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An analysis to study trends in occupational exposure to antineoplastic drugs among health care workers☆

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ABSTRACT

The use of antineoplastic agents for the treatment of cancer and other non-neoplastic diseases is an increasingly common practice in hospitals. As a result, workers involved with handling antineoplastic drugs may be accidentally exposed to these agents, placing them at potential risk for long term adverse effects. To date, the challenge of protecting workers' health is persisting and expanding, with an increasing number of publications demonstrating that contamination of antineoplastic drugs (ADs) is still present on work surfaces after cleaning procedures are concluded. In this paper, five workplaces were selected for surveillance of professional exposure to ADs. Hospital pharmacies involved in the study were set in the North (Units A1 and B2), Center (Units C3 and D4) and South (Unit E5) of Italy. Contamination levels on a number of work surfaces and trends over a 10-year period are presented. Environmental and biological levels were obtained by high performance liquid chromatography (HPLC) coupled with tandem mass spectrometry (MS/MS). A strong reduction of surface contamination was evidenced since 2003, when the recommended procedures for the safe handling of antineoplastic drugs started to be followed by health care workers. Employers' adherence to these recommendations allowed risk characterisation to achieve other important goals. The percentage of positive urine samples was found to be around 30% in the 1990s and 2% in the 2000s. Moreover, no positive samples were detected in 2006 or 2007. In conclusion, our study emphasized that one helpful strategy to reduce risk to all potentially exposed workers is also provided by a data-storage system that allows potential risks of working to be rapidly identified and controlled.

1. Introduction

The traditional approach to workers' health protection from exposure to cytostatic antineoplastic drugs (ADs) was pioneered in the 1970s and 1980s, when special guidelines and protective measures were introduced; e.g. the Canadian Society of Hospital Pharmacists issued the very first guideline for the handling of cytotoxic drugs in 1981 [1]. In the following decades, numerous guidelines were published in several countries [2–6]. In Italy, the National Institute for Occupational Health and Prevention issued the Official Italian Rules entitled "Guidelines for Protecting the Safety and Health of Hospital Workers Exposed to Antineoplastic Drugs" in 1999 [7]. Guidelines and regulations on safe working with ADs were introduced because workers who handle these drugs are at risk of suffering adverse health effects, such as hair loss, skin rashes [8,9] and delayed effects on reproduction [10–12]. Furthermore, some antineoplastic drugs are genotoxic [13,14] and are known or suspected to cause cancer [15–17]. The International Agency for Research on Cancer (IARC) has classified 10 antineoplastic drugs as group 1, (carcinogenic to humans) and 10 as group 2A (probably carcinogenic to humans).

To date, the challenge of protecting workers' health is persisting and expanding, with an increasing number of publications demonstrating that contamination of ADs is still present on work surfaces after cleaning procedures are concluded [18–21]. It is therefore important to have knowledge of the potential occupational exposure to antineoplastic drugs. Environmental and biological monitoring thus assumes the role of documenting the results of risk characterisation. This paper presents contamination levels on a number of work surfaces and contamination trends over a 10-year period. Environmental and biological levels were obtained by high performance liquid chromatography (HPLC) coupled with tandem mass spectrometry (MS/MS).

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Table 1
Mean amounts (g) of CP handled by pharmacy technician working in hospitals located different regions of Italy.

	Workplace	Mean handled amount (g)		
		Survey years	Sampling day (range)	Annually (range)
Northern Italy	Hospital Unit A1	1998–2001	1.5 (0.9–2.0)	117(98–123)
		2002–2005	1.8 (0.9–2.9)	232 (211–246)
		2006–2007	2.8 (2.6–2.9)	235 (223–246)
	Hospital Unit B2	1998–2001	1.4 (0.9–2.7)	290 (223–445)
		2002–2005	4.5 (0.9–6.6)	114 (98–125)
		2006–2007	8.8 (8.8)	434 (423–446)
Central Italy	Hospital Unit C3	1998–2001	1.2 (0.9–1.9)	196 (111–342)
		2002–2005	1.4 (0.9–2.6)	248 (111–478)
		2006–2007	2.7 (2.6–2.8)	296 (211–380)
	Hospital Unit D4	1998–2001	8.9 (0.9–26.7)	854 (764–988)
		2002–2005	10.3 (6.8–14.8)	1,163 (980–1,456)
		2006–2007	13.8 (12.9–14.8)	1,796 (1634–1958)
Southern Italy	Hospital Unit E5	1998–2001	8.9 (8.1–9.8)	2,423 (1,890–2,456)
		2002–2005	8.3 (6.8–9.8)	2,598 (2,156–2,890)
		2006–2007	20.7 (18.8–22.8)	3,345 (3,124–3,567)

Traditionally, in the 1970s, HPLC in combination with ultraviolet detection (UV), fluorescence (FL) or electrochemical detection (ECD) was employed to determine antineoplastic drugs in biological fluids and environmental matrices. However, due to the lack of sensitivity and specificity of UV detection, the HPLC–UV methods were scarcely developed [22,23]. In contrast, mass spectrometry and tandem mass spectrometry detection (MS or MS/MS) have been a common practice for many years. Several MS-based methods [24,25] were developed using gas chromatography (GC–MS) to measure antineoplastic drugs in urine or plasma samples of exposed workers involved in handling these drugs [26–29]. Mass spectrometry was selected as first choice detector thanks to its sensitivity and selectivity. However, since most anticancer agents are non-volatile, thermolabile, polar compounds, they did not fit gas chromatography. To overcome this analytical pitfall, a few drugs were mostly derivatized prior to gas chromatographic analysis. As an example, cyclophosphamide (CP) was tailored to a trifluoroacetic derivative because the molecule undergoes partial decomposition in the gas chromatography injector yielding two separate peaks, one for CP itself and one for an intramolecular cyclization product [28].

Consequently some of these GC–MS methods were not sensitive enough for the assessment of exposure to antineoplastic drugs with low urine levels when occupational activities are carried out under the regimen of the official guidelines. Time consuming and complex GC–MS methods not suitable for routine analysis have been therefore developed for several years. On the other hand, online LC–MS for quantitation purposes was complicated in the early 1980s until interfaces such as atmospheric pressure chemical ionization (APCI) and electrospray ionization (ESI) were introduced. Furthermore, in recent years LC–MS ionization techniques have been improved and MS interfaces have been upgraded either to detect low picogram per milliliter levels of drugs in biological fluids and tissues or to avoid interferences that may affect quantitative results. The universal adoption of measures for the safe handling of cytotoxic antitumor drugs required the limit of detection values (LOD) to be lowered. Thus, the ESI interface demonstrated to be the most successful hyphenation of LC and MS allowing better sensitivity and selectivity than other techniques [30]. Furthermore, LC–MS showed to be the most suitable technique to obtain reproducible assays where uncertainty parameters associated with potential analytical errors may be controlled and measured [31–40].

In this paper we present a strategy of environmental monitoring by wipe sampling designed to study surface contamination of antineoplastic drugs over time. Among cytotoxic drugs handled in hospital care settings, cyclophosphamide (IARC, group 1) was chosen as an indicator for occupational exposure because of its widespread use. Similarly, biomonitoring data, expressed as urine concentrations of cyclophosphamide, ifosfamide and epi-doxorubicin, are reported over a 10-year period when the implementation of guidelines occurred. Since exposure to antineoplastic agents should be avoided because any detectable level is considered to be a hazard, four different LC–ESI–MS/MS methods previously developed and validated were used [34,35,44]. Environmental samples were analyzed using an API 300 triple-quadrupole mass spectrometer [36]. The assay was developed according to the '*Guide for Expression of Uncertainty in Measurement*' issued by EURACHEM in 1998 and reviewed in 2000 [41]. Besides, biological samples were analyzed with three different methods developed and validated according to the standards recommended in the Food and Drug Administration (FDA) Guidance [42]. The first method was carried out to detect cyclophosphamide and ifosfamide simultaneously, the second one to support the need for increasing sensitivity as well as selectivity and the last one to detect anthracyclines in urine samples at trace levels. Therefore an interface such as APCI was used during sample analysis [35].

2. Material and methods

2.1. Description of workplaces

Five workplaces where pharmacy technicians prepared cytostatic drug solutions for chemotherapy treatments were selected. Hospital pharmacies were located on the first floor of each workplace in centralized units called "preparation rooms". The five hospitals involved in this study were set in the North (Units A1 and B2), Centre (Units C3 and D4) and South (Unit E5) of Italy.

The pharmacy technicians prepared all antineoplastic drugs inside biological safety cabinets (BSC), class II. The five hospital pharmacies handled different amounts of CP due to their activities devoted to supplying hospital wards, e.g. day hospital and oncology departments, dissimilar in size and number of beds. Mean amounts of CP handled during the sampling days and the means handled every 4 and 2 years of the whole investigated time period are reported in Table 1.

2.2. Wipe sampling

The samples were collected using a method from previous studies investigating surface contamination by cyclophosphamide, ifosfamide, doxo-epirubicn and daunorubicin [36]. The surfaces were wiped thoroughly with four Kleenex professional wipes (10 cm × 10 cm; Kimberly-Clark®, Irving, TX, USA) and with 9 cm diameter filter paper (Whatman International Ltd., Maidstone, England) which had been wetted with 5.0 mL of water.

The collection of samples was made by wiping in two different directions (up and down, right and left) inside the plastic frame. After sampling the wipe papers were placed in borosilicate glass bottles (50 mL) and stored at 4 °C until sample preparation.

For each collected wipe sample, a new pair of gloves was used to avoid cross-contamination. Surface areas of 100 cm^2 (10 cm × 10 cm interior of plastic frame) were wiped on several work areas, inside and outside the preparation room for each hospital. The wipes were collected by technicians who performed the same procedure in all the investigated hospital units.

2.3. Biological monitoring

Biological monitoring was performed once a day at each workplace in connection with one occasion of wipe sampling on health care workers who handled CP and other antineoplastic agents, such as ifosfamide (IF), doxorubicin (DOXO) and epirubicin (EPI) during their work-shifts. Prior to entering this study, all pharmacy technicians received a questionnaire and were asked to fill it in all its parts. Thus, information was acquired about layout of the preparation room, type and amount of ADs, personal protective equipment (PPE) worn during preparation activities of ADs, and training courses attended by hospital personnel involved in handling cytostatics drugs.

2.4. Urine collection

Spot samples of urine were collected in 50 mL polypropylene bottles with screw caps before and after work. Pre- and post-workshift urine samples were collected from pharmacy personnel working in the investigated hospital units after 6 h of their work-shift since the half life of urinary excretion is roughly 12–24 h for the investigated antineoplastic drugs [40,45]. The urine samples were stored at 4 °C during maximum 24 h. Then aliquots of 5 mL urine were transferred to test tubes and stored at −20 °C until sample preparation. The samples were allowed to thaw at ambient temperature only prior to analysis using the HPLC–ESI–MS/MS system.

3. Evaluation of exposure to antineoplastic drugs

3.1. Study design

In compliance with the rules of the national guidelines, the hospital personnel exposed to ADs was surveyed annually by planning the environmental and biological monitoring of the five workplaces. In our study, levels and trends of surface contamination and urine concentrations of CP, IF, DOXO and EPI are reported over a 10-year period (1998–2008). As the national guidelines were issued in Italy in 1999, but not immediately implemented, programs for safely handling antineoplastic drugs could be followed by workers only during the last few years. By the 2000s, personal protective equipments, i.e. hair covers, special protective gowns, adapted gloves labeled as *chemotherapy gloves* and disposable sleeve covers were used by workers. Therefore, the investigated time period was considered particularly interesting to monitor the environment and the possible biological contamination from ADs because any safe handling programs for hazardous drugs were introduced after the survey was initiated.

Among the different methods available to assess exposure to ADs, i.e. air monitoring, wipe sampling and patches, a commonly used one is wipe sampling [18,21,40]. Since the wipe sampling strategy allows the transferable surface load of antineoplastic drugs to skin to be estimated and dermal exposure to be therefore assessed [21], environmental monitoring by wipe samples was carried out. The obtained data were also reported as a function of time to verify if operation and controls were effective to keep exposure levels as-low-as-reasonably-achievable (ALARA principle).

Thus, a predetermined wipe sampling scheme with selected surface areas was studied. The scheme identified different sampling spots on the working tray of the safety cabinet because in the early stage of this study the hospital pharmacists used to prepare cytostatic drug mixtures on a surgical tissue that was recognized as a potential source of exposure.

Work areas inside the preparation room such as floors, benches, handles of doors opening rooms or refrigerators were also chosen. In order to assess possible contamination outside the investigated preparation room, four spot samples were taken at approximately 1.0 and 3.5 mt from the position where the ADs were handled. The sampling strategy used is reported in Table 2.

Table 2
Detail of the sampling positions wiped inside and outside of the preparation room for each hospital unit.

Sampling area	Sampling positions
BSC	Working tray Working tray (left side) Working tray (right side) At the top of the cabinet Protection glass inside Protection glass outside
Work area	Work table Floor next to BSC Door handle Door handle refrigerator
Other area	Floor at 1 mt Floor at 3.5 mt Corridor located outside the preparation

3.2. Analytical procedures

Wipe and urine samples were prepared and analyzed according to the methods by Sottani et al. [34–36]. Briefly, ADs measurements in wipe samples were obtained using an LC–MS/MS method with a lower limit of quantification (LLOQ) of 125 pg/cm^2 for cyclophosphamide and ifosfamide. Solid phase extraction (SPE) was used for sample concentration and cleanup. Drugs were quantitated in multiple reaction monitoring (MRM) mode. For CP the mass transition of m/z 261 → 140 was used because it ensured the maximum sensitivity and selectivity as depicted in Fig. 1(panel a). The relative extracted ion MRM chromatogram of a processed wipe sample at LLOQ value (125 pg/cm^2) is reported in the same Fig. 1(panel b). Precision and trueness were determined on three different days at the concentrations of 400, 3125 and 6250 pg/cm^2. The overall precision (RSD%) was always less than 9.4%. This method showed an adequate range of concentrations to quantitate levels of CP in the highest percentage of samples collected after 2002. In the first stage of this monitoring study, samples collected from BSC were diluted. To improve the validity of the obtained data the sources of uncertainty were identified and total uncertainty was calculated. Thus, the expanded uncertainty U was evaluated according to the rules of the eurachem/citac guide [41] and QCs levels were expressed

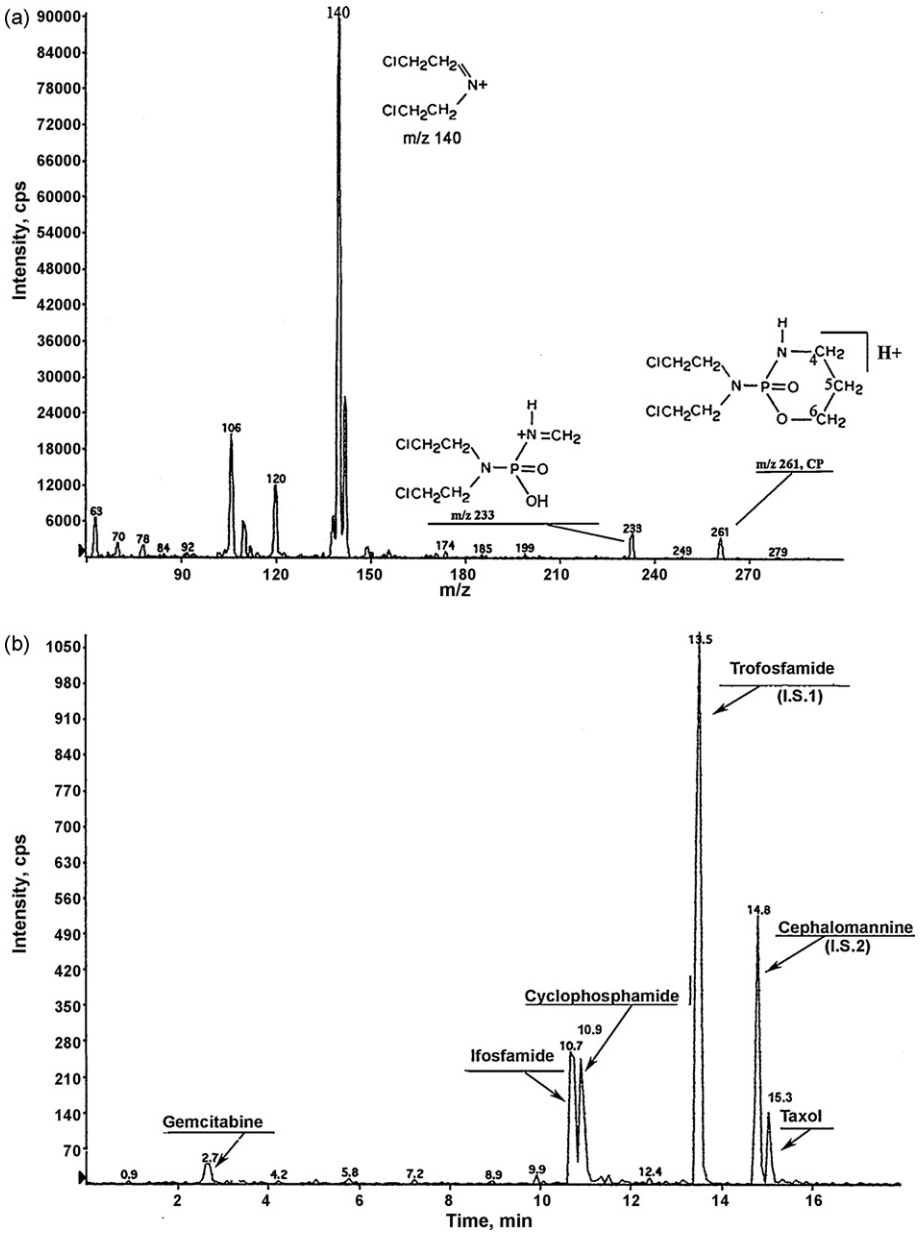

Fig. 1. (a) MS/MS product ion scan of cyclophosphamide (precursor ion *m*/*z* 261). (b) XIC of +MRM chromatogram of a processed wipe samples at the lower limit of quantification (LLOQ) level of 125 pg/cm^2.

following the equation

$$U(y) = [\dot{u}_c(y)]t_{0.95;\nu\text{eff}}Xm$$

where the expanded uncertainty U was obtained by multiplying the combined standard uncertainty $\dot{u}_c(y)$, by a coverage factor K. The choice of the factor is based on the level of confidence desired. For an approximate confidence level of 95%, K is 2 and Xm is the mean value of the n replicates. Data are detailed in Table 3.

In this study the detection of CP, IF, DOXO and EPI in urine samples was carried out using LC–MS/MS. For the determination of CP in human urine of professionally exposed personnel involved in preparing or administering ADs, two different methods were used. The first one was issued in 1998 [34]. HPLC–MS/MS experiments were performed using a triple-quadrupole mass spectrometer API 300, operating in positive ion mode. The methodology was developed using liquid–liquid extraction with ethylacetate and no derivatization procedures were required. The lower limit of quantification was set at 0.2 ng/mL.

The assay was validated by using three quality controls at the concentrations of 0.5, 0.8 and 3.2 ng/mL. The overall precision was always less than 11%. This type of assay was carried out until 2004. Guidelines were then issued in Italy and programs for safely handling hazardous drugs have since been implemented by hospital personnel involved in preventing occupational exposure to hazardous drugs. Thus, the challenge of detecting CP and IF at trace levels led to the development of a new analytical method. This procedure was validated using a PE Sciex API 4000 triple-quadrupole mass spectrometer fitted with a TurboIonSpray (TIS) probe. The lower limit of quantification was substantially different and was set at 0.02 ng/mL for CP. The linearity of this method was studied to assess cyclophosphamide at the concentrations expected when all safety measures were adopted by workers during their activities. Linearity ranged from 0.02 to 0.4 ng/mL in urine. Validation was performed by using trofosfamide as internal standard. A typical MRM chromatographic profile is reported in Fig. 2(panel b).

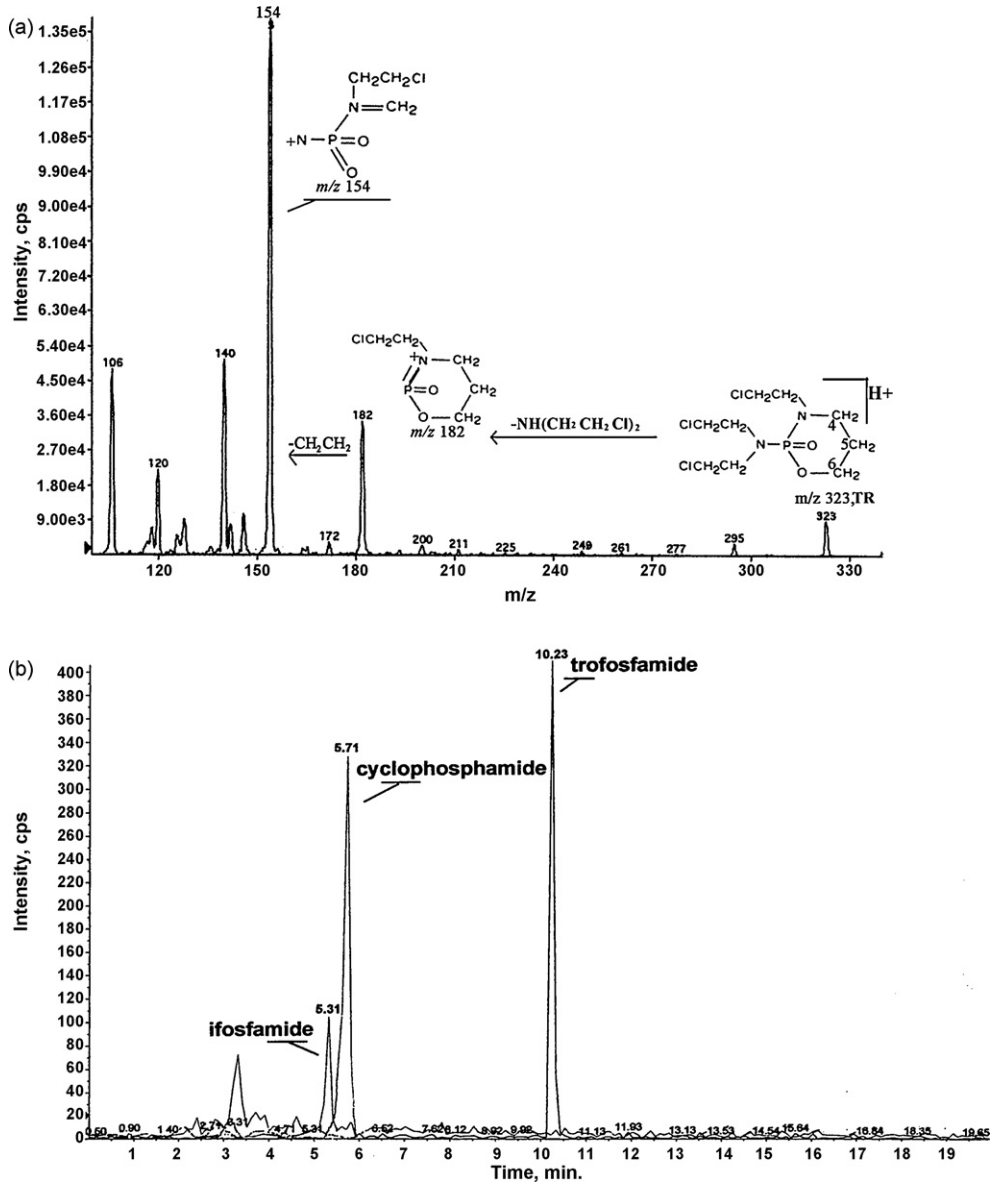

Fig. 2. (a) MS/MS product ion scan of trofosfamide, internal standard (precursor ion *m*/*z* 323). (b) XIC of +MRM chromatogram of a processed urine samples at the lower limit of quantification (LLOQ) level of 0.02 ng/mL for CP analyzed using an API 4000 Sciex.

In order to detect anthracyclines in human urine at trace levels a procedure validated using a PE Sciex API 4000 triple-quadrupole mass spectrometer was used [44]. The assay was linear over the range 0.1–2.0 ng/mL, with a lower limit of quantification of 0.10 ng/mL for doxorubicin and epirubicin.

All performance parameters and cleanup procedures relative to each analytical procedure are summarized in Table 3.

4. Results

4.1. Wipe sampling

For each hospital unit (A1, B2, C3, D4 and E5) the surface contamination levels of CP are expressed as pg/cm^2 and are reported in Tables 4, 5 and 6, respectively. Concentrations are presented as geometric means (GMs) and concentrations less than the limit of detection (<LOD) were assigned a value equal to the LOD divided by two (30 pg/cm^2). To provide additional information about the shape of the distribution the 50th and 75th percentiles were calculated. GMs were given every two years e.g., 1998–1999, 2000–2001, covering the survey period 1998–2007. Therefore, for a single hospital unit a number of 12, 8 and 6 wipe samples were analyzed and GMs were obtained for the three sampling areas, i.e. BSC, work area and other area.

The GM amounts of CP inside BSC (hospital unit A1) ranged between 7755 pg/cm^2 and <LOD during the 10-year period of survey (Table 4). The surface loading data from the *work area* ranged between 2357 pg/cm^2 and <LOD. Besides, data obtained by analyzing samples collected in *other areas* of the preparation room gave geometric means included between 951 pg/cm^2 and <LOD. Contaminations lasted only until 2005 and was found inside BSC for the majority of surfaces with 100% of positive samples. In particular, 50% of positive samples were obtained on the floor next to BSC in 2004 and 2005. No positive samples were found in 2006 and 2007.

GM contamination of CP was found to be higher inside the BSC of hospital unit B2 than inside the BSC of A1. GM values ranged between 18,286 and 535 pg/cm^2 (Table 4). The same results were obtained for *work area* (8036–226 pg/cm^2) and *other area* (1524–99 pg/cm^2). The mean handled amounts were also higher

Table 3
Detail of the HPLC–MS/MS methods employed to detect CP, IF, DOXO and EPI in wipe and urine samples of professionally exposed workers in the investigated hospital units over 10-years of survey.

Refs.	Instru-menta-tion	Analytes	Matrix		Clean up procedure	Range of concentration	LLOQ LOD	QCs ± (U)	Accuracy/Relative Error (RE)	Overall Precision %RSD	Recovery%
Sottani et al. [36]	PE-Sciex API 300	Gemcitabine, taxol, cyclophosphamide and ifosfamide	Wipe samples	Hypersil BDS C8 stationary phase 150 × 4.6 mm	SPE OASIS HLB (0.2 g; 6 mL)	125–10000 (pg/cm)	125 pg/cm; 62.5 pg/cm	400 ± 39 pg/cm^2; 3125 ± 201 pg/cm^2; 6250 ± 361 pg/cm^2	1.9%RE; −8.6%RE; −7.4%RE	8.8%; 8.0%; 6.7%	85 ± 8.2; 83 ± 7.9; 88 ± 8.5
Sottani et al. [34]	PE-Sciex API 300	Cyclophosphamide and ifosfamide	Urine	Hypersil BDS C8 stationary phase 150 × 4.6 mm	Liquid–Liquid extraction (ethylacetate)	0.2–3.2 (ng/mL)	0.2 ng/mL; 0.05 ng/mL	0.5 ng/mL; 0.8 ng/mL; 3.2 ng/mL	102%; 99%; 98%	6.1%; 9.3%; 9.0%	>85
		Cyclophosphamide					0.02 ng/mL; 0.01 ng/mL		107.5%; 99.8%; 104.6%	15%; 10.7%; 9.0%	83.5 ± 14.6; 76.9 ± 16.5; 77.1 ± 16.8
Sottani et al. [35]	PE-Sciex API 4000	Ifosfamide	Urine	Hypersil BDS C8 stationary phase 150 × 4.6 mm	SPE cartridge C18 (2 mL PBS, pH 7)	0.02–0.4 (ng/mL)	0.04 ng/mL; 0.02 ng/mL	0.025 ng/mL; 0.15 ng/mL; 0.3 ng/mL	101.3%; 98.4%; 99.2%	14.1%; 14.3%; 6.9%	88.5 ± 4.9; 81.5 ± 1.76; 81.3 ± 1.22
Sottani et al. [44]	PE-Sciex API 4000	Doxorubicin, epirubicin, daunorubicin and idarubicin	Urine	Hypersil BDS C8 stationary phase 150 × 4.6 mm	SPE cartridge C18 (2 mL PBS, pH 7)	0.1–2.0 (ng/mL)	0.1–0.04 ng/mL; 0.03–0.01 ng/mL	0.2 ng/mL; 0.5 ng/mL; 1.0 ng/mL	6.0–5.5%[a]; 2.2–4.2%[a]; 1.0–5.2%[a]	9.59–9.92%[a]; 9.04–10.63%[a]; 5.3–5.18%[a]	102.0 ± 3.8; 98.7 ± 10.1[a,b]

[a] Data are referred to doxorubicin and epirubicin only.
[b] Data are reported at 0.1 μg/L spiking level only.

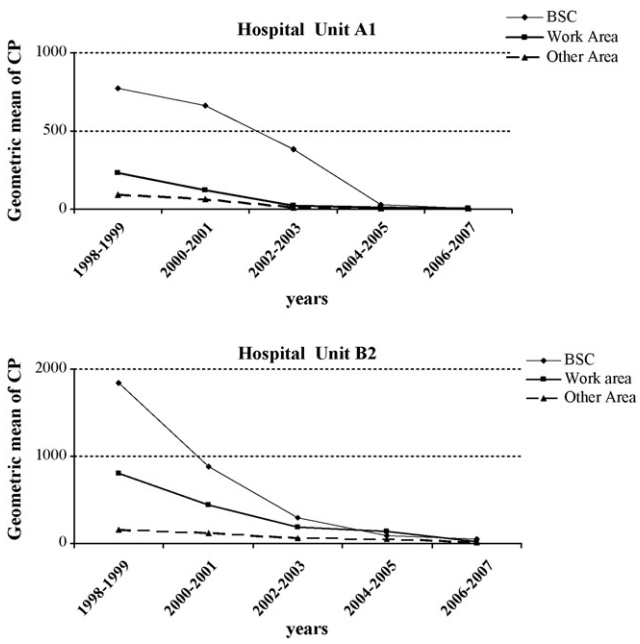

Fig. 3. Time trends (1998–2007) of CP concentrations (pg/cm^2) for hospitals located in the Northern Italy based on 2-year geometric mean of all wiped surfaces.

for unit B2 than A1. The pharmacist involved in preparing cytostatic drug solutions handled 2700 mg of CP in 2001 and 6670 mg in 2003 during the days of sampling. Therefore, GM contaminations seem to reflect the exposure of a single day because the mean amounts of CP handled annually were the same for the two hospitals (see Table 1). However, both hospital units located in the North of Italy, showed a reduction of surface contamination over time, i.e. in 2003 all the concentrations were less than 50% of those detected in 1998 (Fig. 3).

The GM amounts of CP measured on the surface positions sampled on the BSCs of hospital units C3 and D4 located in the Center of Italy ranged between 6057 pg/cm^2 <LOD and 7012–265 pg/cm^2, respectively. Generally, the working tray position sampled inside the BSC gave the highest contamination values during the 10-year period of survey. In Table 5, the 75th percentile reflects these data for both investigated units and ranges between 10120 pg/cm^2 and <LOD for hospital unit C3 and between 19,602 and 635 pg/cm^2 for hospital unit D4.

Normally, the GM amounts in the investigated points of the preparation room were lower on the *work areas* compared with the floor next to the BSC. Also, among the sampling positions of the *other area*, the floors at 1.0 and 3.5 m from BSC had the highest GMs of CP. The maximum surface loading value found on the door handles was 705 pg/cm^2 for hospital unit D4 in 2005. Finding measurable amounts of CP could reasonably be due to the larger quantities handled annually by the pharmacy technicians in this hospital pharmacy rather than in unit C3. This is in agreement with the time trends of contamination of CP based on the 2-year GMs of all wiped surfaces For hospital unit D4, a moderate increase of GM amounts was shown in 2006–2007 when compared to the previous survey period, while an overall reduction of surface contamination was observed over the 10-year period of evaluation of exposure to ADs.

Similar results were obtained for hospital unit E5 located in the South of Italy where the GM amounts of CP detected on surface positions sampled on BSC ranged between 39,054 and 183 pg/cm^2 during the survey period 1998–2007 (Table 6). The other sampling areas had GMs amounts ranging from 2944 to 38 pg/cm^2 (*work area*) and from 1520 to 84 pg/cm^2 (*other area*). Among all the hos-

Table 4
Geometric means and selected percentiles of wipe sample CP concentrations (pg/cm^2) for hospitals UA1 and UB2 located in northern Italy.

	Survey years	Geometric mean (range)	Selected percentiles		*n*	Percentage above LOD (%)
			50th	75th		
UA1						
BSC	1998–1999	7755 (501–11204)	15750	28001	12	100
	2000–2001	6618 (1150–98000)	4650	21750	12	100
	2002–2003	3834 (801–17002)	4000	7250	12	100
	2004–2005	315 (582–1804)	703	1089	12	67
	2006–2007	<LOD	<LOD	<LOD	12	0
Work area	1998–1999	2357 (504–12501)	3200	3561	8	100
	2000–2001	1216 (251–18004)	1225	2325	8	100
	2002–2003	236 (30–600)	427	525	8	75
	2004–2005	114 (250–800)	140	450	8	50
	2006–2007	<LOD	<LOD	<LOD	8	0
Other area	1998–1999	951 (<LOD–21000)	701	6751	6	84
	2000–2001	644 (550–2702)	1002	1451	6	84
	2002–2003	90 (<LOD–1302)	<LOD	107	6	33
	2004–2005	65 (<LOD–450)	<LOD	158	6	33
	2006–2007	<LOD	<LOD	<LOD	6	0
UB2						
BSC	1998–1999	18286 (5000–122900)	13250	56251	12	100
	2000–2001	8844 (1352–45670)	9885	15675	12	100
	2002–2003	2942 (1800–22905)	4150	7203	12	92
	2004–2005	864 (503–7600)	845	1593	12	92
	2006–2007	535 (342–5010)	555	820	12	100
Work area	1998–1999	8036 (5111–14402)	7850	9630	8	100
	2000–2001	4367 (2493–5900)	4015	4850	8	100
	2002–2003	1866 (1700–9004)	2950	4450	8	87
	2004–2005	1355 (450–3300)	1765	3050	8	100
	2006–2007	226 (<LOD–8640)	216	1300	8	63
Other area	1998–1999	1524 (332–9900)	941	4775	6	100
	2000–2001	1202 (551–3454)	1065	1717	6	100
	2002–2003	555 (<LOD–2300)	820	1527	6	83
	2004–2005	515 (173–1280)	605	990	6	100
	2006–2007	99 (<LOD–980)	86	638	6	50

pitals, the mean handled amounts of CP were the highest over the 10-year of survey. This is in agreement with the GMs obtained by analyzing all the wipe samples collected from the sampling areas. The time trends of these three representative areas depict a reduction of surface contamination that lasted until 2004. The reported time trend is given by the CP amount that was 141,580 pg/cm^2 as 75th percentile of the distribution curve during the first 2 years of survey. Also, a CP reduction was observed during the last years of survey and only 60% of the samples being positive.

4.2. Biological monitoring

For each hospital unit (A1, B2, C3, D4 and E5) urine concentrations of CP, IF DOXO and EPI are expressed as ng/mL and are reported in Tables 7, 8 and 9, respectively. Concentrations are shown as geometric means (GMs). Also, the 50th, 75th and 95th percentiles were calculated to provide additional information about the shape of the distribution. GMs are given every two years, e.g. 1998–1999, 2000–2001, covering the 1998–2007 survey period. By 2004, nearly all the datasets of the studied biomarkers were found to contain values below the limit of detection of the analytical methods used. Therefore, in order to perform statistical calculations of all censored data, it was necessary to use a method of calculating GMs and percentiles that took into account data below LOD. A further complication arose also because there were multiple limits of detection that had changed over time. As the simplest method was to set all values below LOD to a half LOD, for CP and IF, the assigned values were 0.025 ng/mL up to 2005 and 0.005 ng/mL between 2006 and 2007; while for DOXO and EPI, the assigned values were 0.02 ng/mL between 2004 and 2007. This method allowed the differences in mean exposures to be calculated overall when censoring was particularly heavy because the majority of data set had up to 90% of results below LOD. In Table 7, the detail of the cyclophosphamide urine concentrations shown as pre-shift and post-shift values is reported. During the biannual survey (1998–1999) all the hospital units had nearly 70% of urine samples below LOD for nurses preparing or administering this drug. The GMs ranged between 0.04 and 0.268 ng/mL, the highest mean value was being detected in urines of personnel who prepared cyclophosphamide in the hospital located in the South of Italy. Post-shift values were positive until 2003 and GMs ranged between 0.027 and 1.042 ng/mL with a 95th percentile set at 5.745 ng/mL indicating that the possible sources of exposure that were being evidenced by wipe testing were consistent with an uptake of this drug. In the exposure survey of 1998–1999 the questionnaire revealed that nurses of the Hospital Pharmacy E5 were used to keeping food and beverages in the drug storage located inside the preparation room. In the other hospital units a common practice was to use a surgical tissue on the inner surface of the BSC. Since positive wipe samples were found both inside and outside the BSC in the pharmacy it is plausible that cyclophosphamide releases within the BSC were spread to surfaces outside the BSC by (presumably) the malfunctioning of the laminar flow of the BSC itself.

Ifosfamide showed a similar trend over the 10-year survey carried out in the five workplaces during the surveillance monitoring at the pharmacy units or oncology wards. Table 8 shows GMs urine levels and the relative percentiles of the distribution of these levels detected in the five workplaces. Nurses preparing or administering cytotoxic drugs were still being exposed to ifosfamide, but their exposure decreased considerably between 1998 and 2007.

Table 5
Geometric means and selected percentiles of wipe sample CP concentrations (pg/cm^2) for hospitals UC3 and UD4 located in central Italy.

	Survey years	Geometric mean (range)	Selected percentiles		*n*	Percentage above LOD (%)
			50th	75th		
UC3						
BSC	1998–1999	6057 (7220–81204)	5750	10120	12	100
	2000–2001	6639 (701–67002)	7155	13175	12	100
	2002–2003	1318 (414–5500)	1076	1955	12	100
	2004–2005	177 (<LOD–1200)	217	385	12	75
	2006–2007	<LOD	<LOD	<LOD	12	0
Work area	1998–1999	2021 (1199–4200)	2647	3383	8	100
	2000–2001	1501 (452–2803)	1840	2025	8	100
	2002–2003	444 (213–2224)	715	1168	8	87
	2004–2005	207 (<LOD–905)	366	433	8	75
	2006–2007	<LOD	<LOD	<LOD	8	0
Other area	1998–1999	1103 (<LOD–7303)	2395	5232	6	84
	2000–2001	1436 (492–2310)	1765	2307	6	100
	2002–2003	157 (<LOD–904)	161	575	6	33
	2004–2005	83 (<LOD–321)	91	255	6	50
	2006–2007	42 (<LOD–220)	<LOD	<LOD	6	16
UD4						
BSC	1998–1999	7012 (1014–33000)	9170	19602	12	100
	2000–2001	3136 (140–135051)	2555	20592	12	92
	2002–2003	610 (121–3404)	775	1142	12	100
	2004–2005	265 (300–704)	380	470	12	98
	2006–2007	457 (<LOD–28200)	365	635	12	92
Work area	1998–1999	2345 (1304–24005)	1600	2335	8	100
	2000–2001	1002 (164–10631)	1565	2462	8	87
	2002–2003	183 (<LOD–720)	176	285	8	87
	2004–2005	165 (<LOD–705)	202	430	8	75
	2006–2007	368 (<LOD–2004)	695	1077	8	75
Other area	1998–1999	666 (155–1203)	880	901	6	100
	2000–2001	344 (<LOD–905)	715	845	6	84
	2002–2003	162 (13–1104)	137	770	6	67
	2004–2005	259 (215–1802)	377	1335	6	67
	2006–2007	76 (<LOD–933)	<LOD	196	6	34

As far as doxorubicin and epirubicin are concerned, pre-shift levels showed GMs below LOD, as always detected by LC–MS/MS during the 2002–2007 time period (Table 9). Post-shift detectable levels of doxorubicin and epirubicin were obtained in the biannual survey carried out in 2002–2003. In total, 25 nurses were monitored in the hospital of Northern Italy and 4 urines over 50 samples had concentrations of doxorubicin that ranged between 0.391 and 0.834 ng/mL. Since these nurses administered doxorubicin (2A; IARC), questions were asked about the administration of this drug such as disconnecting patients infusion systems and nursing care (e.g. washing the patient or urine collection), and about the use of personal protective equipment during such activities. In the 2003 survey, cleaning activities were reported by these four nurses from oncology wards and since a mixture of ADs was administered we could not be sure which drug was responsible for nurse exposure. This was the reason why this activity was not recorded during the 2003 survey. In any case the nursing tasks performed with doxorubicin may be regarded as a possible cause of uptake of this drug. As already discussed by Ziegler et al. [40], the urine measurements may also be largely influenced by exposure in the

Table 6
Geometric means and selected percentiles of wipe sample CP concentrations (pg/cm^2) for hospitals UE5 located in southern Italy.

	Survey years	Geometric mean (range)	Selected percentiles		*n*	Percentage above LOD (%)
			50th	75th		
BSC	1998–1999	39054 (1705–690004)	26700	141580	12	100
	2000–2001	15504 (1105–97005)	22387	38500	12	100
	2002–2003	3837 (894–21500)	3600	10564	12	100
	2004–2005	219 (<LOD–1204)	610	1005	12	58
	2006–2007	183 (<LOD–1054)	317	878	12	58
Work area	1998–1999	2944 (700–16500)	3602	8253	8	100
	2000–2001	5047 (2394–12330)	4800	6875	8	100
	2002–2003	1054 (380–5500)	1700	3485	8	87
	2004–2005	141 (<LOD–2405)	<LOD	1502	8	37
	2006–2007	38 (<LOD–190)	<LOD	<LOD	8	12
Other area	1998–1999	1520 (302–9135)	1021	6810	6	100
	2000–2001	83 (<LOD–300)	105	216	6	50
	2002–2003	104 (<LOD–453)	131	388	6	50
	2004–2005	258 (<LOD–1100)	610	850	6	66
	2006–2007	84 (<LOD–291)	112	221	6	50

Table 7
Geometric means and selected percentiles of cyclophosphamide urine concentrations (ng/mL) for all the investigated hospitals.

	Workplace	Survey years	Nurse/pharmacy personnel	No of subject	Cyclophosphamide (ng/mL)								Percentage below LOD
					Pre-shift				Post-shift				
					Geometric mean (range)	Selected percentiles			Geometric mean (range)	Selected percentiles			
						50th	75th	95th		50th	75th	95th	
Northern Italy	Hospital Unit Al, hospital Unit B2	1998–1999	Drug preparing	4	0.040 (<LOD–1.300)	<LOD	<LOD	0.505	0.147 (<LOD–6.113)	<LOD	2.193	5.150	73%
			Drug administering	18									
		2000–2001	Drug preparing	4	<LOD	<LOD	<LOD	<LOD	0.152 (<LOD–3.112)	0.068	1.243	2.543	75%
			Drug administering	18									
		2002–2003	Drug preparing	4	<LOD	<LOD	<LOD	<LOD	0.028 (<LOD–0.443)	<LOD	<LOD	<LOD	88%
			Drug administering	21									
		2004–2005	Drug preparing	4	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	100%
			Drug administering	18									
		2006–2007	Drug preparing	4	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	100%
			Drug administering	18									
Central Italy	Hospital Unit C3, hospital Unit D4	1998–1999	Drug preparing	4	0.075 (<LOD–1.026)	0.033	0.283	0.877	1.311 (<LOD–4.221)	1.722	2.468	4.221	50%
			Drug administering	18									
		2000–2001	Drug preparing	4	0.040 (<LOD–1.250)	<LOD	<LOD	0.504	1.165 (<LOD–4.221)	1.987	2.554	3.777	70%
			Drug administering	18									
		2002–2003	Drug preparing	4	<LOD	<LOD	<LOD	<LOD	0.027 (<LOD–2.554)	<LOD	<LOD	<LOD	99%
			Drug administering	46									
		2004–2005	Drug preparing	4	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	100%
			Drug administering	24									
		2006–2007	Drug preparing	4	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	100%
			Drug administering	24									
Southern Italy	Hospital Unit E5	1998–1999	Drug preparing	4	0.268 (<LOD–0.987)	0.456	0.832	0.987	1.042 (<LOD–5.987)	1.709	2.601	5.745	20%
			Drug administering	21									
		2000–2001	Drug preparing	4	0.033 (<LOD–0.832)	<LOD	<LOD	0.528	0.361 (<LOD–5.987)	0.456	2.443	5.221	65%
			Drug administering	21									
		2002–2003	Drug preparing	4	<LOD	<LOD	<LOD	<LOD	0.034 (<LOD–3.443)	<LOD	<LOD	0.951	97%
			Drug administering	26									
		2004–2005	Drug preparing	4	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	100%
			Drug administering	26									
		2006–2007	Drug preparing	4	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	100%
			Drug administering	26									

Table 8
Geometric means and selected percentiles of ifosfamide urine concentrations (ng/mL) for all the investigated hospitals.

Workplace	Survey years	Nurse/pharmacy personnel	No of subject	Ifosfamide (ng/mL)								Percentage below LOD
				Pre-shift				Post-shift				
				Geometric mean (range)	Selected percentiles			Geometric mean (range)	Selected percentiles			
					50th	75th	95th		50th	75th	95th	
Hospital Unit Al, hospital Unit B2	1998–1999	Drug preparing	4	0.047 (<LOD–0.987)	<LOD	<LOD	0.808	0.121 (<LOD–4.221)	<LOD	1.068	2.537	70%
		Drug administering	18									
	2000–2001	Drug preparing	4	<LOD	<LOD	<LOD	<LOD	0.077 (<LOD–4.221)	<LOD	0.134	2.526	84%
		Drug administering	18									
	2002–2003	Drug preparing	4	<LOD	<LOD	<LOD	<LOD	0.029 (<LOD–1.546)	<LOD	<LOD	<LOD	98%
		Drug administering	21									
	2004–2005	Drug preparing	4	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	100%
		Drug administering	18									
	2006–2007	Drug preparing	4	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	100%
		Drug administering	18									
Hospital Unit C3, hospital Unit D4	1998–1999	Drug preparing	4	0.031 (<LOD–0.102)	<LOD	<LOD	0.088	0.248 (<LOD–2.221)	0.476	1.243	2.205	60%
		Drug administering	18									
	2000–2001	Drug preparing	4	0.035 (<LOD–0.543)	<LOD	<LOD	0.169	0.081 (<LOD–2.221)	<LOD	0.643	1.539	75%
		Drug administering	18									
	2002–2003	Drug preparing	4	<LOD	<LOD	<LOD	<LOD	0.027 (<LOD–0.543)	<LOD	<LOD	<LOD	99%
		Drug administering	46									
	2004–2005	Drug preparing	4	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	100%
		Drug administering	24									
	2006–2007	Drug preparing	4	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	100%
		Drug administering	24									
Hospital Unit E5	1998–1999	Drug preparing	4	0.057 (<LOD–0.678)	0.072	0.089	0.429	0.216 (<LOD–2.901)	0.432	1.098	2.219	40%
		Drug administering	21									
	2000–2001	Drug preparing	4	0.027 (<LOD–0.070)	<LOD	<LOD	0.045	0.101 (<LOD–2.901)	0.025	0.561	1.039	72%
		Drug administering	21									
	2002–2003	Drug preparing	4	<LOD	<LOD	<LOD	<LOD	0.031 (<LOD–0.944)	<LOD	<LOD	0.323	97%
		Drug administering	26									
	2004–2005	Drug preparing	4	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	100%
		Drug administering	26									
	2006–2007	Drug preparing	4	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	100%
		Drug administering	26									

Table 9
Geometric means and selected percentiles of doxorubicin and epirubicin urine concentrations (ng/mL) for all the investigated hospitals.

	Workplace	Survey years	Nurse/pharmacy personnel	No. of subject	Doxorubicin (ng/mL)								Percentage above LOD
					Pre-shift				Post-shift				
					Geometric mean (range)	Selected percentiles			Geometric mean (range)	Selected percentiles			
						50th	75th	95th		50th	75th	95th	
Northern Italy	Hospital Unit A1, hospital Unit B2	2002–2003	Drug preparing	4	<LOD	<LOD	<LOD	<LOD	0.034 (<LOD–0.834)	<LOD	<LOD	0.593	8%
			Drug administering	21									
		2004–2005	Drug preparing	4	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	0
			Drug administering	18									
		2006–2007	Drug preparing	4	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	0
			Drug administering	18									
Central Italy	Hospital Unit C3, hospital Unit D4	2002–2003	Drug preparing	4	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	0%
			Drug administering	46									
		2004–2005	Drug preparing	4	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	0
			Drug administering	24									
		2006–2007	Drug preparing	4	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	0
			Drug administering	24									
Southern Italy	Hospital Unit E5	2002–2003	Drug preparing	4	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	0%
			Drug administering	26									
		2004–2005	Drug preparing	4	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	0%
			Drug administering	26									
		2006–2007	Drug preparing	4	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	0%
			Drug administering	26									
	Workplace	Survey years	Nurse/pharmacy personnel	No. of subject	Epirubicin (ng/mL)								Percentage above LOD
					Pre-shift				Post-shift				
					Geometric mean (range)	Selected percentiles			Geometric mean (range)	Selected percentiles			
						50th	75th	95th		50th	75th	95th	
Northern Italy	Hospital Unit A1, hospital Unit B2	2002–2003	Drug preparing	4	<LOD	<LOD	<LOD	<LOD	0.033 (<LOD–0.765)	<LOD	<LOD	0.654	8%
			Drug administering	21									
		2004–2005	Drug preparing	4	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	0
			Drug administering	18									
		2006–2007	Drug preparing	4	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	0
			Drug administering	18									
Central Italy	Hospital Unit C3, hospital Unit D4	2002–2003	Drug preparing	4	<LOD	<LOD	<LOD	<LOD	0.023 (<LOD–0.721)	<LOD	<LOD	<LOD	2%
			Drug administering	46									
		2004–2005	Drug preparing	4	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	0
			Drug administering	24									
		2006–2007	Drug preparing	4	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	0
			Drug administering	24									
Southern Italy	Hospital Unit E5	2002–2003	Drug preparing	4	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	0%
			Drug administering	26									
		2004–2005	Drug preparing	4	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	0%
			Drug administering	26									
		2006–2007	Drug preparing	4	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	0%
			Drug administering	26									

previous 24 h or may more strongly reflect the extent of exposure over the previous week. Therefore the use of urinary rather than blood measurements after 6 h of exposure needs to be reviewed in the future occupational exposure assessment, even if this strategy is a common practice, since it is widely acceptable to workforces and sample collection is quite easy. Detectable urine concentrations of epirubicin were evidenced by analyzing samples collected from the pharmacy technicians who prepared this drug. In the 2003 survey, wipe samples were taken from inside and outside BSC and from eight different surfaces of work areas (sampling collection strategy was the same as that in use for CP and IF). Significant concentrations were found on the outside surface of the protective glass of the safety cabinet. These wipe sample results provide evidence of epirubicin contamination of work surfaces and suggest the occurrence of dermal contact.

5. Discussion and conclusions

The recent introduction of the successful hyphenation of LC and mass spectrometry, given by the atmospheric pressure ionization interfaces, enabled analytical methods to be developed and validated with high specificity and selectivity. These prerequisites played an important role during the development of safety programs to protect workers from hazardous exposures to antineoplastic drugs. The levels of cyclophosphamide detected in the wipe samples collected on the inside and outside surfaces of the biological cabinets allowed potential sources of contamination to be identified. These results were related to improper activities that have been recorded during the biannual (1998–1999) survey of the hospital in Southern Italy, i.e. Unit E5. Food and beverages were prepared, stored, and consumed in work areas by the personnel involved in preparing antineoplastic drugs. Inadvertent ingestion was therefore a problematic issue. In this context, food and beverages were likely contaminated with airborne particles of cyclophosphamide, possibly leading to drug uptake by dermal contact. When performing wipe sampling in all the other hospital units (A1–D4), some nursing care activities (e.g. washing patients or urine collection) and particular tasks with doxorubicin were found not to be safe for those who handled cyclophosphamide (ifosfamide) and/or anthracyclines because significant concentrations of these drugs were found not only inside the BSC, but also spread in the work areas. Special attention was given to these activities, identified as possible sources of exposure when no safe handling programs for hazardous drugs were properly implemented. Transferable surface load of antineoplastic drugs to the skin through dermal contact with contaminated surfaces, as demonstrated here, is a significant route for potential dermal exposure. Therefore, wipe testing and biological monitoring are important to estimate the dose that could be taken up in the body. Both the environmental and biological monitoring strategies were successful because work practices related to both drug preparation and administration were implemented every year of survey. That is clearly shown by the time trends of the geometric mean concentrations of cyclophosphamide reported every two years over a period ranging from 1998 to 2007. It is interesting to highlight the strong reduction of surface contamination since 2003, when the recommended procedures for the safe handling of antineoplastic drugs started to be followed by health care workers. Likewise, detectable urine concentrations of cyclophosphamide and ifosfamide were approximately 10-fold lower in 2003 than in 1998. Urine levels of epi-doxorubicin were found to significantly decrease between 1998 and more recent years. Since this particular trend implies the hypothesis that a possible route of exposure is dermal exposure, wipe testing was likely related to biomonitoring data providing also a useful and powerful tool to assess a possible route of exposure to antineoplastic drugs. Trends of exposure to several antineoplastic agents among workers involved in preparing or administering these drugs have never before been presented by us. To identify and assess hazards before any workers were exposed to ADs, attention was given to the following recommended topics: (a) evaluation of the whole working environment, including physical layout of work areas; (b) equipment, i.e. ventilated cabinets and PPE used during work practices; (c) decontamination of BSC and cleaning of surfaces and (d) estimate of volume, frequency of handling and forms of drugs handled by pharmacy technicians.

In this study, we found that an effective program for safely handling hazardous drugs requires annual reviews on the basis of the workplace evaluation. Therefore, our paper emphasizes an important point. To achieve the crucial aim tasked of reducing risk to all potentially exposed workers in occupational settings one helpful strategy is provided by a data-storage system that allows potential risks of working to be rapidly identified and controlled.

Employers' adherence to these recommendations allowed risk characterisation to achieve other important goals. The percentage of positive urine samples was found to be around 30% in the 1990s and 2% in the 2000s. Moreover, no positive samples were detected in 2006 or 2007.

Since antineoplastic drugs have no established occupational exposure limits (OELs), it is a common practice to verify if operation and controls are effective to keep exposure level as-low-as-reasonably-achievable, as addressed by the old ALARA principle. However, in the absence of established OELs, employers and workers often lack the necessary guidance on the extent to which occupational exposures should be controlled. An attempt aimed at ensuring that the installed controls work properly was developed by the National Institute for Occupational Safety and Health (NIOSH) in 2008. NIOSH posted a draft document [43] about a technique, called control banding (CB), used to guide the assessment and management of workplace risks. This is a generic technique that determines control measures based on a range or "band" of hazards and exposures (i.e. small, medium, large exposure). Therefore, among occupational safety experts and health practitioners there is a growing need to establish "a target range of exposure concentrations" also for chemotherapeutic agents. It could be a useful approach to correlate this range to the extent of exposures so that the developed safety programs may be annually reviewed on the basis of such evaluation. In the absence of OELs, the assessment of different ranges of concentrations combined with professional judgment could be suitable to determine the level of control that is necessary to minimize risks to workers.

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