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# Accessible analytical methodology for assessing workplace contamination of antineoplastic drugs in limited-resource oncology health-care settings

Claudio Müller-Ramírez[1*], Katherine Squibb[2] and Melissa McDiarmid[2]

## Abstract

**Background:** Environmental monitoring of workplaces where antineoplastic drugs are handled constitutes an essential tool to assess occupational exposures among health-care workers. Consequently, availability of simple, sensitive, and affordable analytical methodologies is needed, particularly in health-care settings with limited resources that restrict environmental monitoring studies.

**Methods:** Previously validated methodologies for simultaneous determination of ifosfamide, cyclophosphamide, and paclitaxel were modified and re-validated in order to create a more sensitive and more accessible liquid chromatography-based analytical method for measuring levels of workplace contamination generated by the handling of antineoplastic drugs in oncology healthcare settings with limited resources.

**Results:** An HPLC-UV methodology was developed and validated to simultaneously determine ifosfamide, cyclophosphamide, and paclitaxel in field wipe samples collected from oncology health-care settings with limited resources. Solid-phase extraction was incorporated to concentrate analytes and improve their detection and quantification. Adequate limits of detection for ifosfamide ($0.02 \ ng/cm^2$), cyclophosphamide ($0.1 \ ng/cm^2$), and paclitaxel ($0.03 \ ng/cm^2$) were obtained. Also, mean recoveries between 88.7 and 96.2 % were achieved.

**Conclusions:** The analytical method described here using a more widely available instrumentation provides an excellent alternative to LC-MS when establishing workplace contamination levels produced by the handling of antineoplastic drugs in non-high-income country oncology health-care settings.

**Keywords:** Occupational exposures, Antineoplastic drugs, Environmental monitoring study, Accessible analytical methods

## Background

Antineoplastic drugs (ANDs) have increased in their use given the ongoing rise of number of cancer cases worldwide (Connor and McDiarmid 2006). Consequently, health-care workers are increasingly exposed to these hazardous drugs (HDs) due to work duties. This phenomenon has been studied in North American and European developed countries as well as in Australia for several decades to date (Kopp et al. 2013; Hedmer and Wholfart 2012).

Important advances in health-care worker protection have been achieved by characterizing these occupational exposures to ANDs, either through environmental or biological monitoring studies (Pampal et al. 2014; Sottani et al. 2007; Brouwers et al. 2007). Occupational safety and health organizations have published safety guidelines for the handling of ANDs as a measure to reduce unnecessary occupational exposures (OSHA 1986; OSHA Directorate of Technical Support 1995, 1999; NIOSH Alert 2004). Nowadays, implementation of these safety guidelines is a common feature among oncology health-care settings around the globe; however, adherence to them is not always a condition that can easily be assessed by simple

* Correspondence: claudiomuller@udec.cl
[1]Department of Pharmacy, School of Pharmacy, University of Concepcion, Barrio Universitario S/N, Concepcion 3349001, Chile
Full list of author information is available at the end of the article

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visual inspection in order to establish occupational risks or the efficacy of hazard controls in the workplace (Davis et al. 2011; Connor et al. 2012; McDiarmid et al. 2010).

Non-high-income countries, like their developed peers, have adopted these safety guidelines to protect their health-care workers from unnecessary occupational exposures to ANDs. However, little has been done to assess current extent of surface contamination generated by the handling of these drugs by conducting environmental monitoring studies.

Costs associated with sensitive analytical techniques and methods, such as liquid or gas chromatography coupled to tandem mass spectrometry (GC-MS/MS or LC-MS/MS) are often unaffordable for non-high-income country Ministry of Health laboratories (Zeedijk et al. 2005; Smith et al. 2014).

Assessing workplace environmental contamination by measuring levels of drug residues on work surfaces plays a key role when assessing occupational exposures to ANDs (Friese et al. 2015; Kiffmeyer et al. 2013; Fabrizi et al. 2012; Nussbaumer et al. 2011; Floridia et al. 1999; Maeda and Miwa 2013; Sabattini et al. 2005). Biological monitoring studies, on the other hand, constitute a more accurate estimation of drug uptake and internal occupational exposure. However, these types of studies require even more sensitive instrumentation, which is more expensive and also may require human subject's approval since bodily fluids are needed (Davis et al. 2011; Turci et al. 2003). The methodology described here relates to the use of a less sensitivity analytical tool, but one which is more likely to be available to hospitals or government laboratories in non-high-income countries, and it is still usable for measuring low levels of workplace contamination generated by the manipulation of ANDs in health-care settings.

## Methods

Previously validated methods for simultaneous determination of five antineoplastic drugs, among them ifosfamide (IF), cyclophosphamide (CP), and paclitaxel (PX), in a single run were modified and re-validated (Larson et al. 2003). Selection criteria for these three HDs were based upon (1) the frequency of their usage (preparation and administration) at the health-care facility where field wipe samples were collected from; (2) previously published works for quantitatively determining ANDs as workplace contaminants (Pretty et al. 2010; Larson et al. 2002); and (3) information contained in the International Agency for Research on Cancer (IARC) monographs for human carcinogenic drugs, as well as in the National Institute for Occupational Safety and Health (NIOSH) Alert for handling HDs (NIOSH Alert 2004; IARC 2015).

Also, specific modifications to the original analytical methodology consisted of (1) replacing a C8 column by a C18 column as the stationary phase because of its more wide availability in analytical laboratories, along with its versatility when separating and analyzing compounds with different physicochemical properties as it is in this case; (2) incorporating an internal standard; (3) slightly varying the gradient elution of the mobile phase in order to decrease the time of analysis; and (4) including a concentration step of wipe samples based on solid-phase extraction to increase the sensitivity of the method, as well as ease of wipe sample storage and transportation. Hexamethylphosphoramide (HMPA) was considered as an adequate internal standard for the proposed method as it was described in some other works (Pretty et al. 2010; De Jonge et al. 2004). Detection of all drugs was carried out at 195 nm.

Table 1 summarizes the chromatographic conditions of the method described here. Chromatographic analyses were made in duplicates and reported as the area ratios of the analytes and that of the internal standard.

## Instrumentation

Analyses of all ANDs were performed on a liquid chromatograph Merck-Hitachi (Japan) equipped with a binary pump L-6200A, an ultraviolet detector L4250, and an interface D-6000. Data acquisition was made through chromatography data station manager HSM. Surface-wipe samples were extracted by using a negative pressure Burdick and Jackson SPE manifold (CA, USA). As for the evaporation procedure, an Organomation Mayer II-2 analytical evaporator (MA, USA) was employed. Also, a Mettler Toledo pH meter (OH, USA) was utilized to adjust 10 mM phosphate buffer to pH 6.0.

**Table 1** Experimental chromatographic conditions for the analysis of ifosfamide, cyclophosphamide, and paclitaxel in workplace wipe samples

| Chromatography component | Chromatographic characteristics |
|---|---|
| Stationary phase | Waters Symmetry® C18, 5 μm, 4.6 × 150 mm column |
| Mobile phase | Acetonitrile:10 mM phosphate buffer pH 6 |
| | 0–9.9 min, 25 % A, 75 % B |
| | 10–20 min, 60 % A, 40 % B |
| | 20.1–25 min, 25 % A, 75 % B |
| | A = 100 % ACN, B = 100 % buffer ($KH_2PO_4$ 1.1936 g, $K_2HPO_4$ 0.2143 g, dissolve in 1 L of DI water, adjust at pH 6 with phosphoric acid) |
| Flow rate | 1.0 mL/min |
| Detection wavelength | 195 nm |
| Injection volume | 20 μL |

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### Reagents

Stock solutions of the analytes under study, positive and negative control solutions, as well as the mobile phase were prepared using methanol and acetonitrile Lichrosolv®, along with ortho-phosphoric acid, monobasic and dibasic potassium phosphate (Merck, Darmstadt, Germany), and submicron-filtered water (Fisher Scientific). Ethylacetate Suprasolv® was used to elute analytes from solid-phase extraction cartridges.

Ifosfamide, cyclophosphamide, paclitaxel, and hexamethylphosphoramide HPLC certified standards (purity >98 %) were purchased from Sigma-Aldrich (St. Louis, MO, USA).

### Preparation of stock and standard solutions

Stock solutions of each antineoplastic drug, including that of the internal standard, were prepared in methanol at 400 µg/mL. Thus, standard solutions were elaborated by diluting known aliquots of each stock solution with a mixture of methanol, acetonitrile, and 10 mM phosphate buffer pH 6 (25:10:65 *v/v*) matching a desorbing solvent used to collect field wipe samples (Larson et al. 2002). Stock solutions were frozen at −20 °C and standard solutions refrigerated at 5 °C. The frozen stock solutions were stable for 2 months, and the refrigerated standard solutions were stable for 3 weeks (data not shown).

### Linearity

Linear responses of the instrument were tested by running calibration standard solutions containing IF, CP, and PX up to 30 µg/mL. These compounds were analyzed separately and in mixture. The internal standard HMPA was added at 20 µg/mL to each solution. Recoveries of ±10 % of the nominal concentration levels were accepted.

### Sensitivity: detection and quantification limits

Three low-level standard and blank solutions were prepared and analyzed on three different days to build linear regression plots that were used to estimate both the limit of detection (LOD) and limit of quantification (LOQ) according to

$$LOD = (3.3s)/b \qquad (1)$$

$$LOQ = (10s)/b \qquad (2)$$

*s* corresponds to the standard deviation of the intercept and *b* to the slope of the linear regression plot (International Conference on Harmonization of Technical Requirements for Registration of pharmaceuticals for Human Use: Validation on Analytical Procedures, Text and Methodology, Q2(R1), 1996). All these values were first calculated as nanograms per milliliter (ng/mL), and then converted into nanograms per square centimeter (ng/cm$^2$) units as can be seen in the "Sample processing" section, Eq. 3.

### Wipe media and surface sampling recovery

The selected methodology for performing and processing environmental wipe samples was taken from the work of Larson et al. (2002, 2003) and Pretty et al. (2010). Additionally, solid-phase extraction (SPE) performed on Hypersep® C18 cartridges 200 mg/3 mL (Thermo Scientific, Waltham, MA) for sample enrichment was incorporated in order to enable detection of low concentration levels of all three ANDs in field wipe samples.

Two filter papers (Whatman 42, 55 mm diameter) previously wetted with 250 µL of the desorbing solvent (methanol: acetonitrile: 10 mM potassium phosphate buffer pH 6, 25:10:65 *v/v*) were used to wipe a templated area of 400 cm$^2$. The desorbing solvent had been found to efficiently extract and provide acceptable wipe sample recoveries of all three ANDs under study in the current work (Pretty et al. 2010).

Extraction efficiency from wipe media was tested by preparing control standard solutions as follows: two filter papers were wetted with 250 µL of the desorbing solvent and spiked with appropriate aliquots of antineoplastic drug stock solutions at specific concentrations assuming quantitative extraction. The wipes were then placed together in a 125-mL wide mouth polypropylene screw-cap Nalgene® jar to be processed and analyzed as it is described in the sample processing below.

### Sample processing

The internal standard was added at 20 µg/mL to each jar, along with the necessary volume of desorbing solvent to complete 10 mL, considering liquid is already present in the filter papers. Extra precaution was taken to eliminate any bubbles of air located between the filter papers. The jars were then sonicated for 10 min with the liquid in the jars completely immersed below water level to assure homogeneity. After sonication, all droplets generated by condensation on the inner wall of the jars were placed back together into the sonicated liquid. Filtration of the supernatant (8–9 mL) was performed with a 10-mL plastic syringe connected to a 0.22-µm syringe-driven filter (Millex®) and received in a 15-mL glass tube. Afterwards, a 2-mL aliquot of the filtered solution was loaded and dried under vacuum for 5 min on a preconditioned Hyperserp® C18 200 mg/3 mL Thermo Scientific cartridge with 3 mL of methanol and 3 mL of deionized water. Then, the analytes of interest retained on the cartridge were eluted with 2 mL of ethyl acetate, which was completely evaporated under nitrogen at room temperature (20 °C). The residue was finally reconstituted with 200 µL of the desorbing solvent.

All wipe samples were obtained from an area of 400 cm$^2$. Concentration units (ng/mL) were converted into mass/area units as follows:

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$$[10 \text{ mL} (X \text{ ng}/\text{mL})]/400 \text{ cm}^2 = 0.025 \, X \text{ ng}/\text{cm}^2 \quad (3)$$

Thus, a concentration value of $X$ ng/mL corresponds to 0.025 of the value as mass/area (ng/cm$^2$).

### Wipe sample enrichment (concentration) study

Three levels of concentrated and non-concentrated spiked wipe samples containing IF, CP, and PX at 5, 10, and 15 μg/mL and HMPA at 20 μg/mL were prepared on three different days. Enrichment factors were calculated as the recovery ratios of concentrated and non-concentrated spiked wipe sample levels.

### Storage stability study of wipe samples

Two spiked wipe sample sets were prepared as quality control subjects to be studied under storage conditions. These sets consisted of three known concentration levels of spiked wipe samples within the linear range of the method containing IF, CP, and PX at 5.0, 10.0, and 15.0 μg/mL and HMPA at 20 μg/mL; the first set was frozen at −20 °C with no SPE procedure involved, and the second was kept at room temperature (20 °C) on the SPE cartridges protected from light. Both sets of spiked wipe samples remained under these storage conditions for 2 months. All these samples were then processed as described above and quantified in terms of the amount of each drug recovered after the 2-month storage period. Additionally, a $t$ test for paired samples ($N = 27$) was run to check for statistical difference of mean recoveries at the two storage conditions since the data appeared normally distributed (SYSTAT 12 for Windows, Version 12.02.00).

### Recovery, repeatability, and reproducibility studies of wipe samples

Two sets of quality control wipe samples were used to cover the linear range proposed in the analytical method: (1) laboratory control samples (LCS) were identically prepared as those calibration standard solutions (see "Linearity" subsection) but at different concentration levels for each drug (i.e., 3.5, 6.0, 8.0, 9.5, and 15.0 μg/mL). The internal standard was added at 20 μg/mL, and no SPE procedure was involved at this stage. (2) Performance quality control (PQC)-spiked wipe samples with and without SPE procedure were elaborated by adding known amounts of IF, CP, and PX (i.e., 4.0, 5.5, 7.0, 13.0, and 15.0 μg/mL and HMPA at 20 μg/mL) on filter papers assuming quantitative extraction recovery. Mean recoveries (accuracy) of each drug between 80 and 120 % of the nominal concentration level were considered acceptable for analytical purposes (FDA Guidance for Industry and Bioanalytical Method 2001).

Similar to recovery, repeatability and reproducibility (precision) were determined by analyzing PQC wipe samples on 1 and 5 days, respectively. Relative standard deviation values of less than 2 % were considered suitable for analytical purposes (FDA Guidance for Industry and Bioanalytical Method 2001).

## Results

### Linearity

Linear responses were observed up to 15 μg/mL, accepting this value as the upper limit of the dynamic linear range for IF, CP, and PX. Table 2 shows concentration levels, linear regression equations, and coefficients of determination for all ANDs under study. Five consecutive injections of each set of calibration solutions were analyzed. Thus, coefficients of determination ($r^2$) equal or greater than 0.990 were considered adequate for the proposed method.

Figure 1 shows representative chromatograms of a blank solution, a standard solution, a spiked wipe sample solution, and a field wipe sample containing ANDs along with the internal standard HMPA. No matrix interferences or background signals were observed at the analytes' retention times.

### Sensitivity

Limits of detection and quantification were calculated for IF, CP, and PX as described above and are summarized in Table 3. These values provided appropriate sensitivity when establishing levels of workplace contamination produced by the handling of ANDs.

### Wipe sample enrichment study

Sample enrichment factors, gained through the concentration step on SPE cartridges, were close to ten (see Table 4). Therefore, this value was considered when analyzing field wipe samples.

**Table 2** Chromatographic method linearity parameters

| Antineoplastic drug | Concentration level (μg/mL) | Linear regression equation | Coefficient of determination ($r^2$) |
|---|---|---|---|
| Ifosfamide | 3, 5, 7.5,10, 12.5, 15 | $y = 2227x − 0.4$ | 0.9934 |
| Cyclophosphamide | 2.5, 5, 7.5, 10, 12.5, 15 | $y = 2211x − 1249$ | 0.9941 |
| Paclitaxel | 1, 3, 6, 9, 12, 15 | $y = 86{,}543x − 25{,}469$ | 0.9969 |
| Hexamethylphosphoramide (IS) | 20 | – | – |

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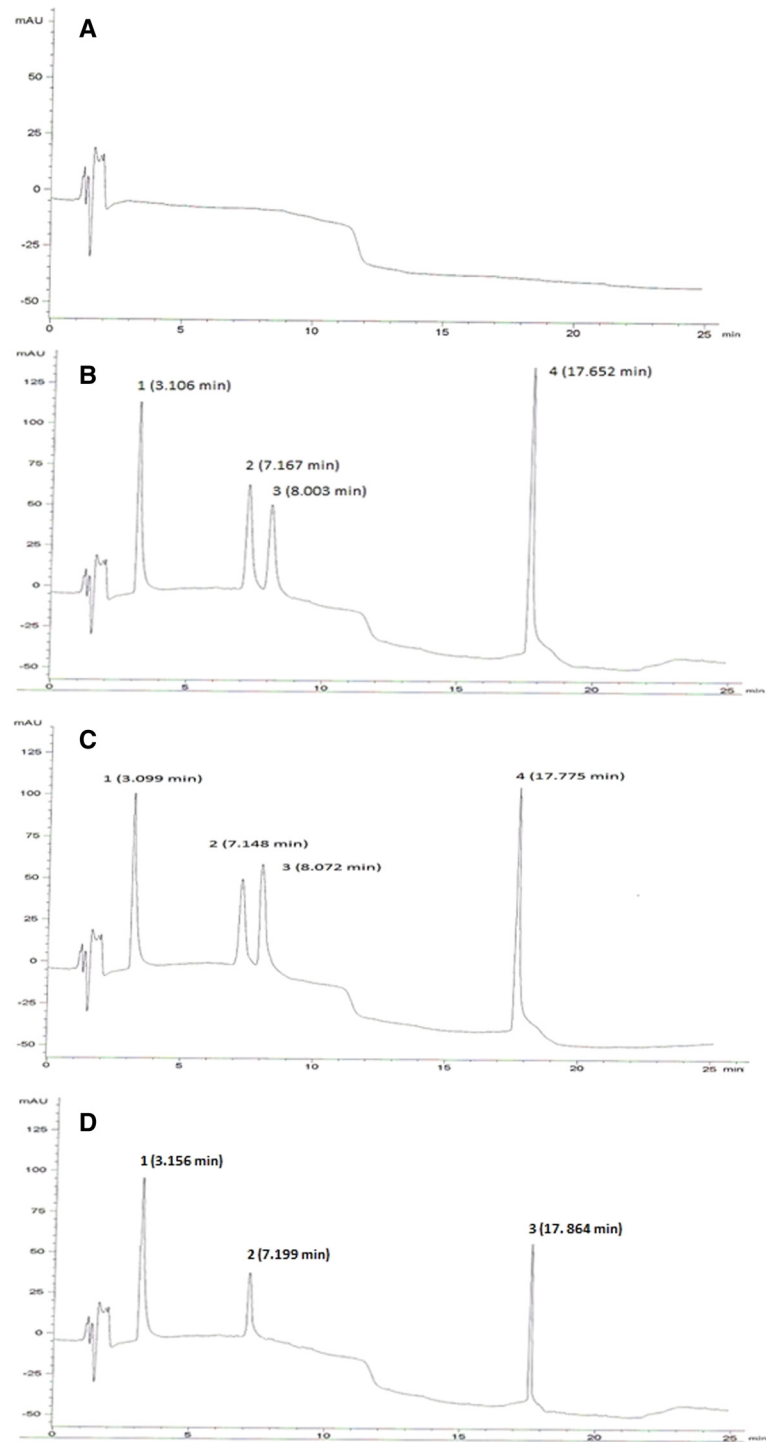
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**Fig. 1** Representative chromatograms of ifosfamide, cyclophosphamide, paclitaxel, and the internal standard hexamethylphosphoramide. **a** A blank solution. **b** A standard solution containing (*1*) hexamethylphosphoramide (20 μg/mL), (*2*) ifosfamide and (*3*) cyclophosphamide (10 μg/mL), and (*4*) paclitaxel (9 μg/mL). **c** A spiked wipe sample containing (*1*) hexamethylphosphoramide (20 μg/mL), (*2*) ifosfamide (4 μg/mL), (*3*) cyclophosphamide (5 μg/mL), and (*4*) paclitaxel (7 μg/mL). **d** A field wipe sample containing (*1*) hexamethylphosphoramide (20 μg/mL), (*2*) ifosfamide (2.5 μg/mL), and (*3*) paclitaxel (4.8 μg/mL). Flow rate 1.0 mL/min, gradient elution (see Table 1) and detection at 195 nm

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**Table 3** Detection and quantification limits for ifosfamide, cyclophosphamide, and paclitaxel

| Antineoplastic drug | Limit of detection | | | Limit of quantification | | |
| --- | --- | --- | --- | --- | --- | --- |
| | Instrumental (ng/mL)[a] | Wipe media (ng/cm$^2$)[b] | Concentrated wipe media (ng/cm$^2$)[c] | Instrumental (ng/mL)[a] | Wipe media (ng/cm$^2$)[b] | Concentrated wipe media (ng/cm$^2$)[c] |
| Ifosfamide | 10 | 0.2 | 0.02 | 32 | 0.8 | 0.08 |
| Cyclophosphamide | 41 | 1 | 0.1 | 124 | 3 | 0.3 |
| Paclitaxel | 13 | 0.3 | 0.03 | 39 | 1 | 0.1 |

[a]Calculated as described in "Sensitivity" section
[b]Based on the 400-cm$^2$ wipe area with extraction into 10 mL, no further concentration steps
[c]Based on the 400-cm$^2$ wipe area with extraction into 10 mL, tenfold further concentration step

### Storage stability study of wipe samples

No significant decrease of recovery was detected for the spiked wipe samples under specific storage conditions during the 2-month period as it can be seen in Table 5 (96.4 to 99.3 %). The $t$ test for paired samples showed that there was no evidence that the recovery means were different ($p = 0.738$), suggesting that both storage conditions are equally effective in retaining analytes' chemical stability up to 2 months.

### Recovery, repeatability, and reproducibility studies of wipe samples

Table 6 summarizes the extraction recoveries (accuracy) for the laboratory control samples and performance quality control spiked wipe samples. Table 7 shows repeatability and reproducibility (precision) of the method.

In general, recovery (accuracy) and precision (repeatability and reproducibility) values were in accordance with the analytical purposes of the method, 80–120 % of nominal concentration and ≤2 % of relative standard deviation, respectively.

### Discussion

Scarcity of documented occupational exposures to antineoplastic drugs in non-high-income countries makes it difficult to assess occupational risks for workers who directly or indirectly participate in the handling of ANDs. To date, environmental monitoring studies conducted in health-care settings with limited resources are uncommon; therefore, quantitative information about workplace contamination levels produced by the handling of HDs is unknown. Similarly, medical surveillance programs contribute to partially assess occupational risks associated with exposures to HDs by gathering qualitative information from workers (World Health Organization/Pan American Health Organization 2013). Nevertheless, availability of quantitative information is more desirable when aiming to protect workers from occupational exposures in the workplace, especially if dealing with ANDs.

Specific modifications of the original analytical methodology resulted in valuable improvements. Consequently, the proposed method was able to reduce the total time of analysis to 25 min for separating and measuring all three drugs contained in environmental wipe samples, increasing the throughput when compared to the original chromatographic method (65 min), this is due to the use of the C18 column instead of the C8 stationary phase, along with the slight variation of the gradient elution of the mobile phase. Ifosfamide and cyclophosphamide are hydrophilic compounds whereas paclitaxel presents hydrophobic properties.

**Table 4** Wipe sample enrichment factors for ifosfamide, cyclophosphamide, and paclitaxel

| Nominal concentration (µg/mL) | Recovery of concentrated spiked wipe samples (mean ± SD %) | Recovery of non-concentrated spiked wipe samples (mean ± SD %) | Ratio concentrated non-concentrated spiked wipe samples |
| --- | --- | --- | --- |
| Ifosfamide | | | |
| 5 | 1018.0 ± 0.45 | 92.0 ± 0.87 | 11.1 |
| 10 | 907.0 ± 1.2 | 111.0 ± 2.4 | 8.2 |
| 15 | 1042.0 ± 1.9 | 105.3 ± 1.7 | 9.9 |
| Cyclophosphamide | | | |
| 5 | 896.0 ± 1.3 | 108.0 ± 0.54 | 8.3 |
| 10 | 982.0 ± 0.32 | 96.0 ± 0.71 | 10.2 |
| 15 | 1009.3 ± 1.8 | 119.3 ± 1.2 | 8.5 |
| Paclitaxel | | | |
| 5 | 985.0 ± 1.4 | 98.0 ± 0.48 | 10.0 |
| 10 | 957.0 ± 2.7 | 115.0 ± 1.8 | 8.3 |
| 15 | 988.7 ± 0.12 | 105.3 ± 0.69 | 9.4 |

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**Table 5** Comparative recovery percentage of spiked wipe samples at varied storage conditions: (1) −20 °C and (2) on SPE cartridges at room temperature (20 °C) and protected from light

|  | Wipe samples stored at −20 °C | Wipe samples stored on SPE cartridges at room temperature (20 °C) | Paired *t* test *p* value[a] |
|---|---|---|---|
| Antineoplastic drug | Mean recovery ± SD % | Mean recovery ± SD % | 0.738 |
| Ifosfamide | 96.6 ± 9.9 | 97.3 ± 4.1 | |
| Cyclophosphamide | 97.1 ± 6.6 | 95.1 ± 4.4 | |
| Paclitaxel | 96.4 ± 6.3 | 99.3 ± 8.8 | |

*N* = 27
[a]95 % confidence interval

Also, the incorporation of an internal standard contributed to better recovery percentages (accuracy 80–120 %) and repeatability and reproducibility (precision ≤2 % of RSD) when processing and extracting field wipe samples.

Furthermore, solid-phase extraction for sample enrichment was successfully performed achieving tenfold concentration factors. In accordance, the method was able to detect concentration levels as low as 0.02 ng/cm$^2$ (i.e., IF 0.02 ng/cm$^2$, CP 0.1 ng/cm$^2$, and PX 0.03 ng/cm$^2$), which are comparable to those provided by LC-MS and GC-MS methods. For example, limits of detection from varied environmental monitoring studies reported in the work of Turci et al. (2003) ranged from 0.01 to 0.02 ng/cm$^2$ for CP (GC-MS), 0.01 ng/cm$^2$ for IF (LC-MS), and 0.1 ng/cm$^2$ for PX (LC-MS). Similarly, Pretty et al. (2010) described these values for the same drugs (i.e., IF and CP 0.1 ng/cm$^2$ and PX 0.07 ng/cm$^2$). At this time, the study did not include any LC-MS test for comparing sensitivity levels.

As for LOQs, there are fewer articles involving environmental monitoring studies where these values were reported apart from LODs (Berruyer et al. 2015; Guillemette et al. 2014; Bobin-Dubigeon et al. 2013; Castiglia et al. 2008; Acampora et al. 2005; Hedmer et al. 2005). From an analytical stand point, it is important to differentiate between reporting environmental contamination levels as above LOD and LOQ. In theory, samples above LOQ should be reported as those that are accurately quantifiable by any validated analytical method (Connor and McDiarmid 2006; FDA Guidance for Industry and Bioanalytical Method 2001). However, from an occupational safety scenario, any level above LOD should be reported as such, given the importance of detecting traces of these highly toxic ANDs in the workplace when aiming to reduce unnecessary occupational exposures among health-care workers.

Additionally, SPE cartridges ease sample storage in the event that samples might not be analyzed immediately or in case that specimens need to be shipped to other research facilities for a more complete analysis, thus providing a safer way to handle wipe samples containing HDs during transportation.

## Conclusions

A more accessible liquid chromatography method was validated to quantitatively determine ifosfamide, cyclophosphamide, and paclitaxel in workplace wipe samples collected from oncology health-care settings. The analytical method was demonstrated to have adequate validation parameters, including linearity, sensitivity, accuracy, and precision. These analytical features make the proposed

**Table 6** Wipe sample extraction recoveries (accuracy)

| Antineoplastic drug | Type of sample | Recovery interval (%) | Mean recovery and (RSD) (%) |
|---|---|---|---|
| Ifosfamide | LCS | 90.5–111.8 | 98.8 (5.6) |
| | PQC | 85.2–115.0 | 95.7 (8.1) |
| | PQC + SPE | 80.3–107.9 | 96.2 (10.9) |
| Cyclophosphamide | LCS | 93.0–104.6 | 98.5 (7.9) |
| | PQC | 91.9–106.7 | 94.9 (8.5) |
| | PQC + SPE | 87.3–103.8 | 93.5 (12.8) |
| Paclitaxel | LCS | 89.3–115.6 | 108.2 (10.1) |
| | PQC | 83.4–108.8 | 92.7 (9.8) |
| | PQC + SPE | 79.8–113.0 | 88.7 (7.3) |

*LCS* laboratory control sample, *PQC* performance quality control sample, *SPE* solid-phase extraction, *RSD* relative standard deviation

**Table 7** Wipe sample extraction repeatability and reproducibility (precision)

| Antineoplastic drug | Type of sample | Relative standard deviation (%) | |
|---|---|---|---|
| | | Intra-day[a] | Inter-day[b] |
| Ifosfamide | LCS | 1.6 | 1.3 |
| | PQC | 1.9 | 2.0 |
| | PQC + SPE | 1.7 | 2.1[c] |
| Cyclophosphamide | LCS | 1.4 | 1.9 |
| | PQC | 2.2[c] | 1.8 |
| | PQC + SPE | 1.5 | 1.7 |
| Paclitaxel | LCS | 1.5 | 1.8 |
| | PQC | 1.9 | 2.0 |
| | PQC + SPE | 1.7 | 2.3[c] |

*LCS* laboratory control sample, *PQC* performance quality control sample, *SPE* solid-phase extraction
[a]Analyzed on the same day (*N* = 3)
[b]Analyzed on five different days (*N* = 15)
[c]Values out of acceptance criterion

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analytical method an excellent alternative to be considered when assessment of occupational risks associated with antineoplastic drug exposures among health-care workers is required, particularly in non-high-income countries when the state-of-the-art analytical technology may be unavailable or unaffordable for health-care settings or Ministries of Health laboratories.

The more accessible chromatographic method was successfully applied to the evaluation of workplace contamination generated by the handling of antineoplastic drugs in oncology health-care settings with limited resources (data not shown).

### Competing interests
The authors declare that they have no competing interests.

### Authors' contributions
CMR as the main author performed the study design, carried out all experiments, and participated of data interpretation and manuscript elaboration. KS contributed to the data analysis and manuscript preparation. MM articulated the realization of the research and participated of the manuscript's elaboration. All authors have read and approved the final manuscript.

### Author details
[1]Department of Pharmacy, School of Pharmacy, University of Concepcion, Barrio Universitario S/N, Concepcion 3349001, Chile. [2]Division of Occupational and Environmental Medicine, School of Medicine, University of Maryland, 11 South Paca Street, Suite 200, Baltimore, MD 21201, USA.

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