological Exposure Indices 2019."

To fulfil those recommendations, 3 solutions for near real-time results are offered: i-QCRx™ from B&W Tek. (Plainsboro, NJ, USA), fluorescence covalent microbead immunosorbent assay (FCMIA) by Luminex Corporation (Austin, TX, USA), and BD® HD Check by BD (Franklin Lakes, NJ, USA) [10]; therefore, those systems lack in sensibility. Instead, lower limits of detection (LODs) are achievable using liquid chromatography tandem mass spectrometry (LC-MS/MS) systems for the quantification of ADs [11].

A substantial ADs contamination decrease was shown in 2016 after the introduction of safe practices and guidance values. Simon et al. [12] investigated the ability of a closed-system transfer device to reduce the occupational exposure to 10 cytotoxic drugs, while Chauchat et al. [13] observed that the proportion of samples with detectable concentrations of cyclophosphamide, in 83 Canadian centres (953 surfaces sampled), stayed relatively constant (40–60%) ascribing the higher contamination to a larger quantity of drugs handled. Dugheri et al. [14] described a reduction on ADs surface contamination for data collected >9 years (2009–2017) in Italian hospitals. However, in 2010 a study involving 3 university hospital-based cancer centres from the United States, which followed National Institute for Occupational Safety and Health (NIOSH) recommendations for safe-handling practices in preparing and administering ADs, reported that contamination of at least 1 of the 5 drugs (cyclophosphamide, iphosphamide, 5-fluorouracil, paclitaxel, and cytarabine) was detected in 75% of the pharmacy wipe samples and 43% of the infusion wipe samples [15].

Another important assessment is the one concerning workers who are not directly involved in ADs administration or preparation because they could lead to the improper exposure to anticancer drugs ubiquitous contaminations in the healthcare environment. A series of multisite studies on ADs contamination conducted by a research team in British Columbia: through interviews and observations, recreated the drugs travel to identify the potentially contaminated surfaces and thus the job categories with the potential for ADs exposure by dermal contact [16]. Recently, Mucci et al. [17] reported cyclophosphamide and iphosphamide contaminations in the spaces between the hospital exit and the preparation and administration units, identifying possible migration routes of these substances. Moreover, another risk factor could be represented by patients and workers carrying ADs contamination from hospitals to domestic environments [18].

The regulations concerning workers' safety and health occupationally exposed to cytostatics are both ambiguous and lack legally binding occupational exposure

limits for active compounds of ADs to be compliant with the continuously changing treatment and therapies standards, and with the newest scientific data concerning health effects of occupational exposure to these chemicals. Hence, without a validated, highly sensitive, compound-selective analytical method for measuring suitable biomarkers of occupational exposure which would allow knowing the true extent of exposure, the multi-element monitoring by wipe test represents a more thorough and complete investigation into ADs contamination of work environments.

Therefore, some authors have introduced the percentile values as reference values for a substance-independent guideline, in order to interpret the data obtained by monitoring exposure risk at hospital workplaces. These studies conducted on high number of samples have proposed hygienic guidance values for surface wipe sampling based on 75th percentiles and 95th percentile [19,20]. Recently, surface exposure levels (SELs) for 21 ADs based on 75th and 90th percentile values were proposed by Dugheri et al. [21] both for preparation and administration units joined with a traffic-light color-coding system.

To facilitate the interpretation of the surface monitoring results and to provide a solid basis for improving occupational safety and ADs contamination control, the authors proposed an update to SELs by an innovative analytical protocol for simultaneously assessing 30 ADs in the healthcare environment. Furthermore, an evaluation of the contamination of the operators' gloves was carried out.

MATERIAL AND METHODS

To evaluate ADs contamination on working surfaces of Careggi University Hospital, Florence, Italy, 1449 wipes were collected and analysed from January 2020 to December 2021. This campaign included 8 administration and 1 preparation unit. The total amount of ADs prepared by the Pharmacy ADs Preparation unit, considering only the drugs which were monitored, in the 2-year period corresponded to 58 616 preparations equivalent to 45.13 kg of ADs handled (Table 1).

Hospital programs followed the Italian guidelines (G.U. 236, 7.10.1999), specifically: a) staff were trained and re-trained in safety equipment and maintenance, research updates, and emergency care); b) closed system devices were used for drug transfer between preparation and administration units to prevent any escape of hazardous drugs; and c) cleaning procedures can be distinguished in 2 phases, one carried out by pharmacy technicians for small surfaces such as the laminar flow hoods, syringe pumps, and phone handsets utilizing 0.2% Marseille soap solution, 0.115% sodium hypochlorite, and 70% ethanol, in this order; another carried out by cleaning personnel on floors and other spaces utilizing quaternary ammonium-based products.

To deal with the high number of in-patients and day hospital admissions, and thus the high number of ADs preparations, since 2012 the preparation and administration unit introduced ChemoClave closed system drug transfer devices (ICU Medical Inc., San Clemente, CA, USA), the CareFusion set (Becton Dickinson, Franklin Lakes, NJ, USA) and the Cyto-Set (B-Braun, Milan, Italy) for multivia infusion to help minimize exposure to hazardous drugs. Moreover, since 2014 the Diana Hazardous Drug Compounding System (ICU Medical Inc., San Clemente, CA, USA), a needle-free, user-controlled automated compounding system for the safe reconstitution and preparation of hazardous drugs, has been used.

The Pharmacy ADs Preparation unit – inside the Pharmacy Department – protected by an anteroom, is equipped with 4 IIA2-class biological safety cabinets and is ventilated with 70% recirculated air and 30% fresh air. General working procedures, technical and personal protective equipment, as well as safety precautions, are standardized.

The levels of 5-fluorouracil (5-FU), busulfan (BSF), carboplatin (CarboPt), cyclophosphamide (CP), cisplatin (CisPt), cytarabine (CTB), dacarbazine (DC), daunorubicin (DNR), docetaxel (DTX), doxorubicin (DXR), epirubicin (EPI), etoposide (ETP), fotemustine (FTM), gemcitabine (GEM), idarubicine (IDC), iphosphamide (IP), irinotecan (IRT), melphalan (MP), methotrexate (MT), mitomycin C (MITC), oxaliplatin (OxaliPt), paclitaxel (PTX), pemetrexed (PMX), raltitrexed (RTX), topotecan (TPT), vinblastine (VNB), vincristine (VNC), vindesine (VND), vinorelbine (VNR), were all measured in each wipe sample (altogether 43 470 measurements). Cephalomannine (CPM) and 5-chlorouracil (5-ClU) were chosen as internal standards for liquid chromatography triple quadrupole mass spectrometry quantification.

Wipe sampling

Wipe samples were collected from the preparation and administration units at the beginning (B-WS) and at the end of the work shift (E-WS); while for assessing gloves contamination, wipe samples were swab directly

Table 1. Annual quantities of each antineoplastic drugs (ADs) manipulated by Careggi's Pharmacy AD Preparation Unit, Florence, Italy, 2020–2021

Active ingredient	Drug dose [g]		Preparations [n]		Bottles [n]	
	2020	2021	2020	2021	2020	2021
5-FU	10 846.6	10 959.8	3803	3806	2169 (5000 mg*)	2192 (5000 mg)
BSF	23.3	17.7	167	136	388 (60 mg)	295 (60 mg)
CarboPt	729.8	690.6	1784	1814	1155 (600 mg) 81 (450 mg)	1093 (600 mg) 77 (450 mg)
CP	2075.6	1931.9	1789	1656	2076 (1000 mg)	1932 (1000 mg)
CisPt	74.1	69.7	914	867	741 (100 mg)	697 (100 mg)
CTB	1934.9	1732.7	1349	1259	967 (2000 mg)	866 (2000 mg)
DC	210.9	143.1	314	212	358 (500 mg) 316 (100 mg)	243 (500 mg) 215 (100 mg)
DNR	4.1	4.2	40	39	203 (20 mg)	209 (20 mg)
DTX	97.0	85.4	894	812	606 (160 mg)	534 (160 mg)
DXR	46.8	40.1	706	668	936 (50 mg)	804 (50 mg)
EPI	106.5	89.7	936	672	532 (200 mg)	449 (200 mg)
ETP	216.1	185.9	1229	1067	216 (1000 mg)	186 (1000 mg)
FTM	21.5	12.3	177	104	103 (208 mg)	59 (208 mg)
GEM	2824.3	2904.8	1696	1767	1384 (2000 mg) 56 (1000 mg)	1423 (2000 mg) 58 (1000 mg)
IDC	2.0	2.1	97	113	201 (10 mg)	216 (10 mg)
IP	1835.2	1011.8	351	235	1835 (1000 mg)	1012 (1000 mg)
IRT	294.6	324.2	1242	1314	589 (500 mg)	648 (500 mg)
MP	23.5	19.6	73	63	470 (50 mg)	393 (50 mg)
MT	361.2	352.2	501	510	240 (50 mg) 240 (1000 mg) 120 (5000 mg)	240 (50 mg) 240 (1000 mg) 120 (5000 mg)
MITC	4.9	11.5	427	642	240 (40 mg) 180 (10 mg)	240 (40 mg) 180 (10 mg)
OxaliPt	231.0	219.1	1580	1538	1155 (200 mg)	1095 (200 mg)
PTX	469.5	446.6	3324	3199	1565 (300 mg)	1489 (300 mg)
Albumin-PTX	87.5	85.9	439	435	875 (100 mg)	859 (100 mg)
PMX	612.8	589.5	726	736	980 (500 mg) 1225 (100 mg)	943 (500 mg) 1179 (100 mg)
RTX	2.4×10^{-2}	0.9×10^{-2}	5	2	12 (2 mg)	5 (2 mg)
TPT	13.8×10^{-2}	7.4×10^{-1}	50	14	34 (4 mg)	19 (4 mg)
VNB	3.3	2.1	318	215	330 (10 mg)	215 (10 mg)
VNC	1.1	1.1	653	690	579 (2 mg)	541 (2 mg)
VND	2.6×10^{-2}	1.2×10^{-2}	5	2	5 (5 mg)	2 (5 mg)
VNR	6.1	3.7	152	95	122 (50 mg)	75 (50 mg)

5-FU – 5-fluorouracil, BSF – busulfan, CarboPt – carboplatin, CP – cyclophosphamide, CisPt – cisplatin, CTB – cytarabine, DC – dacarbazine, DNR – daunorubicin, DTX – docetaxel, DXR – doxorubicin, EPI – epirubicin, ETP – etoposide, FTM – fotemustine, GEM – gemcitabine, IDC – idarubicine, IP – iphosphamide, IRT – irinotecan, MP – melphalan, MT – methotrexate, MITC – mitomycin C, OxaliPt – oxaliplatin, PTX – paclitaxel, PMX – pemetrexed, RTX – raltitrexed, TPT – topotecan, VNB – vinblastine, VNC – vincristine, VND – vindesine, VNR – vinorelbine.

* Relative bottle grammage.

on operators' hands, between each glove pair change. Wipe sampling was performed using a standardized kit, which comprises: a 5×5 cm, 3-layer nonwoven fabric wetted with 500 µl of an equimolar water/methanol solution stored in a 5-ml disposable syringe with a Luer-Lok connection fitting and tweezers equipped with disposable pipette tips. Each wipe was held with tweezers and wiped in the 3 standard directions (down, left, and right) over an area of 20×20 cm, for what concerns the door handles it was sampled a smaller area, around 10×10 cm. The same procedure was performed for the external faces of the healthcare workers' gloves at the moment of their replacement (every 30 min). The desorption of the ADs from the wipe was performed with 2 ml of equimolar water/methanol solution containing 40 ng/ml of 5-ClU and 10 ng/ml of CPM as internal standards (ISs). The samples were then filtered through a 0.2 µm GHP Acrodisc 13-mm filters (Pall Corporation, New York, USA).

Analytical methods

The determination of 30 ADs was performed through a Shimadzu Nexera X2 LC system coupled with a Shimadzu LCMS 8050 triple quadrupole equipped with an electrospray source (ESI) (Shimadzu Corp., Kyoto, Japan). The LC analysis was performed both on a Cortecs® UPLC T3 2.1×100 mm, 1.6 µm particle size (Waters Corporation, Milford, USA) and an Agilent® Poroshell 120 HILIC-Z 2.1×100 mm, 2.7 µm particles size (Agilent Technologies, Santa Clara, CA, USA). According to the methods reported by Dugheri et al. [22,23], the column switch was automated thanks to the Shimadzu CTO-20AC switching valve program.

A sample was considered positive for a drug if the value was above the method LOQ and if both the quantifier and qualifier ions were within the tolerance.

Data analysis

Since data were not normally distributed different percentile values were calculated depending on surface types. Moreover, due to the variety of samples, the statistical analysis of surface wipes was kept distinct from the gloves one.

Statistical analysis was carried out with Excel (Microsoft Office 365, Microsoft, Redmond, USA); for calculations of 90th percentile values, ADs concentrations that fell below the LOQ were assigned the value LOQ/2 [24].

Only 90th percentile values were considered for the calculations of SELs, because lower values such as the 75th percentile, would give no relevant information on surface contaminations, falling below the analytical quantitation limits. In addition, the proposal of only 1 value of SEL for each ADs, allowed to simplify the traffic-light color-coding system: a green color for the contaminations under the 90th percentile and red color for those above it.

A further distinction among the gloves samples was made because the gloves of pharmacy personnel were collected after each preparation session, while the gloves of administration unit nurses were collected only after the connection of ADs preparation to the patients' intravenous line. All sampled gloves were made of nitrileand compliant with the Istituto Superiore per la Prevenzione e la Sicurezza sul Lavoro (ISPESL) guidelines of 2010, which means that were tested by producers to 4–5 most used ADs.

The weekly glove contamination for the compounding technicians was calculated in 2 steps: at first, the glove contamination results were used to obtain an average contamination value (50th percentile) for a single preparation session (30 min), and then the value was multiplied by the number of weekly sessions generally conducted by the same operator, which was estimated at 12 preparation sessions per week by short interviews with the pharmacy personnel. An average glove surface of 400 cm^2 was used for the calculations.

All data concerning the amount of ADs utilized and the preparation made through the 2-year period by the Pharmacy AD Preparation Unit were managed with the software ONCOSYS (MTT-pro s.r.l. (Noemalifi group) – Trento, Italy).

RESULTS

The environmental ADs monitoring data were collected in Careggi University Hospital between 2020 and 2021 for a total of 1449 wipe samples, resulting in 43 470 measurements. Only 28.8% were found positive, which corresponds to 417 wipe samples.

In this 2-year period, 70 wipes concerned the monitoring of gloves contamination, both from pharmacy and administration unit personnel. Of the total 650 collected in 2020, 388 regarded 4 different administration units while 262 belong to the preparation unit. For what concerns the 2021 year, 425 wipes were sampled in 7 different administration units and 304 in the preparation unit, for a total of 729 wipes.

Samples were taken at the beginning and the end of work shifts, allowing to calculate 90th percentile values (reported in Table 2) for each ADs both in preparation and administration units on different surfaces.

Table 2. The 90th percentile of antineoplastic drugs (ADs) detected positive on different surfaces from preparation and administration units, Florence, Italy, 2020–2021

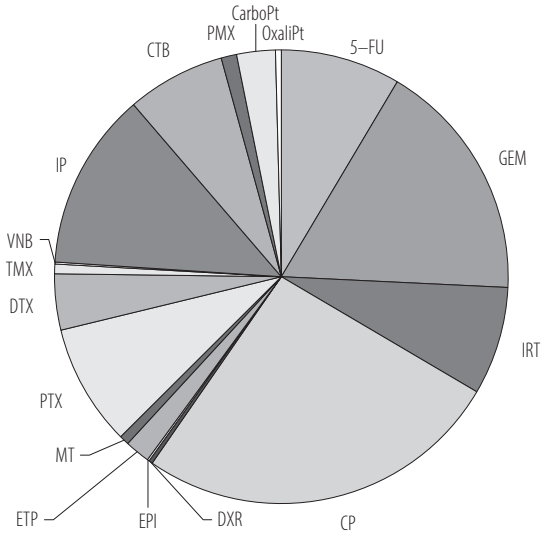
Variable	Antineoplastic drugs [pg/cm^2] (90th percentile)															
	floor		door handle		bed area		laminar flow hood		bathroom floor		WC		bathroom faucet		other surfaces	
	B-WS	E-WS	B-WS	E-WS	B-WS	E-WS	B-WS	E-WS	B-WS	E-WS	B-WS	E-WS	B-WS	E-WS	B-WS	E-WS
5-FU																
prep	<0.75	<0.75	<0.75	<0.75	–	–	<0.75	<0.75	–	–	–	–	–	–	<0.75	<0.75
adm	<0.75	**8.2**	<0.75	<0.75	<0.75	<0.75	–	–	**4.9**	**23.2**	**12.4**	**39.0**	<0.75	<0.75	<0.75	<0.75
GEM																
prep	<1.40	<1.40	<1.40	<1.40	–	–	<1.40	<1.40	–	–	–	–	–	–	<1.40	<1.40
adm	**22.0**	**34.0**	<1.40	<1.40	<1.40	<1.40	–	–	**175.6**	**281.8**	**31.0**	**421.8**	<1.40	<1.40	<1.40	<1.40
IRT																
prep	<0.27	<0.27	<0.27	<0.27	–	–	<0.27	<0.27	–	–	–	–	–	–	<0.27	<0.27
adm	<0.27	<0.27	<0.27	<0.27	<0.27	<0.27	–	–	**42.8**	**107.0**	**124.3**	**72.0**	<0.27	<0.27	<0.27	<0.27
CP																
prep	**9.4**	**5.6**	<0.17	<0.17	–	–	<0.17	<0.17	–	–	–	–	–	–	<0.17	<0.17
adm	**31.0**	**31.7**	<0.17	**80.0**	<0.17	**5.1**	–	–	**101.3**	**122.4**	**15.8**	**1380.2**	**6.9**	**25.9**	<0.17	<0.17
DXR																
prep	<0.58	<0.58	<0.58	<0.58	–	–	<0.58	<0.58	–	–	–	–	–	–	<0.58	<0.58
adm	<0.58	<0.58	<0.58	<0.58	<0.58	<0.58	–	–	<0.58	<0.58	<0.58	<0.58	<0.58	<0.58	<0.58	<0.58
DC																
prep	<0.22	<0.22	<0.22	<0.22	–	–	<0.22	<0.22	–	–	–	–	–	–	<0.22	<0.22
adm	<0.22	<0.22	<0.22	<0.22	<0.22	<0.22	–	–	<0.22	<0.22	<0.22	<0.22	<0.22	<0.22	<0.22	<0.22
EPI																
prep	<0.53	<0.53	<0.53	<0.53	–	–	<0.53	<0.53	–	–	–	–	–	–	<0.53	<0.53
adm	<0.53	<0.53	<0.53	<0.53	<0.53	<0.53	–	–	<0.53	<0.53	<0.53	<0.53	<0.53	<0.53	<0.53	<0.53
ETP																
prep	<1.06	<1.06	<1.06	<1.06	–	–	<1.06	<1.06	–	–	–	–	–	–	<1.06	<1.06
adm	<1.06	<1.06	<1.06	<1.06	<1.06	<1.06	–	–	<1.06	<1.06	**21.8**	<1.06	<1.06	<1.06	<1.06	<1.06
MT																
prep	<0.12	<0.12	<0.12	<0.12	–	–	<0.12	<0.12	–	–	–	–	–	–	<0.12	<0.12
adm	<0.12	<0.12	<0.12	<0.12	<0.12	<0.12	–	–	<0.12	<0.12	<0.12	<0.12	<0.12	<0.12	<0.12	<0.12
PTX																
prep	<0.92	<0.92	<0.92	<0.92	–	–	<0.92	<0.92	–	–	–	–	–	–	<0.92	<0.92
adm	<0.92	<0.92	<0.92	<0.92	<0.92	<0.92	–	–	**187.2**	**150.4**	**20.5**	**769.8**	<0.92	<0.92	<0.92	<0.92

DTX																
prep	<12.93	<12.93	<12.93	<12.93	–	–	<12.93	<12.93	–	–	–	–	–	–	<12.93	<12.93
adm	<12.93	<12.93	<12.93	<12.93	<12.93	<12.93	–	–	<12.93	<12.93	<12.93	**7.4**	<12.93	<12.93	<12.93	<12.93
TMX																
prep	<0.37	<0.37	<0.37	<0.37	–	–	<0.37	<0.37	–	–	–	–	–	–	<0.37	<0.37
adm	<0.37	<0.37	<0.37	<0.37	<0.37	<0.37	–	–	<0.37	<0.37	<0.37	<0.37	<0.37	<0.37	<0.37	<0.37
TPT																
prep	<0.17	<0.17	<0.17	<0.17	–	–	<0.17	<0.17	–	–	–	–	–	–	<0.17	<0.17
adm	<0.17	<0.17	<0.17	<0.17	<0.17	<0.17	–	–	<0.17	<0.17	<0.17	<0.17	<0.17	<0.17	<0.17	<0.17
VNC																
prep	<0.78	<0.78	<0.78	<0.78	–	–	<0.78	<0.78	–	–	–	–	–	–	<0.78	<0.78
adm	<0.78	<0.78	<0.78	<0.78	<0.78	<0.78	–	–	<0.78	<0.78	<0.78	<0.78	<0.78	<0.78	<0.78	<0.78
VNB																
prep	<2.20	<2.20	<2.20	<2.20	–	–	<2.20	<2.20	–	–	–	–	–	–	<2.20	<2.20
adm	<2.20	<2.20	<2.20	<2.20	<2.20	<2.20	–	–	<2.20	<2.20	<2.20	<2.20	<2.20	<2.20	<2.20	<2.20
VNR																
prep	<0.28	<0.28	<0.28	<0.28	–	–	<0.28	<0.28	–	–	–	–	–	–	<0.28	<0.28
adm	<0.28	<0.28	<0.28	<0.28	<0.28	<0.28	–	–	<0.28	<0.28	<0.28	<0.28	<0.28	<0.28	<0.28	<0.28
FTM																
prep	<0.18	<0.18	<0.18	<0.18	–	–	<0.18	<0.18	–	–	–	–	–	–	<0.18	<0.18
adm	<0.18	<0.18	<0.18	<0.18	<0.18	<0.18	–	–	<0.18	<0.18	<0.18	<0.18	<0.18	<0.18	<0.18	<0.18
MITC																
prep	<0.08	<0.08	<0.08	<0.08	–	–	<0.08	<0.08	–	–	–	–	–	–	<0.08	<0.08
adm	<0.08	<0.08	<0.08	<0.08	<0.08	<0.08	–	–	<0.08	<0.08	<0.08	<0.08	<0.08	<0.08	<0.08	<0.08
IDC																
prep	<3.09	<3.09	<3.09	<3.09	–	–	<3.09	<3.09	–	–	–	–	–	–	<3.09	<3.09
adm	<3.09	<3.09	<3.09	<3.09	<3.09	<3.09	–	–	<3.09	<3.09	<3.09	<3.09	<3.09	<3.09	<3.09	<3.09
IP																
prep	<0.17	<0.17	<0.17	<0.17	–	–	<0.17	<0.17	–	–	–	–	–	–	<0.17	<0.17
adm	**7.0**	**9.2**	<0.17	<0.17	<0.17	<0.17	–	–	**46.0**	**13.2**	<0.17	<0.17	<0.17	<0.17	<0.17	<0.17
CTB																
prep	<0.3	<0.3	<0.3	<0.3	–	–	<0.3	<0.3	–	–	–	–	–	–	<0.3	<0.3
adm	**42.0**	**13.2**	<0.3	<0.3	<0.3	<0.3	–	–	**20.4**	<0.3	<0.3	<0.3	<0.3	<0.3	<0.3	<0.3
MP																
prep	<0.90	<0.90	<0.90	<0.90	–	–	<0.90	<0.90	–	–	–	–	–	–	<0.90	<0.90
adm	<0.90	<0.90	<0.90	<0.90	<0.90	<0.90	–	–	<0.90	<0.90	<0.90	<0.90	<0.90	<0.90	<0.90	<0.90

Table 2. The 90th percentile of antineoplastic drugs (ADs) detected positive on different surfaces from preparation and administration units, Florence, Italy, 2020–2021 – cont.

Variable	Antineoplastic drugs [pg/cm^2] (90th percentile)															
	floor		door handle		bed area		laminar flow hood		bathroom floor		WC		bathroom faucet		other surfaces	
	B-WS	E-WS	B-WS	E-WS	B-WS	E-WS	B-WS	E-WS	B-WS	E-WS	B-WS	E-WS	B-WS	E-WS	B-WS	E-WS
BSF																
prep	<0.47	<0.47	<0.47	<0.47	–	–	<0.47	<0.47	–	–	–	–	–	–	<0.47	<0.47
adm	<0.47	<0.47	<0.47	<0.47	<0.47	<0.47	–	–	<0.47	<0.47	<0.47	<0.47	<0.47	<0.47	<0.47	<0.47
PMX																
prep	<0.43	<0.43	<0.43	<0.43	–	–	<0.43	<0.43	–	–	–	–	–	–	<0.43	<0.43
adm	<0.43	<0.43	<0.43	<0.43	<0.43	<0.43	–	–	<0.43	<0.43	<0.43	**60.7**	<0.43	<0.43	<0.43	<0.43
RTX																
prep	<0.40	<0.40	<0.40	<0.40	–	–	<0.40	<0.40	–	–	–	–	–	–	<0.40	<0.40
adm	<0.40	<0.40	<0.40	<0.40	<0.40	<0.40	–	–	<0.40	<0.40	<0.40	<0.40	<0.40	<0.40	<0.40	<0.40
DNR																
prep	<2.76	<2.76	<2.76	<2.76	–	–	<2.76	<2.76	–	–	–	–	–	–	<2.76	<2.76
adm	<2.76	<2.76	<2.76	<2.76	<2.76	<2.76	–	–	<2.76	<2.76	<2.76	<2.76	<2.76	<2.76	<2.76	<2.76
VIND																
prep	<28.57	<28.57	<28.57	<28.57	–	–	<28.57	<28.57	–	–	–	–	–	–	<28.57	<28.57
adm	<28.57	<28.57	<28.57	<28.57	<28.57	<28.57	–	–	<28.57	<28.57	<28.57	<28.57	<28.57	<28.57	<28.57	<28.57
CisPt																
prep	<73.95	<73.95	<73.95	<73.95	–	–	<73.95	<73.95	–	–	–	–	–	–	<73.95	<73.95
adm	<73.95	<73.95	<73.95	<73.95	<73.95	<73.95	–	–	<73.95	<73.95	<73.95	<73.95	<73.95	<73.95	<73.95	<73.95
CarboPt																
prep	<13.65	<13.65	<13.65	<13.65	–	–	<13.65	<13.65	–	–	–	–	–	–	<13.65	<13.65
adm	<13.65	<13.65	<13.65	<13.65	<13.65	<13.65	–	–	<13.65	**7.9**	<13.65	**942.8**	<13.65	<13.65	<13.65	<13.65
OxaliPt																
prep	<1.75	<1.75	<1.75	<1.75	–	–	<1.75	<1.75	–	–	–	–	–	–	<1.75	<1.75
adm	<1.75	<1.75	<1.75	<1.75	<1.75	<1.75	–	–	<1.75	<1.75	<1.75	<1.75	<1.75	<1.75	<1.75	<1.75

B-WS – before the work shift, E-WS – end of the work shift, adm – administration unit, prep – preparation unit, TMX – tamoxifen.
Other abbreviations as in Table 1.
Bolded are values greater than the LOQ of the substance.



Abbreviations as in Tables 1 and 2.

Figure 1. Wipes detected positive for each antineoplastic drug (AD), Florence, Italy, 2020–2021

Total positive determinations from administration units were 45% out of 388 in 2020, while in 2021 the positive ones were 30% of 425. A similar decrease was observed for the pharmacy unit, in fact, in 2020 23% of 262 wipes were positives, while in 2021 the contaminated were only 9% of 304. Furthermore, an analysis of the overall data, even including gloves, showed that the 7 most frequently detected substances were CP (13.5%), GEM (9.4%), IP (6.5%), PTX (5.0%), 5-FU (4.3%), IRT (4.0%), and CTB (3.6%).

Without considering the wipe sampled on gloves, the number of wipes collected in the 2-year period was 1379, of which the 13.8% was positive to CP, 9.1% to GEM, 6.7% to IP, 4.6% to PTX, 4.5% to 5-FU, 4.1% to IRT, 3.7% to CTB, 2.1% to DTX, 1.5% to CarboPt, 0.9% to ETP, 0.6% to PMX, 0.4% to MT and TMX, 0.2% to OxaliPt, 0.1% to DXR, EPI and VNB showed in Figure 1.

Upon scrutiny of the sampling site, the highest concentration of positives was on the WC (84%) and bathroom floor (82%) of the administration units, while in preparation unit the floors (24%) were the more contaminated ones, as reported in Table 3.

Table 4 reported the number of wipes detected positive for each ADs divided into 2 main categories: wipes collected only in administration units and those sampled only in preparation unit; distinguished in those sampled before and after the work shift.

Considering the ADs contaminations found on different surfaces and units, Figure 2 shows the frequencies of positive wipes to fall in 4 different ranges of quantitation: ≤10 pg/cm^2, between 11–100 pg/cm^2, between 101–1000 pg/cm^2 and ≥1001 pg/cm^2. The upper panel regards data concerning the administration units, showing that the highest contaminations come from the bathroom surfaces. While the lower one regards the preparation unit, which instead highlights the frequency to found very low contaminations.

The results obtained for the glove contaminations of 8 ADs, expressed in terms of average session contamination (50th percentile of found contaminations), weekly contamination, and minimum and maximum quantities detected, are reported in Table 5. As can be

Table 3. Wipes sampled for each surface and relative contamination detected to at least one antineoplastic drugs (ADs), Florence, Italy, 2020–2021

Surface	Positive wipes [n (%)]			
	preparation unit		administration unit	
	B-WS	E-WS	B-WS	E-WS
Floor	50 (18)	50 (24)	91 (58)	89 (64)
Door handle	99 (11)	99 (11)	74 (20)	78 (24)
Bed area	–	–	131 (18)	131 (23)
Laminar flow hood	89 (16)	89 (18)	–	–
Bathroom floor	–	–	33 (82)	38 (82)
WC	–	–	25 (68)	25 (84)
Bathroom faucet	–	–	14 (14)	14 (21)
Other surfaces	55 (11)	55 (16)	25 (4)	25 (8)
Total	293 (14)	293 (16)	393 (35)	400 (41)

B-WS – before the work shift, E-WS – end of the work shift.

Table 4. Samples detected positive to each antineoplastic drugs (ADs) for all collected wipes, Florence, Italy, 2020–2021

AD	AD detections [n (%)]				
	administration unit		preparation unit		total
	B-WS (N = 393)	E-WS (N = 400)	B-WS (N = 293)	E-WS (N = 293)	
5-FU	23 (5.9)	34 (8.5)	1 (0.3)	4 (1.4)	62 (4.5)
GEM	43 (10.9)	63 (15.8)	4 (1.4)	15 (5.1)	98 (9.1)
IRT	25 (6.4)	30 (7.5)	0 (0)	1 (0.3)	56 (4.1)
CP	67 (17)	83 (20.8)	22 (7.5)	18 (6.1)	190 (13.8)
DXR	0 (0)	0 (0)	0 (0)	2 (0.7)	2 (0.2)
EPI	0 (0)	1 (0.3)	0 (0)	0 (0)	1 (0.1)
ETP	6 (1.5)	4 (1.0)	1 (0.3)	2 (0.7)	13 (0.9)
MT	1 (0.3)	3 (0.8)	1 (0.3)	0 (0)	5 (0.4)
PTX	17 (4.3)	37 (9.3)	4 (1.4)	5 (1.7)	63 (4.6)
DTX	10 (2.5)	18 (4.5)	0 (0)	1 (0.3)	29 (2.1)
TMX	2 (0.5)	3 (0.8)	0 (0)	0 (0)	5 (0.4)
VNB	0 (0)	0 (0)	0 (0)	1 (0.3)	1 (0.1)
IP	33 (8.4)	35 (8.8)	11 (3.8)	13 (4.4)	92 (6.7)
CTB	27 (6.9)	16 (4.0)	2 (0.7)	6 (2.0)	51 (3.7)
PMX	1 (0.3)	5 (1.3)	0 (0)	2 (0.7)	8 (0.6)
CarboPt	5 (1.3)	12 (3)	0 (0)	3 (1.0)	20 (1.5)
OxaliPt	0 (0)	2 (0.5)	0 (0)	1 (0.3)	3 (0.2)

Abbreviations as in Tables 1 and 2.

seen, values in the order of ng/weeks were obtained, due to the abundance of samples which presented undetectable contamination levels.

Administration unit personnel gloves were 22 of which only one showed contamination to MT ≤10 pg/cm^2.

DISCUSSION

Biological and environmental monitoring of occupational exposure to hazardous chemicals, such as ADs, are crucial to identify the most suitable risk-control strategies in health risk assessment at workplaces. Thus, the risk assessment of handling ADs can be carried out in different ways, such as researching biological effects [25], detection of substances or their metabolites in blood or urine [26], calculating the Cytotoxic Contact Index [27], monitoring their presence in the work environment – in the air [28] or on work surfaces. Industrial hygienists, conforming to the "as low as reasonably achievable" (ALARA) principle, widely use wipe tests to monitor surface contaminations, combined with analytical methods able to detect ADs at levels as low as pg/cm^2. Periodic environmental monitoring of sites where ADs are prepared and administered is recommended, although there is no guidance concerning which drug should be monitored, the preferred sampling sites, the appropriate test methods, or the needed LODs.

The development of LC-MS/MS methods for simultaneous analysis of numerous compounds has piqued the interest of authors' research group, to assess surface ADs contaminations in healthcare places. Since NIOSH indicated that there are >100 antineoplastic agents used in health care, it is essential to simultaneously detect as many ADs as possible, providing a complete investigation into surface contaminations and thus on exposure risk for healthcare workers. So, in these last years, simultaneous detection of several cytostatics by the mean of modified C18 stationary phases, combining hydrophobic and polar selectivity, is growing in importance in the field of LC methods [29]. Cancer treatments often include >1 cytotoxic drugs, this increases the probability of having at least 1 positive finding, so it is crucial to analyse as many ADs as possible at

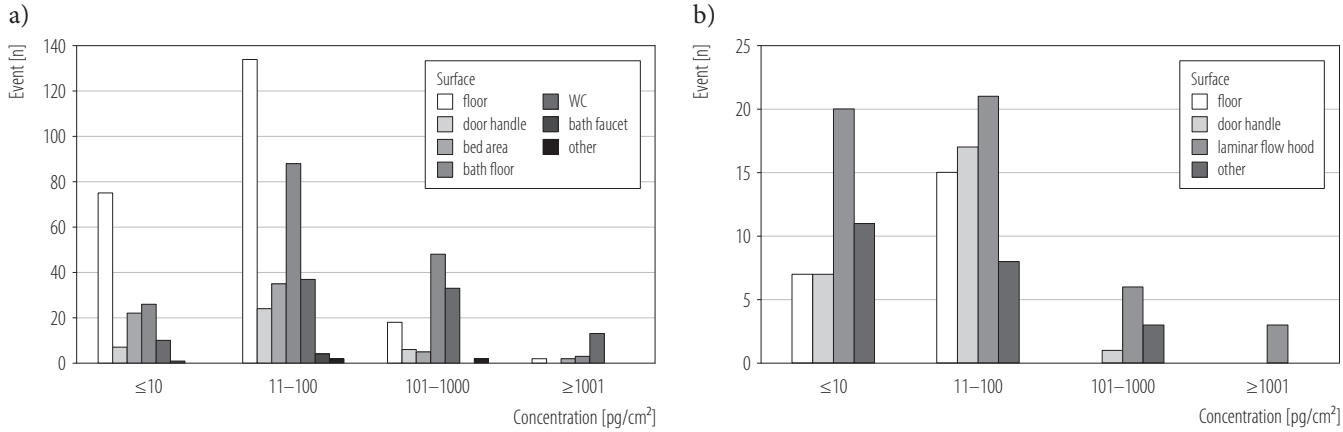


Figure 2. Frequency histograms of antineoplastic drugs (ADs) contamination: a) administration units, b) preparation unit, Florence, Italy, 2020–2021

the same time. In this study a high-throughput procedure based on 2 Ultra-High Performance Liquid Chromatography (UHPLC)–MS/MS analytical methods was used. The automated switching of the 2 analytical columns, Cortecs® UPLC T3 and Hilic-Z Poroshell® 120, between one analysis and the other, made possible to come up with an LC-MS/MS approach capable of detecting 30 ADs in only 23 min, which could beascribed to 1890 determinations per day.

Analysing both data concerning the number of ADs preparations and the wipe sampling campaign, it is easy to assess that the ADs which are handled in the highest quantity (in terms of mg and bottles) (Table 1), 5-FU, GEM, CP, IP, PTX, PMX apart from OxaliPt, are the ones which produce the most contamination. Following the law of large numbers, a higher risk is connected to the handling of a higher number of hazardous substances, increasing the frequency of unexpected events, being impossible to have contamination equal to 0. To give an idea, Careggi Hospital between 2020 and 2021 was opened on average of 22 200 ADs bottles per year.

From the analysis of obtained data, it is important to highlight that nearly 85% of samples collected in the pharmacy unit (both before and after the work shift) present for all the ADs analysed a level under the LOQs. This is an indicator of the high quality of good practices in working procedures and safety precautions adopted by Careggi Hospital. While for what concerns the administration units, this percentage decreases to 60% more or less for both B-WS and E-WS; it is important to report that most contaminated samples collected in these wards came from the bathroom, especially from the floor (82% out of 71) and WC surface (76% out of 50). Thus, it is plausible to think that most of the contamination in

Table 5. The majority of antineoplastic drugs (ADs) detected on gloves of Pharmacy AD Preparation Unit personnel, Florence, Italy, 2020–2021

Antineoplastic drug	Contamination				
	session (50th percentile) [pg/cm²] (M)	weekly [ng]	min [pg/cm²]	max [pg/cm²]	gloves detected positive [n]
GEM	0.70	3.36	5	2,457	11
CP	0.09	0.41	12	107	6
PTX	0.46	2.22	26	438	10
IRT	0.14	0.66	8	22	2
MT	0.06	0.29	3	50	2
IP	0.09	0.42	1	16	2
PMX	0.22	1.04	18	600	2
CarboPt	6.83	32.76	20	414	3

Abbreviations as in Table 1.

the administration units comes from the biological fluids of patients who were treated with ADs.

Since wipe sampling is a suitable control to characterize worker exposure and surface contamination over time, the 90th percentile calculations have been proposed as SELs, as previously reported [21]. The hereby proposed levels are one order of magnitude lower than the European limit of 100 pg/cm^2, exception made for the values of IRT, GEM, CP, and PTX on WC and bathroom floor surfaces of administration units, as could be seen in Table 2.

Interesting considerations could be done analysing, not only the numbers of positive wipes but also the quantities of detected ADs contaminations. Referring to the ALARA principle can be seen in Figure 2, that the highest number of contamination falls in the range of 11–100 pg/cm^2 both in administration and preparation units. In the former could be seen a tendency to detect contamination in the range 101–1000 pg/cm^2 or higher, regarding only bathroom surfaces; while in the latter this tendency is oriented towards the lowest values (≤10 pg/cm^2).

Since hands are the most likely skin area to be contaminated with ADs, as most tasks involving cytotoxics are done using the hands, the medical gloves are the most important PPE. When handling cytotoxic drugs, they are the first line of protection, so the choice of safer gloves must be contextualized to the physical-chemical properties of the used ADs and the handling time. In Europe, the medical gloves are legally covered by the European Council Directive 93/42/EEC, the European Standard (EN) 455, and the UNI EN 16523-1:2019, and permeation test is not required for gloves used in ADs handling. This constitutes a severe deficiency, while in the US, medical gloves must be fulfilled by American Society of Testing and Materials (ASTM) D 6978-05 which proposes a permeation breakthrough limit equal to 10 ng min^{-1} cm^{-2} carried out with a minimum of 9 ADs, 7 of which mandatory.

Recently, a study on dermal ADs exposure – using CP as a marker – showed a weekly limit value of 740 ng [30].

Being the present data inadequate to create an actual dermal exposure assessment such as the overmentioned, the authors decided to estimate the external glove contamination for an average preparation session and then use it to estimate weekly contamination. The results, shown in section 3, express low weekly contamination, in the order of nanograms per week. However, these results do not take into account the capacity of many drugs, depending on their chemical-physical properties, to permeate through the gloves. Considering the indulgent glove permeation limit for ADs of 10 ng min^{-1} cm^{-2}, a fast and easier method to evaluate actual dermal ADs contamination will be needed in order to assess properly the healthcare operators' risk.

The difference in the amount of glove contamination between administration and preparation units could be ascribed to the fact that in the administration unit samples were collected after the installation/switching of the ADs intravenous lines which, according to the obtained results, is associated to a lower risk of contamination. Future developments might involve the sampling of gloves utilized in areas associated with higher risk, such as bathrooms.

Although the low contamination results obtained in this case study, when such quantities of preparations are involved in hospital pharmacies, robotic automation presents an opportunity for improving safety and efficiency in the compounding process by increasing accuracy and consistency for patients and reducing ADs direct exposure for compounding staff. This technique is increasing its experienced widespread adoption in hospital pharmacies for intravenous compounding. There are currently several robots and automated devices that are marketed for sterile ADs. To achieve the lowest levels of contamination and the best protection for workers and the environment, robotic ADs compounders are dependent on work practices surrounding the actual compounding. The decreased staff exposure to toxic chemotherapies improves working conditions (reducing fatigue and musculoskeletal disorders) and limits human resources expenditure. Additional research is needed to evaluate the place of robotic AD compounders in patient and worker safety. The choice to use robotics should consider the needs and the financial possibilities of each institution. That is why this type of control and production method varies from one hospital to another. Thus, in order to make the whole process secure and to ensure the quality and safety of patient care, a proactive hazard analysis method using Failure Mode Effect and Criticality Analysis or Functional Resonance Accident Model can be employed to identify potential chemotherapy process failures.

CONCLUSIONS

Directives 2019/983 and 2019/130 on the protection of workers from the risks related to exposure to carcinogens at work are a key legal solution in the field of public health in the European Union, focused on the issue of occupational cancer. The campaign carried out

in Careggi Hospital revealed that following the good practices in working procedures and safety precautions, the risk of contamination is lowered but not avoided. Thus, the role of legal regulation harmonized throughout the European Union and capable of including manufacturers and importers, has still an enormous part in ensuring reliable risk management of cytostatic drugs. The ADs contaminations monitoring also confirms that the biological fluids of patients receiving antineoplastic therapies are the principal source of contamination when safety procedures are correctly applied, as it is shown by the higher percentage of positive wipe samples found in administration units. New SELs were proposed for a wider range of substances, with values mainly <100 pg/cm^2, except the ones concerning bathroom environments.

Moreover, a deeper study must be carried out concerning the gloves contamination and thus the estimation of weekly ADs contamination of pharmacy personnel.

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