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Antineoplastic drugs in healthcare settings: Occupational exposure and risk graduation

Maria Francisca Portilha-Cunha [a, b], Pedro Norton [c, d], Arminda Alves [a, b], Ana R.L. Ribeiro [b, e], Adrián M.T. Silva [b, e], Mónica S.F. Santos [c, d, *]

[a] LEPABE—Laboratory for Process Engineering, Environment, Biotechnology and Energy, Faculty of Engineering, University of Porto, Rua Dr. Roberto Frias, 4200-465, Porto, Portugal
[b] ALiCE—Associate Laboratory in Chemical Engineering, Faculty of Engineering, University of Porto, Rua Dr. Roberto Frias, 4200-465, Porto, Portugal
[c] EPIUnit, Instituto de Saúde Pública, Universidade do Porto, Rua das Taipas 135, 4050-600, Porto, Portugal
[d] Laboratório para a Investigação Integrativa e Translacional em Saúde Populacional (ITR), Universidade do Porto, Rua das Taipas 135, 4050-600, Porto, Portugal
[e] Laboratory of Separation and Reaction Engineering—Laboratory of Catalysis and Materials (LSRE− LCM), Faculty of Engineering, University of Porto, Rua Dr. Roberto Frias, 4200-465, Porto, Portugal

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ABSTRACT

Antineoplastic drugs (ADs) are hazardous medicinal products highlighted in the EU strategic framework on health and safety at work 2021−2027. To minimize workers' chronic exposure in oncologic settings, regular monitoring programs for these drugs are crucial and mandatory in the EU (Directive 2004/37/EC). No surveillance exists in Portugal, thus we intended to assess environmental contamination and to perform occupational exposure and risk graduation in a Portuguese tertiary hospital. Wipe sampling and liquid chromatography−tandem mass spectrometry were employed to analyze thirteen drugs of concern (bicalutamide, capecitabine, cyclophosphamide, cyproterone, doxorubicin, etoposide, flutamide, ifosfamide, imatinib, megestrol, mycophenolate mofetil, paclitaxel, prednisone), eight for the first time worldwide, in 152 surface samples over three sampling campaigns. Surface contamination before general cleaning (worst-case scenario) was higher and more widespread in the pharmacy (84%−98 % positive samples) than in the day-care hospital (40%−72 %). No samples were found above the "action limit" (10000 pg/cm^2), but concentrations were frequently above the "safe"/alert level (100 pg/cm^2), particularly for cyclophosphamide and ifosfamide (largest campaign's 90th percentiles: 2197 pg/cm^2 and 1898 pg/cm^2). Despite the approach's nuances, the maximum daily dermal intake calculated (1.6 μg/day, considering a single genotoxic drug) was lower than the acceptable daily intake. This study provided knowledge regarding surface contamination in a European hospital, where occupational exposure to some ADs of concern cannot be ruled out and follow-up monitoring is recommended, even if workers seem unlikely to develop cancer from handling them. Furthermore, this work contributes to the implementation of regular environmental monitoring programs for ADs in Portugal, enhancing compliance with EU recommendations.

1. Introduction

Antineoplastic drugs (ADs) are considered hazardous medicinal products (HMPs), since they are potentially carcinogenic, mutagenic, and/or reprotoxic (CMR) substances [1]. Traces of ADs, or their metabolites, have been detected in biological fluids of healthcare workers [2]. In fact, a significant association between occupational exposure to ADs and increased genotoxic risk for healthcare workers has been established, based on the increased frequency of several biological indicators compared to controls [3−6]. Moreover, both acute and chronic effects have been reported, mainly in pharmacy professionals and nurses [3,7,8].

* Corresponding author. EPIUnit, Instituto de Saúde Pública, Universidade do Porto, Rua das Taipas 135, 4050-600, Porto, Portugal.
E-mail address: monica.santos@ispup.up.pt (M.S.F. Santos).
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Consequently, concerns regarding long-term exposure of professionals to ADs have grown, as can be inferred from the numerous guidelines and good occupational hygiene practices published worldwide [8–10]. Hence, preventing occupational exposure to ADs by monitoring their presence in healthcare settings and implementing mitigation measures is crucial, especially considering that a substantial rise in their prescription is expected in the near future due to an expected increase in new cancer cases (47 % between 2020 and 2040) [11]. In addition, it is important to note that monitoring programs are actually mandatory for CMR substances in the European Union (EU) under Directive 2004/37/EC [12].

Despite the combination of environmental and biological assessment being considered the best approach to accurately assess the exposure of humans to CMR substances [13], the latter is a cumbersome practice [14]. Nowadays, the former is largely used to assess exposure to ADs and to take corrective measures. Surface contamination is the preferred indicator of human exposure to ADs through environmental assessment, since direct skin contact with contaminated surfaces is the primary exposure route (inhalation or ingestion of ADs may also occur but to a much lesser extent [9,15]). Indeed, ADs presence on surfaces of healthcare units has been reported worldwide with single sampling campaigns [9,16], as well as with long term [17] or cross-sectional studies [18–20]. However, percentages of positive samples and contamination levels of ADs have been highly variable, with large-scale studies reporting 90th percentiles in the pg/cm^2 range, despite some samples reaching values in the order of hundreds of ng/cm^2 [18–21]. Hence, the literature evidences that results obtained in a given occupational context cannot be generalized nor used to assess the exposure risk in a different setting (where the exposed population has different characteristics due to differences in cancer treatment approaches, operating conditions, safety measures in place, among others), meaning that each specific situation must be individually studied to correctly assess the exposure risk of the professionals occupying these facilities.

In Portugal, for instance, up to the authors' best knowledge, no organized medical surveillance program for healthcare workers exists, and compliance with the International Society of Oncology Pharmacy Practitioners (ISOPP) standards for the safe handling of ADs is voluntary, albeit recommended in the EU [10]. In fact, although safe handling guidelines are applied in major hospitals in large cities, manipulation of ADs in small hospitals from small towns is made under still largely unknown and possibly hazardous conditions [10]. In total, only three studies regarding surface contamination with ADs have been reported in Portugal between 2014 and 2018 [22–24]; however, these studies presented some limitations: (i) the inclusion of three or less surrogate compounds, which leads to a possible underestimation of exposure risk due to the wide variety of drugs in use and their different properties; and (ii) the use of methods with relatively low selectivity and sensitivity, that resulted in a high percent of samples where ADs were detected below the limits of quantification (ng/cm^2 level) [22]. Furthermore, no follow-up assessments have been reported since then, no regular monitoring program of surface contamination levels has been implemented in Portugal and, thus, the occupational risk of healthcare workers exposed to ADs has not been assessed.

To surpass some of the limitations mentioned above, a method with good sensitivity and very low detection limits was previously developed for multitarget analysis of 13 drugs in workplace surfaces [25]: bicalutamide (BIC), capecitabine (CAP), cyclophosphamide (CYC), cyproterone (CYPR), doxorubicin (DOX), etoposide (ETO), flutamide (FLU), ifosfamide (IFO), imatinib (IMA), megestrol (MEG), mycophenolate mofetil (MMF), paclitaxel (PAC), and prednisone (PRE). These drugs were chosen based on their frequent use in current chemotherapy preparations by the partner hospital, their consumption in Portugal [26] and/or for being drugs of high concern, as evidenced by the International Agency for Research on Cancer (IARC) carcinogenic classification of some drugs [27] and by their inclusion in "The European Trade Union Institute's list of HMPs" (Table 1). CYPR and PRE are not considered ADs, but they were included in the present study for being commonly administered concurrently in cancer treatments, while MMF was included for being widely used as an immunosuppressant. It is worth noting that this is the first time that eight of these pharmaceuticals (BIC, CAP, CYPR, FLU, IMA, MEG, MMF, PRE) are monitored on occupational surfaces worldwide, which is a remarkable novelty of the present study.

Although environmental contamination assessment can inform on how, where and (possibly) when exposure to hazardous substances occurred, it is through occupational risk assessments that it is possible to appropriately eliminate, control, or reduce health risks associated with workplace hazards. Nonetheless, the occupational risk is only qualitatively discussed in the literature, by comparing environmental contamination with proposed guidance values, since no allowable or acceptable values have been formally set for ADs. Moreover, very few articles were found in the literature regarding quantitative risk assessment for the cancer risk due to handling of ADs [21,28–30].

Hence, the main objectives of this study were: (i) to measure the environmental (surface) contamination by the target drugs in different oncologic areas of a tertiary hospital in Portugal; and (ii) to assess the occupational exposure and potential risks for the professionals working there. Each of the three sampling campaigns also had a secondary objective: the first acted as a screening to select the most critical surfaces to be studied; the second to determine whether there was accumulation of contamination over a working week; and the third aimed at quantifying the contamination after some changes to the layout and procedures. Furthermore, this study was intended to act as a basis for the implementation of a regular monitoring program in the partner hospital, and eventually in other hospitals in the country (since none currently exists) or even abroad, enhancing the compliance with the EU Directive 2004/37/EC, which specifically highlights ADs since an amendment from 2022.

2. Materials and methods

2.1. Chemicals and reagents

BIC, CAP, CYC, CYPR, DOX, ETO, FLU, IFO, IMA, MEG, MMF, PAC, and PRE analytical standards of 98–99 % purity and cyclophosphamide-d4 (CYC-d4) were acquired from Sigma-Aldrich (St. Louis, MO, USA) or Cayman Chemical Company (Ann Arbor, MI, USA). Acetonitrile, isopropanol, methanol, and Milli-Q water were of LC–MS grade and were supplied by Merck (Darmstadt, Germany). Formic acid was purchased from Sigma-Aldrich (St. Louis, MO, USA). Stock standard solutions were prepared at a concentration of 100 mg/L in acetonitrile. Working solutions were prepared at 10 mg/L in acetonitrile.

2.2. Safety considerations on AD's handling

For standards' preparation, exhaustive controls on handling procedures, storage conditions, and safety rules were followed, as recommended by the manufacturers. All procedures were performed in a safety hood with vertical laminar airflow and work surfaces were protected by absorbent paper. All materials that contacted with ADs were cleaned with isopropanol and all

Table 1
Hazard classification of the target pharmaceuticals according to the EU Classification, Labelling and Packaging system of carcinogenic, mutagenic, and/or reprotoxic substances [1] and to the IARC carcinogenic classification [27].

Target pharmaceutical	Hazard classification according to the EU Classification, Labelling and Packaging			IARC carcinogenic classification
	Carcinogenic classification	Mutagenic classification	Reprotoxic classification	
BIC	2	–	1B	–
CAP	1B	2	1B	–
CYPR	–	–	–	–
CYC	1B	1B	1A	1
DOX	1B	1B	1B	2A
ETO	1B	–	–	1
FLU	–	–	1B	–
IFO	1A	1A	1A	3
IMA	2	–	1B	–
MEG	1B	–	1A	–
MMF	–	–	1B	–
PAC	2	1B	1B	–
PRE	–	–	–	3

dischargeable materials were treated as hazardous waste.

2.3. Study site

This study was conducted at a tertiary hospital in Portugal, and the settings under evaluation were the hospital's pharmacy (preparation ward) and the oncologic section of the day-care hospital unit (administration ward, with 36 beds/chairs available). These wards are in operation every day, with over 35 000 chemotherapy preparations a year and around 18 000 chemotherapy sessions/administrations a year. Pharmaceutical formulations are prepared in a clean room, transferred to the pharmacy on a metal tray through a medication pass-through box, checked/validated in a working table, transferred to the day-care hospital, placed on preparation tables or on support carts, and then hung on a perfusor support for administration. General cleaning is performed at the end of every workday in both wards (depending on the locations, a commercial disinfectant/biocide (Vyclean®), sodium hypochlorite (200 mg/L) or dish detergent is used), and chairs are cleaned with the biocide between patients.

2.4. Sampling strategy

Contamination of the occupational environments was evaluated in three sampling campaigns, always at the end of the day, before general cleaning (worst-case scenario). A preliminary campaign was performed in late 2020, in the peak of Covid-19: 51 samples (25 from the pharmacy and 26 from the day-care hospital) were taken over three days in different weeks. The main campaign (second) was performed in May 2021, when most procedures were reportedly back to normal (particularly the cleaning frequency): 16 locations were sampled over a working week (five consecutive days, totaling 80 samples) to gather data for a temporal trend analysis, but also to find out if an accumulation of contamination was occurring. A third campaign was performed in April 2023, after the oncologic service moved to new facilities, but where the ADs' circuit was maintained as described in section 2.3. In this case, a total of 21 samples (11 from the pharmacy and 10 from the day-care hospital) were collected in two consecutive days.

The preliminary sampling campaign acted as a screening of the most critical surfaces to be included in future campaigns. Sampling points were chosen based on frequently contaminated locations mentioned in the literature and on observation of workers' daily practices, aiming at the identification of the most potentially contaminated surfaces and/or more frequently handled or touched by professionals and patients. The ADs' circuit (from reception in the pharmacy to administration), the layouts of the pharmacy and the day-care hospital, and any potentially hazardous action/practice or non-compliance with the ISOPP standards for the safe handling of cytotoxics were also considered. Sampled locations from the pharmacy included, among others: surfaces from the biological safety cabinet; storage cabinets and fridges; working tables; trays; door handles; and office objects. In the day-care hospital, some of the sampled locations were: working tables and support carts; perfusion pumps and their supports/handles; patients' chair armrests and support tables; floors; and office objects. The full list of sampled locations can be found in Table A.1 in the Supplementary Material.

2.5. Analytical method for identification and quantification of target drugs on workplace surfaces

A method previously developed by Portilha-Cunha et al. [25] was used to identify and quantify the 13 target pharmaceuticals (BIC, CAP, CYC, CYPR, DOX, ETO, FLU, IFO, IMA, MEG, MMF, PAC, PRE) on workplace surfaces. Wipe sampling was performed by wiping 100 cm^2 of each surface (for uneven surfaces, all area was wiped and estimated), using ¾ of a commercial gauze (10 × 20 cm, 70 % viscose and 30 % polyester, 30 g/m^2; Batist Medical a.s., Červený Kostelec, Czech Republic) embedded in 2 mL isopropanol, each ¼ in a different direction (horizontal, vertical, diagonal). The remaining ¼ of dry gauze was used to absorb the solvent that may have remained on the surface and all gauze parts were placed in a 50 mL Falcon tube for extraction. The internal standard (20 ng CYC-d4) was added to the Falcon tube with the gauze parts, 1 mL acetonitrile (extraction solvent) was added, the content was shaken in an ultrasonic bath for 20 min, the organic solvent was recovered, transferred to a vial and slowly evaporated to dryness under a nitrogen gas stream, and the dried extract was reconstituted in 200 µL acetonitrile. Each reconstituted extract was then analyzed for the presence of the 13 pharmaceuticals by liquid chromatography–tandem mass spectrometry (LC–MS/MS), using an ultra-high performance liquid chromatography apparatus (Shimadzu Corporation; Tokyo, Japan) equipped with two Pumps LC-30AD, an Autosampler SIL-30 AC, an Oven CTO-20 AC, a Degasser DGU-20A5, a System Controller CBM-20A, an LC solution version 5.41SP1, coupled to a triple quadrupole mass spectrometer detector Shimadzu LCMS-8040. Data was acquired and processed using the LabSolutions software package. Separation was performed with a Luna C18 column (150 × 2.1 mm ID, particle size 5 µm;

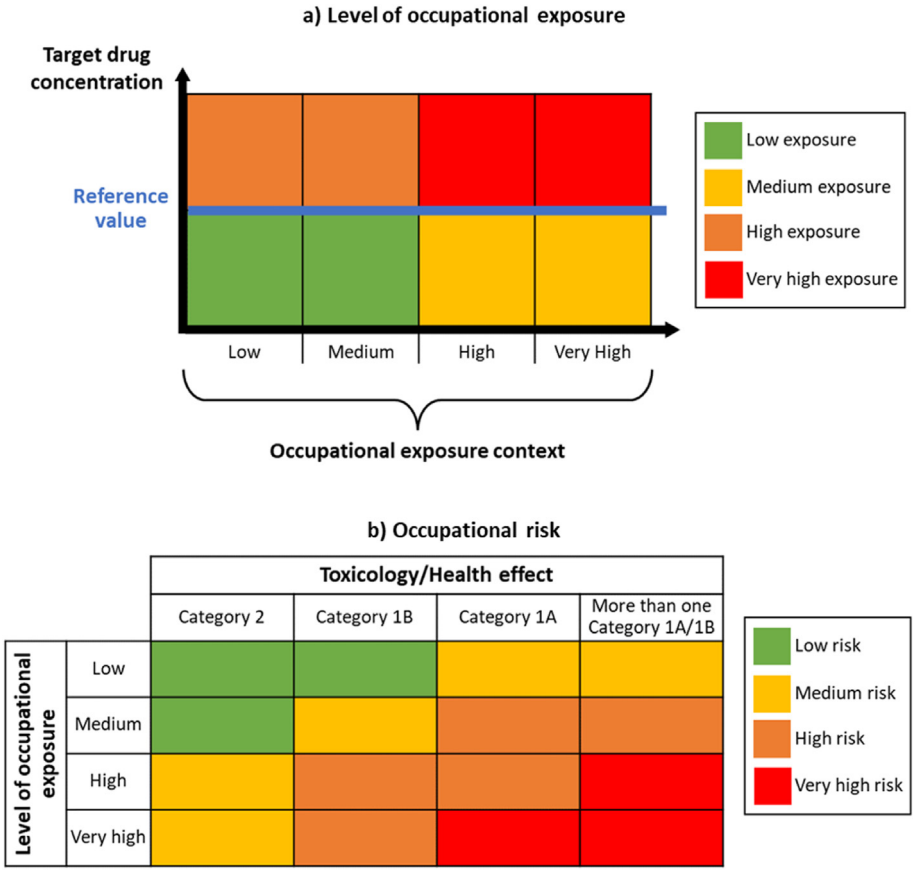

Fig. 1. Qualitative assessment of the risk from occupational exposure to ADs (methodology adapted from DGS (2018)): a) Graduation of the level of occupational exposure; b) Graduation of the occupational risk.

Phenomenex). The mobile phase composition consisted of a binary mixture of water (A) and methanol (B), both acidified with 0.1 % formic acid. Gradient elution started at 5 % B, increased to 20 % B in 15 min, and then to 45 % B in 15 min (30 min), reaching 100 % in another 9 min (39 min). Then, after 2 min at 100 % B, the initial conditions were restored (4 min), and the system was stabilized for 5 min. The flow rate was set at 0.2 mL/min, and the injection volume was 5 μL. Detailed information regarding chromatographic and mass spectrometry information as well as validation parameters (linearity, precision, accuracy, and global uncertainty estimation) can be found in the study by Portilha-Cunha et al. [25] mentioned above. Precision was <15 % CV, except for CAP, DOX, IMA and PAC (CV 32 %, 26 %, 25 % and 25 %, respectively), and accuracy was between 68 % and 96 %, except for CAP, DOX and IMA (251 %, 24 % and 54 %, respectively). Method quantification limits (MQLs) were in the lower pg/cm^2 level: 0.4 (BIC/MMF) – 13.3 (CYPR). Global uncertainty was estimated to be generally below 35 % for concentrations above 100 pg/cm^2 (considered a "safe" substance-independent reference/guidance value). This global uncertainty must be considered when interpreting the concentrations of the target drugs on workplace surfaces, as no correction factors from any uncertainty source were applied to the values presented in this study.

2.6. Color code model for surface contamination

Samples were considered positive if at least one drug was detected above the MQL, while non-positive samples were attributed a value of 0 pg/cm^2. A color code model for surface contamination was used, according to the ranges recommended and in use in the Netherlands [31]: green for [MQL – 100[pg/cm^2; yellow for [100–1000[pg/cm^2; orange for [1000–10 000[pg/cm^2; and red for ≥10 000 pg/cm^2. Since no allowable or acceptable values have been set for ADs' surface concentrations, 100 pg/cm^2 (the threshold for the green range) was considered as a "safe" substance-independent reference or guidance value (meaning it is an alert level) [18,19,31,32] and 10 000 pg/cm^2 is considered the "action limit" [31,32], thus values in the red range are "not acceptable". The middle range was divided into two categories to facilitate a visual notion of the magnitude of the concentrations detected. Thus, for concentrations in the yellow or orange ranges, the exposure risk should be estimated and a follow-up monitoring performed (within three to six months), possibly followed by corrective measures.

2.7. Quantification of occupational exposure to ADs

Occupational exposure to ADs was quantified by calculating the daily dermal intake (DDI), as described by Gerding et al. [21], which is based on the conservative model of Kimmel et al. [33]. The DDI is associated to a particular surface contamination value of a single drug and is given by Eq. (1): $DDI = SA \times SC/BF$, where *DDI* is expressed as μg/day, *SA* is the skin area in contact with the contaminated surface (in cm^2), *SC* is the measured surface contamination (in μg/cm^2) and *BF* is the bioavailability factor (which contemplates drug transfer from the surface as well as skin absorption). This approach assumes that: *SA* is set to 200 cm^2, which corresponds to both palms being in contact with the

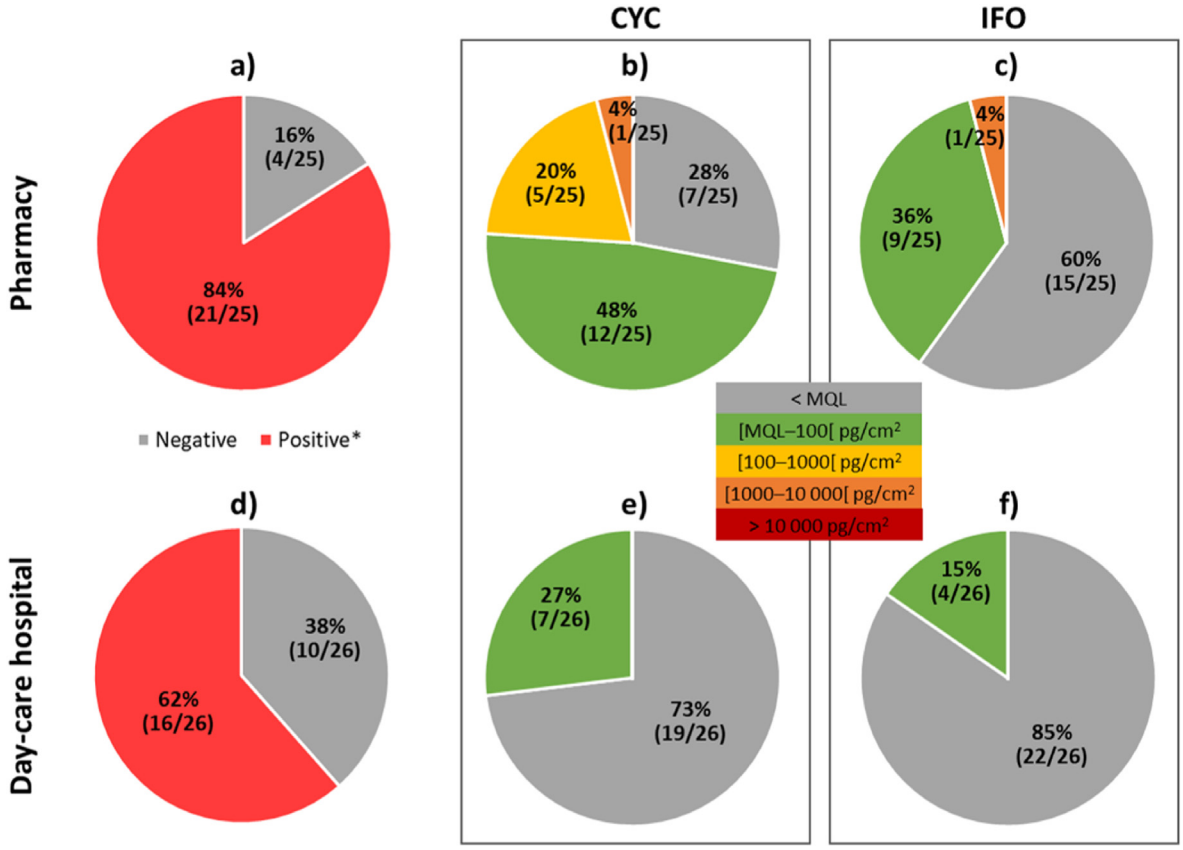

Fig. 2. Surface contamination before general cleaning in a tertiary Portuguese hospital from a preliminary sampling campaign in three days. a) Positive and negative samples from the pharmacy; b) CYC contamination levels in the pharmacy; c) IFO contamination levels in the pharmacy; d) Positive and negative samples from the day-care hospital; e) CYC contamination levels in the day-care hospital; f) IFO contamination levels in the day-care hospital. *At least one of the 13 target drugs was detected above the MQL (Method Quantification Limit).

contaminated surface, without protection; and a dermal transfer and absorption of 100 % from the contaminated surface ($BF = 1$). In this study, a DDI will be calculated for all ADs concentrations reported, before obtaining average values for each of the three sampling campaigns and two settings. Also, the highest concentration found on a surface will be used to calculate the maximum DDI (worst-case scenario).

2.8. Qualitative assessment of the risk from occupational exposure to ADs — a control banding method

A qualitative assessment of the occupational risk from exposure to ADs of workers was estimated based on guidelines from a Portuguese technical guide concerning health surveillance of workers exposed to CMR substances [34], which transposes information from a European Commission report [35] and was drawn up from national and EU legal documents. This control banding methodology comprises three main steps: (i) identification of the exposed worker(s) and graduation of the occupational exposure context; (ii) graduation of the level of occupational exposure; and (iii) graduation of the occupational risk. Step (i) consists in gathering general information about the occupational exposure context, namely professional use of the chemical, operating conditions and exposure control measures (e.g., collective and individual protection equipment). In the second step, the level of occupational exposure is determined by intersecting two parameters, as depicted in Fig. 1a: the result of the occupational exposure context (obtained in step (i)); and the target drug concentration measured in workplace surfaces (environmental assessment). Then, the occupational risk is graduated as either *low*, *medium*, *high* or *very high* (Fig. 1b), by intersecting the level of occupational exposure from step (ii) with the toxicology/health effects of the target substance, which can be categorized through its hazard classification, i.e., the EU Classification, Labelling and Packaging (CLP) system of CMR substances.

2.9. Assessment of the cancer risk from occupational exposure to ADs

The risk of healthcare workers developing cancer due to handling of ADs was evaluated by the methodology proposed by Gerding et al. [21], whose quantitative risk assessment model is based on the threshold of toxicological concern concept. An acceptable daily intake (ADI) of 4 μg/day and, consequently, an acceptable surface contamination level of 20 ng/cm^2 were defined as thresholds of no concern for the occupational exposure of workers to genotoxic drugs. As a starting point for these calculations, the authors considered the maximum lifetime intake of a genotoxic drug stipulated in the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use M7(R1) guideline for treatment-related exposure to a single substance: an ADI of 1.5 μg/day (which was obtained by considering the accepted lifetime excess cancer risk of 1 additional cancer case per 100 000 treated patients). The exposure time was however adjusted to consider an average working life of 40 years (240 exposure days/year), since workers' exposure is significantly different than patients' exposure.

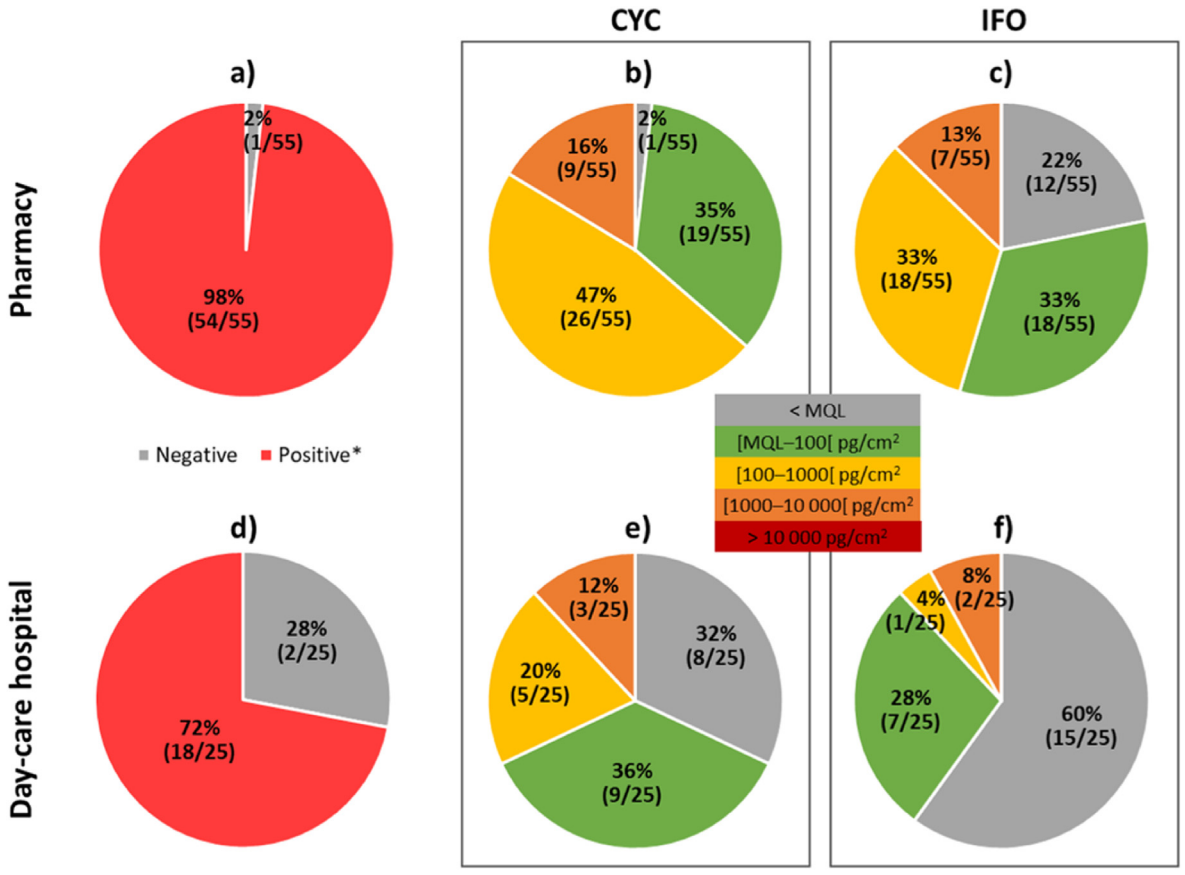

Fig. 3. Surface contamination before general cleaning in a tertiary Portuguese hospital over a working week. a) Positive and negative samples from the pharmacy; b) CYC contamination levels in the pharmacy; c) IFO contamination levels in the pharmacy; d) Positive and negative samples from the day-care hospital; e) CYC contamination levels in the day-care hospital; f) IFO contamination levels in the day-care hospital. *At least one of the 13 target drugs detected above the MQL (Method Quantification Limit).

3. Results

3.1. Occupational environment contamination – first sampling campaign

A total of 152 samples were analyzed in two different hospital locations (pharmacy and day-care units) in three sampling campaigns. Fig. 2 displays the surface contamination from the preliminary sampling campaign (performed in late 2020), which involved 51 samples (Table A.2 in the Supplementary Material): 84 % positive samples were found in the pharmacy (Fig. 2a) and 62 % in the day-care hospital (Fig. 2d). Of the total 51 samples, CYC was the most detected drug (25 samples) followed by IFO (14 samples); MEG was detected in nine samples; BIC, CAP, CYPR, ETO, MMF and PAC were detected in three or less samples; and DOX, FLU, IMA and PRE were not detected in any sample. Concentrations above the green range were only measured in the pharmacy for CYC (Fig. 2b; five samples in the yellow range and one in the orange range) and IFO (Fig. 2c; one sample in the orange range).

3.2. Occupational environment contamination – second sampling campaign

Fig. 3 displays the surface contamination from the main (second) sampling campaign (performed in the spring of 2021), which involved 80 samples (Table A.3 in the Supplementary Material): 98 % positive samples were found in the pharmacy (Fig. 3a) and 72 % in the day-care hospital (Fig. 3d). Of the total 80 samples, CYC and IFO were the most detected drugs (71 and 53 samples, respectively), while CAP, ETO and MEG were detected in four or fewer samples, and BIC, CYPR, DOX, FLU, IMA, MMF, PAC and PRE were not detected in any sample. Concentrations above the green range were consistently found in both settings for CYC and IFO, but never in the red range. For CYC, the 75th and 90th percentiles of surface contamination were respectively 637 and 2197 pg/cm^2 for all samples (650 and 2098 pg/cm^2 for the pharmacy samples; 543 and 3354 pg/cm^2 for the day-care samples), while for IFO they were respectively 413 and 1898 pg/cm^2 for all samples (425 and 1684 pg/cm^2 for the pharmacy samples; 893 and 7690 pg/cm^2 for the day-care samples). Out of the 55 samples from the pharmacy: 63 % were above the guidance value for CYC (Fig. 3b; 47 % and 16 % in the yellow and orange ranges, respectively); and 46 % for IFO (Fig. 3c; 33 % and 13 % in the yellow and orange ranges, respectively). Concerning the 25 samples from the day-care hospital: 32 % were above the guidance value for CYC (Fig. 3e; 20 % and 12 % in the yellow and orange ranges, respectively); and 12 % for IFO (Fig. 3f; 4 % and 8 % in the yellow and orange ranges, respectively). Of the remaining drugs, all values obtained were below the guidance value, except for ETO in one sample from the pharmacy (in the yellow range, but very close to the guidance value).

Concerning each of the 16 locations sampled, the contamination values do not evidence an increase in surface contamination over the five consecutive days nor any another specific trend (Table A.3 in the Supplementary Material). The weekly average of surface contamination of the two most detected drugs (CYC and IFO) is displayed as a boxplot in Fig. 4 for both occupational settings (it is

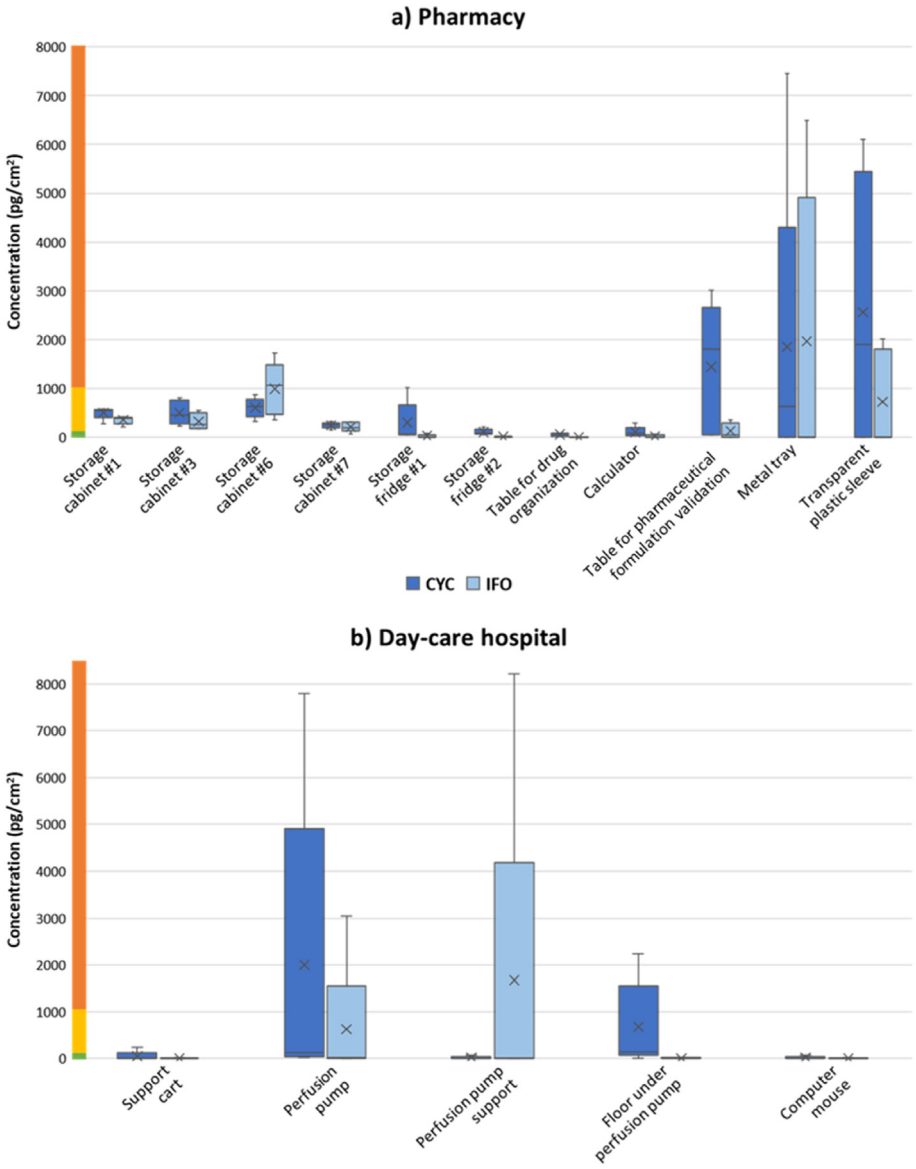

Fig. 4. Boxplot of average of surface contamination (pg/cm^2) over a working week (five consecutive days) for CYC and IFO, in locations from a tertiary Portuguese hospital. a) Pharmacy; b) Day-care hospital. The cross symbol represents the average value, and the horizontal line within the box depicts the median. Color code: green for <100 pg/cm^2 ("safe" level); yellow for [100−1000[pg/cm^2; orange for [1000−10000[pg/cm.^{2}.

worth reminding that a value of 0 pg/cm^2 was attributed to non-positive samples). The highest contamination values in the pharmacy (Fig. 4a) were observed in the metal trays (used to transport medication bags), in the transparent plastic sleeve (used to display preparation information in the clean room) and in the table for pharmaceutical formulation validation (where medication bags are checked before going to the day-care hospital). In the case of the day-care hospital (Fig. 4b), contamination was higher in the perfusion pump, its support, and the floor beneath it.

3.3. Occupational environment contamination — third sampling campaign

Fig. 5 displays the surface contamination from the third sampling campaign (performed in the spring of 2023), which involved 21 samples (Table A.4 in the Supplementary Material): 91 % positive samples were found in the pharmacy (Fig. 5a) and 40 % in the day-care hospital (Fig. 5e). Of the total 21 samples, PAC was the most detected drug (9 samples) followed by CYC (7 samples); IFO and ETO were detected in two and one samples, respectively; while the remaining drugs were not detected in any sample. Concentrations above the green range were only measured for CYC (Fig. 5b: three samples in the yellow range and one in the orange range in the pharmacy; Fig. 5f: one sample in the yellow range in the day-care hospital) and IFO (Fig. 5c; one sample in the yellow range in the pharmacy).

3.4. Quantification of occupational exposure to ADs

DDIs (Eq. (1)) were calculated for all ADs concentrations reported (displayed in Tables A.2, A.3 and A.4 in the Supplementary Material) and grouped by sampling campaign and setting evaluated. These are represented as a boxplot in Fig. 6 (the outliers can be seen in Fig. A.1 of the Supplementary Material) and their average values are displayed in Table 2. The maximum DDI was quantified as 1.6 μg/day, corresponding to the highest surface concentration

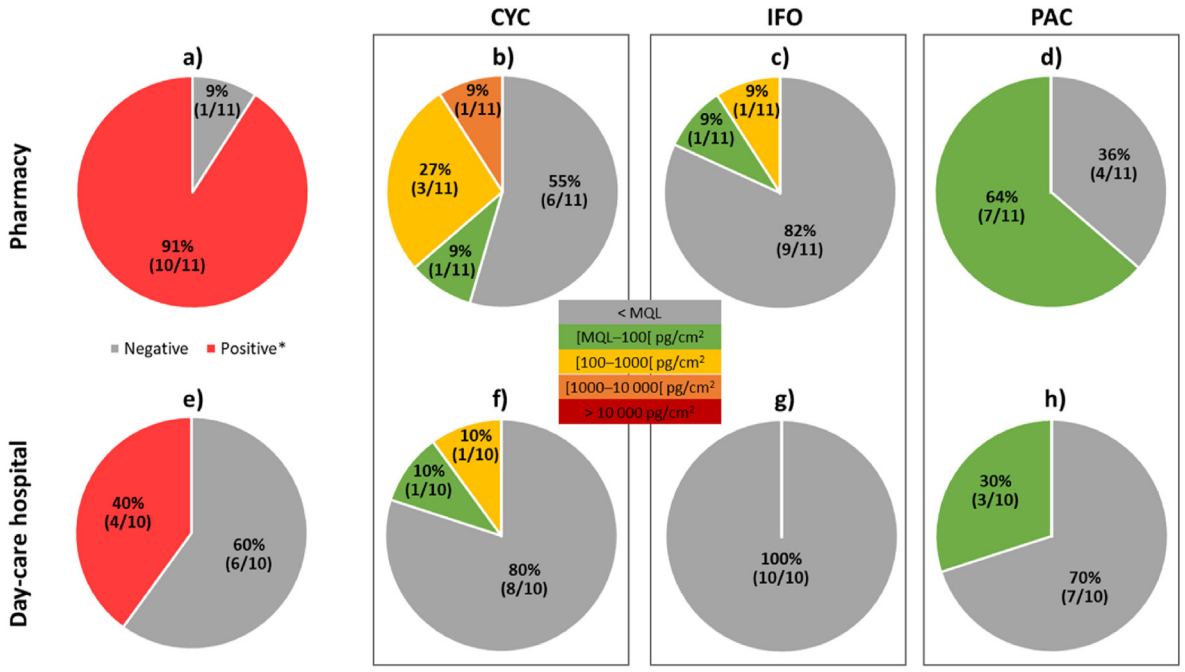

Fig. 5. Surface contamination before general cleaning in a tertiary Portuguese hospital in two consecutive days. a) Positive and negative samples from the pharmacy; b) CYC contamination levels in the pharmacy; c) IFO contamination levels in the pharmacy; d) PAC contamination levels in the pharmacy; e) Positive and negative samples from the day-care hospital; f) CYC contamination levels in the day-care hospital; g) IFO contamination levels in the day-care hospital; h) PAC contamination levels in the day-care hospital. *At least one of the 13 target drugs was detected above the MQL (Method Quantification Limit).

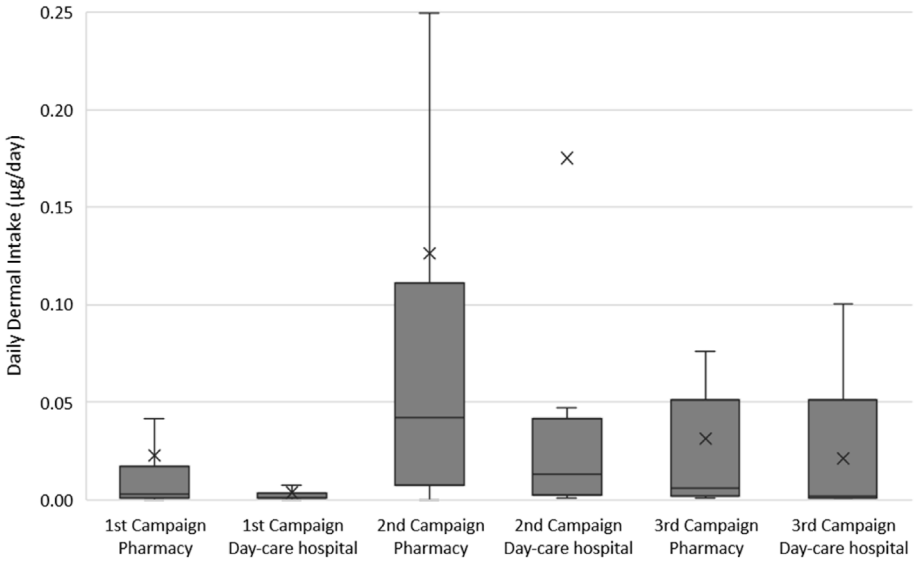

Fig. 6. Boxplot of the daily dermal intake (DDI, µg/day) values calculated for all antineoplastic drug's concentrations reported, for each of the three sampling campaigns and two settings (pharmacy and day-care hospital). The cross symbol represents the average value, and the horizontal line within the box depicts the median.

Table 2
Average values of daily dermal intake (DDI, µg/day) for each sampling campaign and setting evaluated (pharmacy and day-care hospital).

	1st Campaign		2nd Campaign		3rd Campaign	
	Pharmacy	Day-care hospital	Pharmacy	Day-care hospital	Pharmacy	Day-care hospital
DDI (µg/day)	0.023	0.004	0.126	0.175	0.031	0.021

found in any of the three sampling campaigns, which was 8207 pg/cm^2 for IFO, measured in a perfusion pump support/handle in the second campaign.

3.5. Qualitative assessment of the risk from occupational exposure to ADs – a control banding method

As no occupational exposure limit values have been defined for ADs, graduating the level of occupational exposure (step (ii) of the methodology, Fig. 1a) cannot be properly performed. However, if the reference value is taken as the "action limit" of 10 000 pg/cm^2 (proposed in the literature as a threshold above which concentrations are "not acceptable" [31,32], the level of occupational exposure of the professionals from the studied oncologic settings would never be classified as *high* or *very high*, as no concentrations were found above that value in any of the campaigns. Hence, the occupational risk associated with any of the target drugs (step (iii) of the methodology, Fig. 1b) will never be *very high* for these professionals.

This assessment was then focused on the most detected drugs in this study: CYC, IFO, and PAC. These are ADs of very high concern that have been classified as either category 1A or 1B for more than one of the three CMR hazard classes (see Table 1), meaning they fall under the last column of the risk matrix from the guidelines used (Fig. 1b). As such, the occupational risk associated with any of these three ADs is always *medium* or higher, regardless of the occupational exposure context (step (i) of the methodology) and of the level of occupational exposure (step (ii) of the methodology).

4. Discussion

4.1. Occupational environment contamination

Similarly to other studies in the literature, samples were collected at the end of the day and before general cleaning to assess a worst-case scenario of occupational exposure to ADs. Since the three campaigns were carried out under a few different conditions and quite spread out in time, the results were not directly compared (due to the possibility of slightly different exposure contexts). Nonetheless, the results obtained across the three campaigns show that surface contamination with the target drugs is generally more widespread and at higher concentrations in the pharmacy (84%–98 % positive samples) than in the day-care hospital (40%–72 % positive samples), similarly to a lot of studies from the literature. A few reasons that might contribute to these findings could be that: (i) in the pharmacy, more concentrated formulations are manipulated and these are frequently moved between different locations (while the AD circuit in the administration unit is more straightforward); (ii) the pharmacy is overall a small space, where cross-contamination might be easier to occur; and (iii) disinfection of chairs between patients in the day-care hospital might be preventing some drug accumulation. However, this trend is not generalizable, as it is related to the sampling locations chosen, and some studies have actually reported the opposite [14,17,20].

CYC and IFO were clearly the most detected target drugs in the first and second campaigns, and PAC in the third one. Regarding concentration values, no samples were found above the "action limit" of 10 000 pg/cm^2 (red range of the color code model) in any of the campaigns, above which surface contamination is considered "not acceptable" and corrective measures are critical. Still, absence of risk for those workers should not be presumed and follow-up monitoring is recommended, as surface contamination was frequently found above the "safe" (or alert) level of 100 pg/cm^2, particularly for CYC and IFO (two ADs of high concern).

Concerning the preliminary sampling campaign, it was expected that contamination levels would be lower than usual because it was performed at a time when Covid-19 prevention guidelines were very strict. At that time, it was reported that some surfaces (mostly worktops and shared objects) were more frequently cleaned during the day by pharmacists and nurses (outside of the normal cleaning schedule). Indeed, when comparing these results with those obtained in the second campaign (when cleaning procedures were reportedly back to normal), there were fewer positive samples and lower concentrations in the preliminary campaign. Although other reasons could be factoring in, these findings seem to show that cleaning more often could lead to lower surface contamination with ADs, which is in line with studies from the literature reporting that multiple (sequential) cleaning steps provide higher removal of ADs from surfaces [36]. Moreover, storage areas and working tables were a big focus in follow-up campaigns because the samples in the yellow and orange ranges of the screening sampling campaign pertained to these locations.

Based on the second sampling campaign, it was not possible to establish a general trend of surface contamination over the week, as contamination values sometimes varied considerably. In fact, it was not uncommon to find concentrations in the green, yellow and orange ranges for the same location and drug on different days. Still, some locations showed more similar contamination values over the week. Indeed, Fig. 4 shows that contamination values were consistently above the guidance value in the storage cabinets, for CYC and IFO. Contrarily, it was consistently in the green range in: (i) the table for drug organization, the perfusion pump support, and the computer mouse, for CYC; and (ii) the fridges, the table for drug organization, the calculator, the support cart, the floor under the perfusion pump, and the computer mouse, for IFO.

The results of the third sampling campaign showed a reduction in the positive samples from the day-care hospital and generally lower concentration levels. This could be the consequence of the feedback provided to the professionals about the previous state of the environmental contamination that might have led to a behavioral change (indeed, a greater awareness, interest and care of the workers, particularly in the pharmacy, was noticed). In fact, existing literature confirms the strong effect that regular monitoring has on improving work practices and, consequently, on reducing the contamination level. For example, the MASHA project (Research about Environmental Contamination by Cytotoxics and Management of Safe Handling Procedures, https://esop.li/activities-2/projects/masha-projekt/) showed that a reduced number of positive wipe samples and lower amounts of surface concentration were detected after awareness and training the staff about safe handling and implementation of the European Society of Oncology Pharmacy cleaning recommendations: 20 % positive samples with a 90th percentile of 32 pg/cm^2 before training versus 14 % and 21 pg/cm^2 after such training [19]. Nevertheless, other factors might have contributed to these results, such as: possible significant differences in the quantities of the drugs handled by the workers in the sampling day and previous days (whose exact amounts are not known to the authors); or the improvement of the cleaning practices, as well as other changes in the procedures employed. It is further important to note that the third sampling campaign took place in new, temporary facilities, which had different layouts from the settings previously sampled, and this might also have contributed to such results.

The results from the present study are aligned with those from recent literature, since values currently reported are generally in the pg/cm^2 range. Nonetheless, values in the order of hundreds of (up to around 200) ng/cm^2 are still very common [18–21], which are significantly higher than the maximum value detected in this study (8207 pg/cm^2). For example, in a German study known as the Monitoring-Effect Study of Wipe Sampling in Pharmacies (MEWIP)

project [18]: 61 % of wipe samples were positive; the most detected ADs were CYC, gemcitabine, 5-fluorouracil and IFO (out of 8 markers), with 90th percentiles of contamination of 48, 34, 117 and 14 pg/cm^2, respectively; the highest value identified was 1888 ng/cm^2, in a refrigerator door; and the floor in front of the safety cabinet was the most frequently and highly contaminated. Also relevant is a Canadian annual surveillance project (conducted since 2010) [20], which most recently reported that, for a total of 122 healthcare centers: CYC (32 % positive samples, 90th percentile of 16 pg/cm^2) and gemcitabine (23 %, 3.6 pg/cm^2) were the most frequently detected ADs – the highest value was 150 ng/cm^2 in the exterior of a medication bag or syringe; and the front grilles inside biological safety cabinets and armrests of patient's chairs were the surfaces most frequently contaminated. A follow-up study of the MASHA project reported that [37]: (i) over 30 % positive samples were found in 21 out of 28 hospitals from 16 European countries; (ii) the highest values were 130 ng/cm^2 for 5-fluorouracil and 380 ng/cm^2 for CYC, respectively; (iii) gemcitabine, 5-fluorouracil, CYC, and PAC were the most detected ADs (out of 11 markers); and (iv) floors from administration areas, work surfaces of isolators or biological safety cabinets, and armrests of patient's chairs were the most frequently contaminated surfaces.

The settings in the present study seem more contaminated than those from a previous work considering three Portuguese hospitals [24], which identified 40 % positive samples (112 total samples) and the highest value of 179 pg/cm^2 for 5-fluorouracil; however, such monitoring work was limited because only 5-fluorouracil and platinum drugs (cisplatin, carboplatin and oxaliplatin) were evaluated. Contrarily, the other two previous studies in Portuguese facilities [22,23] reported that most surface contamination values were in the ng/cm^2 level, *i.e.* substantially above the values reported in the present study. In one of them, 37 % of 327 samples from two hospitals were positive (and, although not quantifiable, CYC, 5-fluorouracil and/or PAC were further detected in another 36 % samples) and the highest value determined was 21.3 μg/cm^2 for CYC [22]. In the other, the highest contamination was 139.55 μg/cm^2 for CYC and similar contamination was found before and after drug handling: 79 % and 83 % positive samples (30 total samples), respectively [23]. Nonetheless, it is worth noting that these studies were performed several years ago (between 2014 and 2018) and that handling techniques, safety measures and cleaning practices may have changed.

4.2. Quantification of occupational exposure to ADs

According to Gerding et al. [21], the highest mean surface contamination value reported to date was 17.4 ng/cm^2, corresponding to a DDI of 3.5 μg/day. However, as discussed above, the literature reports that ADs' surface contamination from oncologic healthcare settings typically ranges from a few pg/cm^2 to around 200 ng/cm^2, with the latter corresponding to a DDI of 40 μg/day. Moreover, up to the authors best knowledge, the highest value ever reported was significantly higher: 139.6 μg/cm^2 (for CYC [23]), which results in a very high DDI of 27 910 μg/day. Comparatively, the average DDI values obtained in this study (between 0.04 and 0.175 μg/day) are notably lower than any of the above-mentioned values. In fact, even the maximum DDI (1.6 μg/day), obtained from the highest contamination value found in any of the campaigns, is still very low.

This approach was employed to quantify the contribution of dermal exposure and uptake of ADs since it is considered the main route of occupational exposure to these drugs. Nonetheless, it is important to note that the values obtained encompass some uncertainties due to the assumptions of the model. Namely, as discussed by the authors [21], these professionals typically wear gloves when handling ADs, which would have a substantial impact on the actual contact area of unprotected skin with contaminated surfaces. Furthermore, the surface area value recommended by Gerding et al. [21] for both palms (200 cm^2) was used so that results could be directly comparable, despite such value seeming inadequate for most men; still, it was considered appropriate for this study, since almost all workers from the two settings evaluated were female. Also, dermal absorption will likely not be 100 % (as considered in the calculations) and actually varies depending on the drug molecular weight: it is generally assumed that dermal absorption is more likely for drugs with a molecular weight of <500 Da and less likely for >1000 Da [33]. However, this approximation is reasonable for the target drugs from this study, since DOX, ETO and PAC have weights between 500 and 1000 Da, and the remaining drugs are below 500 Da. These worst-case scenario assumptions could lead to an overestimation of the actual exposure of healthcare workers to ADs. Nonetheless, it could also be said that this methodology somewhat underestimates the risk, since neither simultaneous contamination by different ADs nor (consecutive) contact with multiple contaminated surfaces are contemplated; also, contamination of other body parts, such as face, neck and forearms, was not considered but could be relevant.

4.3. Qualitative assessment of the risk from occupational exposure to ADs – a control banding method

The qualitative analysis performed shows that workers from the settings evaluated may be under potential health risks. Indeed, according to the guidelines, *medium* or higher classifications warrant periodic checks of the effectiveness of prevention/control measures and may require their improvement. Moreover, the risk associated with possible combined effects due to the presence of more than one AD (which typically also have one or more categories 1A or 1B) in the occupational environment cannot be estimated by this methodology, but it should not be disregarded.

It is important to note that, despite being a qualitative assessment based on an indirect indicator of exposure (surface contamination), this approach provides relevant information given that no formal surveillance or regular monitoring program for ADs exist in our country. Furthermore, environmental assessment continues to be crucial to properly implement effective control measures, by identifying potential sources of contamination. Nevertheless, a more complete assessment, performed for each specific occupational exposure context of workers and integrating environmental, biological and health data, should be employed to extrapolate definite conclusions. Indeed, biomonitoring is considered a better approach to human exposure assessment to ADs since it reveals the effective exposure of workers (internal dose), even if it can be cumbersome. As such, implementation of a better occupational exposure risk assessment is currently being devised, by complementing the environmental monitoring with a human biomonitoring (assessment of workers' urine contamination).

4.4. Assessment of the cancer risk from occupational exposure to ADs

Comparing the average DDIs (between 0.04 and 0.175 μg/day) and the maximum DDI (1.6 μg/day) obtained in the present study with the ADI of 4 μg/day threshold proposed by Gerding et al. [21], it is possible to conclude that professionals from the settings under evaluation are presumably not at risk of developing work-related cancer due to the handling of ADs. Indeed, in this study, no concentrations were found above (or even near) the conservative acceptable surface contamination level of 20 ng/cm^2.

Nonetheless, it is important to note that this assessment only

focuses on evaluating the genotoxic properties of drugs; hence, it is recommended to complement it with other types of risk assessments, such as the one from the previous section. Furthermore, the calculations from this assessment were based on values concerning exposure to a single genotoxic drug (ADI = 1.5 μg/day) rather than exposure to multiple genotoxic substances (ADI = 5 μg/day). Given that workers are simultaneously exposed to several ADs, this approach may underestimate the risk. Also, contact with multiple contaminated surfaces (potentially by the same drug) is not contemplated. Still, it can be considered an appropriate assessment from a precautionary principle standpoint because of the several worst-case scenario assumptions considered, which lead to an adequate occupational exposure threshold. Indeed, if higher lifetime cancer risks were used instead of the conservative value of 1 additional cancer case per 100 000 individuals, the ADI would be laxer (for example, an ADI of 40 μg/day would be obtained if 1 additional cancer case in 10 000 workers was used, maintaining the other parameters).

4.5. Study limitations

It is recognized that risk assessment and management in the scope of CMR chemical agents, such as ADs, is complex and that there is no single methodology that can encompass all work situations. Moreover, some limitations and uncertainties are typically associated with exposure and risk indicators, as was evidenced in the previous sections. Indeed, the assessment of developing cancer risk due to occupational exposure to ADs was based on many assumptions, which could deviate from the reality to some extent. For example, it was presumed that only the palms are exposed (200 cm^2), whereas it has been reported that contamination might happen during donning and doffing gloves or other protective equipment [38], with up to the entire hands being contaminated.

Furthermore, the results obtained in this study were determined by the surfaces chosen to be sampled, which were somewhat limited, and might not provide the full extent of the occupational settings' state. For example, the hands of healthcare workers were not sampled in this study (due to the solvent used for extraction) – and, according to the literature, it is not uncommon that workers do not always wear gloves, particularly when handling ADs vials or boxes/packages, which have repeatedly been shown to be contaminated [9]. It is further important to note that the notion of "high-touch" surfaces is essential in interpreting the risk, given that the DDI is associated to a particular surface contamination value of a single drug – meaning that neither simultaneous contamination by different ADs nor (consecutive) contact with multiple locations are contemplated in this approach. Indeed, although the sampled locations were considered as the most potentially contaminated, it still is expected that personnel likely touch trays, tables and perfusion pumps more often than storage units or the floor.

It would also be relevant to assess the occupational risk for other workers connected to ADs circuit (manufacturing, transport, storage, preparation, administration, waste disposal, sanitation), such as cleaning personnel, besides pharmacists, nurses and physicians. They may be exposed as well and are normally less protected and less aware of the risks [16,38]. Moreover, the use of data from biological monitoring (internal dose) would be more appropriate than environmental monitoring (external dose) for accurately assessing actual occupational exposure.

5. Conclusions

Surface contamination by ADs was evaluated in the occupational environment in two oncologic areas of a tertiary hospital in Portugal. Three sampling campaigns were performed at the end of the day and before general cleaning, which is considered a worst-case scenario, but no samples were found above the "action limit" of 10 000 pg/cm^2 ("not acceptable" contamination). However, surface contamination was consistently found above the "safe" level of 100 pg/cm^2, particularly for CYC and IFO, which are two ADs of high concern. Thus, absence of risk for the professionals from the settings evaluated should not be presumed. In fact, according to guidelines from *Direção-Geral da Saúde* (DGS – Directorate General of Health, Portugal), the occupational exposure risk will always be *medium* or higher, regardless of the occupational exposure context, when considering hazardous drugs such as CYC, IFO or PAC. Thus, this qualitative assessment evidences the need for periodic follow-up monitoring, which may further support the need for improvement of prevention/control measures. Nonetheless, the workers are presumably not at risk of developing work-related cancer due to the handling of the target drugs, according to a quantitative risk assessment model based on dermal exposure and uptake of genotoxic drugs, although this model holds some uncertainties due to several assumptions and only considers exposure to one drug at a time. Indeed, a DDI of 1.6 μg/day was obtained for the highest contamination value reported (measure of occupational exposure), which is lower than the ADI of 4 μg/day threshold proposed elsewhere.

Reducing contamination, exposure and risk to as low as reasonably achievable levels is the ultimate objective in this research field. To do so, monitoring programs are crucial for leaders and decision-makers of establishments where ADs are handled to thoughtfully devise a strategy of corrective measures. Therefore, this work lays the foundation for the implementation of regular environmental monitoring programs for ADs in Portuguese hospitals (since, up to the authors' best knowledge, none currently exist nor any other formal surveillance), in line with EU recommendations under Directive 2004/37/EC. Such monitoring programs should contemplate the proposed alert and action levels for surface contamination with ADs and, if possible, be accompanied by biological monitoring of exposed personnel and by risk assessments.

Data availability statement

All data generated or analyzed during this study are included in this published article and its supplementary material.

CRediT authorship contribution statement

Maria Francisca Portilha-Cunha: Writing – original draft. **Pedro Norton:** Writing – review & editing. **Arminda Alves:** Writing – review & editing. **Ana R.L. Ribeiro:** Writing – review & editing. **Adrián M.T. Silva:** Writing – review & editing. **Mónica S.F. Santos:** Writing – review & editing, Writing – original draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.emcon.2024.100418.

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