



HAL
open science

A fully validated simple new method for environmental monitoring by surface sampling for cytotoxics

E. Rossignol, M.B. Amiand, J. Sorrieul, J.M. Bard, C. Bobin-Dubigeon

► To cite this version:

E. Rossignol, M.B. Amiand, J. Sorrieul, J.M. Bard, C. Bobin-Dubigeon. A fully validated simple new method for environmental monitoring by surface sampling for cytotoxics. *Journal of Pharmacological and Toxicological Methods*, 2020, 101, pp.106652 -. 10.1016/j.vascn.2019.106652 . hal-03488936

HAL Id: hal-03488936

<https://hal.science/hal-03488936>

Submitted on 21 Jul 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

A full validated simple new method for environmental monitoring by surface sampling for cytotoxics

E Rossignol^a, MB Amiard^a, J Sorrieul, Pr JM Bard^{a,b} Dr C Bobin-Dubigeon^{a,b}

^aICO René Gauducheau, Bd J Monod 44805 Nantes Saint Herblain Cedex, France

^bUniversité de Nantes Faculté de Pharmacie, EA 2160 MMS, IUML FR3473 CNRS

1 rue Gaston Veil, 44000 Nantes, France

Corresponding author at:

Department of Biopathology ICO René Gauducheau, Bd J Monod 44805 Nantes Saint Herblain Cedex,

France Tel: 00 33 02 40 67 99 60; Fax: 00 33 02 40 67 97 62

1 Introduction

Despite spectacular improvement in cancer treatments since two decades, cytotoxic chemotherapies remain often an important step in the cancer patient management.

Antineoplastic drugs are largely handled by healthcare workers in hospitals around the world, exposing them to a risk of toxicity. Briefly, it is well documented that anticancer cytotoxics are recognized as carcinogens and genotoxics [1,2]. Many of these agents are classified by the IARC Monographs [3] in either Group 1 as Carcinogenic to humans or Group 2 as probably or possibly carcinogenic to humans, with the exception of 5FU which belongs to group 3 corresponding to compounds with inadequate evidence of carcinogenicity. Moreover, more than 75% of healthcare according to [4] were women, with dramatic consequence of genotoxicity.

The cytotoxic exposure of health workers could be performed by different routes. Dermal exposure could be considered as the most likely way of exposure [5–8]. However inhalation, should also be taken into account with some specific chemotherapy administration, such as PIPAC with platinum drugs [9].

Conversely to specific anticancer antibodies or tyrosine kinase inhibitors, cytotoxic compounds are not specific to cancer cells, but also interact with normal cells, explaining most of the side effects [10]. 5-Fluorouracil, like gemcitabine, belongs to antimetabolite class with a structural analogy to pyrimidic nucleotides, inducing major enzymatic disturbances (thymidilate synthase for example) leading to the cytotoxicity. Doxorubicin (or Adriamycin) and Epirubicin are largely used compounds, also known as “anthracycline” with multiple mechanisms of action on cells, such as inhibition of topoisomerase II. Among alkylating agents, cyclophosphamide and ifosfamide belong to oxazaphosphorine class. Through active metabolites, by crosslinking DNA, the ability of cancer cells to proliferate is reduced and pro-apoptotic pathways are activated [8].

To limit these environmental exposure risks, individual and collective protections are necessary, from the production units of cytotoxic solution to the patient’s bedside, to respect national [11] and international guidelines

[12]. For example, the use of pressure isolator [13] or closed-system transfer device [14,15] in compounding unit, drastically reduced the contamination levels, as described[16] .

Beside these protective equipments, it seems necessary to perform an environmental monitoring for exposed healthcare workers, by quantifying antineoplastic drugs in the environment. A recent review [17] described the main points of environmental monitoring, especially focused on surface sampling.

Despite the absence of harmonization of threshold surface contamination level, many authors have developed analytical methods to quantify specific molecules as surrogate markers of chemical contamination. According to the studied molecules, the analytical tools for the environmental monitoring should be adapted. Platinum derivatives contamination had been studied with atomic absorption spectroscopy [18], voltammetry [19] or ICP-MS [9][20] and mostly liquid chromatography [14–16], or more recently UPLC [24] were the main separative chosen methods, with UV[25] or MS/MS[21,24,26–29] detection, for a large part of antineoplastic drugs.

In view of future systematic environment monitoring exposure of cytotoxic, we developed a method to quantify 5FU, Gemcitabine (GEM), Epirubicin (EPI), Doxorubicin (DOXO), Cyclophosphamide (CP) and Ifosfamide (IF) in surface sampling. The different cytotoxics were chosen according to the local activities specificity of our hospitals. After the surface wiping with Whatman paper, this method involved a SPE concentration. The validation procedure, according to the international guidances, was fully successfully performed.

2 Materials and methods

2.1 Chemicals and reagents

LCMS-grade methanol and acetonitrile and Whatman[®] paper filter (55-mm diameter ash-less cellulose circle) were purchased from VWR[®] (Strasbourg, France). Acetic acid was obtained from Merck[®] (Fontenay-sous-Bois, France). Atoll XC 100/3, XTREM CAPACITY (Interchim, France) was purchased from Interchim (Montluçon, France).

Internal standards (or IS: [¹³C,²H₃]-doxorubicin used both for DOXO and EPI, [²H₈]-Cyclophosphamide, [²H₈]-Ifosfamide) were purchased from AlsaChim[®] (Illkirch, France). 5-Bromouracil (5BR), used as IS for 5FU and gemcitabine IS, was obtained from Sigma Aldrich[®] (St Quentin Fallavier, France). The method was developed

1 with commercial cytotoxic drugs (Table 1). Desionized water was obtained from Millipore by Milli Q system (18.2
2 Mohm.cm).

3 **2.2 Preparation of calibrators and quality control samples**

4 Commercial cytotoxic vials were used to prepare calibrators and quality control samples (200 mg/100 mL from
5 Medac , for EPI; 2000 mg/50 mL and 1000 mg/50 mL from Baxter, for IF and CP, respectively; 100 mg/mL from
6 Intas, for GEM; 50 mg/25 mL from Teva, for DOXO; and 50 mg/mL from Accord, for 5FU. Stock solutions of
7 studied cytotoxic molecules were prepared independently at 1 mg/mL in methanol:water 70:30 with acetic acid
8 (1%), and frozen at -20°C. The solutions were extemporaneously diluted and spiked over the filters to yield the
9 mixed calibrator amounts: 200, 100, 50, 25, 12.5, 2.5 ng (5FU, EPI and DOXO) and 40, 20, 5, 2.5, 1, 0.2 ng (CP,
10 IF and GEM).

11 For quality control (QC) samples, independent stock solutions were prepared as above, to yield the following
12 amount/filter: 150, 75, 10, 2.5 ng of 5FU, DOXO and EPI and 30, 4, 0.4 and 0.2 ng for CP, IF and GEM for QC
13 High, Medium, Low and LLOQ, respectively. All the calibrators and QC filters were stored at -80°C. Internal
14 standard (IS) solution was extemporaneously diluted to obtain final amount in filter 0.200, 0.375, 0.187 and 0.006
15 ng for 5BR, [¹³C, ²H₃]-DOXO, [²H₈]-CP and [²H₈]-IF, respectively.

16 **2.3 Surface sampling procedure**

17 To assess surface contamination, 55-mm diameter ash-less cellulose circle filters (Whatman[®]) wetted with about
18 400 µL of sterilized water were used on a delimited surface (10X10 cm). Each sampling area was wiped once,
19 using one face of the wetted filter, and a second time with a dry paper filter in the same area. After sampling, the
20 two filters were carefully frozen in 50 mL falcon tube at -20°C, until analysis, **according the following conditions.**

21 **2.4 Analytical conditions**

22 The method was developed and adapted from previous published data [28]. UPLC-MS/MS analysis was performed
23 using an Acquity UPLC H-Class System coupled to a Xevo TQD tandem mass spectrometer (Waters©). HSS T3
24 analytical column (2.1 x 50 mm; 1.8 µm) was used to chromatographically separate molecules. Multiple ion
25 monitoring chromatograms were acquired and analysed using Masslynx 4.1 software (Waters ©).
26

1 Frozen samples were thawed at room temperature (25 min). IS solution was spiked on filter (25 μ L) and acetic acid
2 (1 %- 15 mL) were added, mixed for 20 min and extracted by solid-phase extraction (SPE) Atoll XC 100/3, using
3 the following procedure: (i) conditioning the cartridge with 2 mL of methanol, followed by 2 mL of desionised
4 water; (ii) loading the samples prepared; (iii) drying for 25 min under 10mbar; and (iv) eluting with 1800 μ L of
5 methanol and evaporating for 60 min at 45°C. Then, 200 μ L of acetic acid 1% was added to samples and mixed
6 before transfer in vials for injection (7 μ L).

7 The mobile phase flow was set at 0.5 mL/min and consisted of water:acetic acid (100:0.5 v:v) (A) and
8 acetonitrile:acetic acid (100:0.5 v:v) (B) gradient. The elution was performed with a non-linear gradient from 0%
9 to 20% B (0–1.5 min), then an increase up to 30% B (1.5–4 min) maintained 1 min, and the re-equilibration step to
10 the initial conditions (100% A) was performed from 5.2 to 6.5 min.

11 The temperatures were set at 10°C and 40°C for the autosampler and for the column, respectively. Retention times
12 are listed in Table 2. Tandem mass spectrometry was performed in the positive ion electrospray ionization mode,
13 under following conditions: capillary voltage 3kV, desolvation temperature 500°C, desolvation gas flow
14 (nitrogen) 1200 L/h, source temperature 120°C. The electrospray source temperature was set at 120°C and the
15 dwell times were 0.01 sec. Detection was accomplished in multiple reactions monitoring mode, using argon as
16 collision gas. MS/MS Transitions are detailed in Table 2. MS/MS settings are presented in Table 2.

18 2.5 Validation procedure

19 A full validation procedure was performed, including selectivity, linearity, within-run and between-run precision
20 and accuracy, recoveries of analytes, stability after sample preparation, limit of detection (LOD) and lower limit of
21 quantification (LLOQ). The dilution integrity usually evaluated in validation procedures was not suitable in this
22 context.

23 Calibration standards of seven levels (including blank) and sets of QC samples (four concentrations: QCLLOQ
24 QCL, QCM and QCH) were prepared. Six runs were evaluated according to acceptance criteria as described in the
25 US FDA Guidance of Industry entitled “Bioanalytical Method Validation” [31]. The validation process was in
26 agreement with the EMEA guidance [32].

2.5.1 Selectivity and specificity

In order to evaluate selectivity, a blank sample was tested at each run. In the other hand, six cytotoxics mainly used in production unit (etoposide, cytarabin, cisplatin, irinotecan, docetaxel and methotrexate) were added (100 ng) to QCM samples in duplicate, before the SPE procedure, to check for the absence of interfering peaks.

2.5.2 Calibration curve and sample quantification

The peak area ratios of the molecules of interest to respective internal standards were analyzed by weighted linear regression ($1/x^2$) to estimate the slope, intercept and correlation coefficient of the calibration curve. Standard curves in each analytical run were used to calculate the QC concentrations.

2.5.3 Intra-day and inter-day precision and accuracy

Intra-day precision and accuracy were determined with four different concentrations of QC (QCLOQ, QCL, QCM and QCH) in triplicate, at each run. Precision was expressed as the % relative standard deviation (RSD %) of peak area ratios for the triplicate of each QC. Accuracy was evaluated by calculating the concentration of each QC, using the calibration curve that was run on the same day, and by determining the relative error (R.E. %) of the measurement.

To determine inter-day precision and accuracy, QC (n=4 concentrations) were analyzed on six separate days. Precision was expressed as the C.V. or R.S.D. % for each level of concentration of each QC. Accuracy was evaluated by calculating the percentage difference between the expected concentration and the mean concentration of each QC. Limits of acceptable intra- and inter-day precision and accuracy were set at R.S.D. % < 15 and $\pm 15\%$ deviation from the expected, respectively except for the LLOQ, which was set at R.S.D. % < 20 and $\pm 20\%$ deviation.

2.5.4 Repeatability

The repeatability was performed by analyzing 7 QCH and 7 QCL, after extraction in a single run, without experiment variability (same operator, same reagents, and same calibration). The repeatability, expressed as a coefficient of variation of the measured concentrations (n=30), must be within $\pm 15\%$.

2.5.5 Limit of quantification and detection

The limit of detection (LOD) was set as the lowest concentration of the analytes that could be detected with a signal-to-noise ratio of 3:1. The limit of quantification (LOQ) was defined as the lowest concentration of the calibration samples that could be quantified with an acceptable level of precision (R.S.D. % < 20%) and accuracy (R.E. \pm 20%). LOQ samples were analyzed in triplicate and analyzed as unknown samples, on six different days.

2.5.6 Recovery from filter and mass spectrometric matrix effects

The extraction efficiency and matrix effects for the studied cytotoxics and internal standards added to the filters were determined at four concentrations (QCLOQ, QCL, QCM and QCH concentrations) in triplicate. The mass spectrometric matrix effect, evaluated through the mean relative ionization recovery for the analytes, was calculated as the percentage of the response obtained for extracted blank samples spiked with analytes, relative to the response obtained for analytes, spiked directly in the injection solvent (acetic acid 1%). The global recovery (R %) was evaluated in one run, by comparing the peak area obtained for the 4 QC samples (QCH, QCM, QCL and QCLLOQ, n=3) after extraction with spiked solvent samples (acetic acid 1%) at the same concentrations.

In agreement with validation procedure, blank matrix was injected three times after three injections of QCH in order to evaluate the carry over. This procedure was performed 5 times. The carry-over was evaluated for each compound, including internal standards.

2.5.7 Stability

Long-term stability was studied with 6 QC, kept at -20°C for 6, 12 and 24 months. The effect of Freeze thaw cycles was established on 4 QC. Samples were considered to be stable, if relative deviation is \pm 15% compared to freshly made QC.

Autosampler stability testing were performed on QCL and QCH samples in triplicate kept at 10°C for 12-24h. Samples were considered to be stable when 85–115% of the initial concentrations were found.

3 Results and discussion

3.1 Analytical conditions

1 The environmental monitoring of cytotoxic contamination was performed by choosing different molecules as
2 surrogate markers of contamination. Although 5FU was not so toxic (Class 3 of IARC monography), this cytotoxic,
3 since 50 years, remains one of the most used. Therefore the molecules were chosen to range a large panel of
4 pharmacological classes. Some anti-cancer drugs are administered by oral route (such tyrosine kinase inhibitors or
5 hormonotherapy). It is therefore not necessary to include these molecules to evaluate occupational exposure in
6 preparation areas.

7 The extraction was performed successfully by SPE extraction using Atoll XTREM Capacity. This cartridge was
8 chosen because of its efficiency to extract a large range of molecules from polar weak acid hydrophilic species
9 (such as 5FU) to more lipophilic compounds (DOXO). SPE separation is widely used to study cytotoxics in
10 environmental samples (wastewater and hospital effluents for example)[33].

11 Under optimized UPLC-MS/MS conditions, 5-FU, GEM, IF, CP, DOXO and EPI were separated with retention
12 times 0.59, 0.98, 3.56, 3.70, 3.86 and 4.08 min, respectively (Figure 1). The gradient allows to separate all the
13 studied compounds in less than 8 min. Our method is less time consuming than previous published method [24].
14 Conversely to previous method with a unique molecule, four specific internal standards have been used [23].

15 The chosen column (HSS T3) to separate our analytes could easily separate polar and non-polar compounds with
16 acceptable shape of chromatograms (Figure 1). MS/MS transitions in our method were closed to those previously
17 described [22,23,33].

18 Wipe samples were performed with cellulose filters in delimited rubber surface. Different wiping papers have been
19 studied in previous studies [34], and according to these experiments, the best recovery values were achieved with
20 whatman paper. Our experimental procedure was close previously published data [23,36] including optimal
21 performance with FA. However, conversely to previous data using aqueous pH3 solution [37], water/methanol [38] ,
22 ethyl acetate/methanol [24] or FA/acetonitrile [23], we have chosen to exclude the use of organic solvent to limit
23 inhalation exposure to lab technician, explaining, in part, low global recovery % of our analytes (Table 4).
24 However, our limits of detection remain very interesting compared to the previous published data [36,38] (see
25 above paragraph).

3.2 Validation process

3.2.1 Specificity and selectivity

The retention of times of the analytes and internal standards for all validated runs (n=6) remained stable (R.S.D < 1.5 %). The area of studied cytotoxics were not modified by the presence of different cytotoxic contaminants, tested at the final dose of 100 ng, proving the specificity of the method [39].

3.2.2 Limit of quantification and detection

The lowest LOQ per wipe (surface 10 X10 cm²) were 2.5 ng (25 pg/cm²) for 5FU, DOXO and EPI and were 0.2 ng per wipe (2 pg/cm²) for CP, IF and GEM. The LOD were 0.125 ng (1.25 pg/cm²), 0.5 ng (5 pg/cm²), 0.02 ng (0.2 pg/cm²), 0.04 ng (0.4 pg/cm²) and 0.01 ng (0.2 pg/cm²) for 5FU and DOXO, EPI, CP, IF and for GEM, respectively. The method performances are in the range of previous method, with for example a LOQ for CP about 2 pg/cm² vs 3.7 and 5 pg/cm² respectively for [21,39]. However, it is difficult to compare analytical method each other, as no consensual units of measurement for LOD and LOQ have been defined. Like suggested [17], the expressing LOD and LOQ and surface contamination in pg or ng/cm² should be the best unit. For environmental monitoring the lowest possible limit of detection should be obtained, however a safety effect level for cytotoxics exposure could be precisely defined. As the level of cytotoxic exposure should be as low as possible, we tried with our method to develop the lowest level of quantification. The choice of such strategy has been applied in a large Italian study [38], it has allowed to improve the rules of preparing and administering cytotoxics in Italian hospital.

Different studies suggested technical guidance values based on 50th [41], 75th and 90th percentiles of positive contaminated samples. According to Sessink [36], surface contamination is accepted to a certain level. A threshold of CP surface contamination of 0.1 ng/cm² could be accepted. Between 0.1 to 10 ng/cm², the risk estimate must be monitored within 3 to 6 months. Up to 10 ng/cm² of CP in wiping sample, protection measures such as personal protection, ventilation or specific equipment must be recommended. In regard to these recommendations, our method is suitable to monitor occupational exposure, even in taken into account the low recoveries especially for lipophilic molecules.

3.2.3 Linearity

The calibration curves proved to be linear over the concentration range of 2.5 to 200 ng per wipe (25 to 2000 pg/cm²) for 5FU, DOXO and EPI and 0.2 to 40 ng per wipe (2 to 400 pg/cm²) for CP, IF and GEM when evaluated by weighted (1/x²) linear regression. For the validation the criterion of RE and RSD of less than 15 % was accepted (Table 3). The

1 results of the lowest standard point were -0.7 % and 1.0 %; 1.0 % and 1.3 %; 0.4 % and 1.5 %; -1.0 % and 0.8 %; -1.1 %
2 and 0.7%; -0.4 % and 1.1 % for R.E. and R.S.D., for 5FU, DOXO, EPI, CP, IF and GEM, respectively. For each
3 calibration of our six compounds, the regression coefficients were > 0.9912. As our reference surface was 100 cm², the
4 contamination could easily be expressed in pg/cm² as it is currently recommended [34].rather than in ng/ml like it is the
5 case for different methods [24,34],

6 **3.2.4 Imprecision and inaccuracy**

7 QC samples at different concentrations were used to determine within-run and between-run precision and accuracy
8 were determined with QC samples, as described in the experimental section. Data for within-run and between-run
9 precision and accuracy of the method are presented in Table 4.

10 Within-run imprecision ranged between 8.3 and 16.9 % (LLOQ), 7.6 and 11.7 %, 11.4 and 14.9 %, 6.3 and 11.8 %;
11 4.5 and 13.7 %; 7.3 and 16.5 % (LLOQ) for 5FU, DOXO, EPI, CP, IF and GEM respectively. Between-run
12 precision ranged between 11.3 to 18.1 % (LLOQ); 6.6 to 10.6 %; 10.6 to 14.2 %; 6.9 to 19.9 % (LLOQ); 4.7 to
13 16.4 % (LLOQ) and 7.5 to 15.1 % (LLOQ) and the range of accuracy was -6.7 to -0.7 %; -10.9 to 1.1 %; -9.0 to 2.9
14 %; -7.7 to 1.1 %; -2.5 to 4.5 % and -6.3 to 1.6 % for 5FU, DOXO, EPI, CP, IF and GEM, respectively. The
15 obtained values are in agreement with validation acceptance [39]. **The CV of retention times for all the analytes
16 were less than 1%, except for GEM CV less than 1.5 %, demonstrating the robustness of the method.**

17 **3.2.5 Recovery from samples**

18 Table 5 summarizes extraction recovery %, ionization recovery % and global recovery expressed as process efficiency
19 %recovery. The mean relative ionization recovery for the studied analytes and their respective internal standards ranged
20 between 98 ± 6 % and 105 ± 4 %.The mean percent of global recoveries from filters were also evaluated and ranged
21 between 14 ± 2 % (for EPI) and 83 ± 6.8 % (IF). These large recoveries must be taken into account to express the final
22 surface contamination, individually for each cytotoxic. This high variability of total recovery could be explained by a
23 large diversity of physico-chemical characteristics of our pooled analytes, from highly polar (5FU) to less polar
24 molecules such as DOXO or EPI

25 The carry-over for all the studied compounds and internal standard was acceptable as it was estimated to be less than 2.0
26 %.

3.2.6 Stability

The results of stability testing on extracted samples are summarized in Table 6. The extracted solutions were stable for at least 24 hours when kept in the instrument rack inside the auto sampler, maintained at 15 °C, as the estimated loss of concentration is lower than 15% (extracted short term stability), confirming the good stability of our extracts. As previously published works [34,43], it is necessary to analyze sample within 24h after thawing. Samples were considered to be stable after 24months at -20°C as C.V % were less than 8.0 %.

3.3 Environmental sampling

In order to evaluate our method in “real life”, environmental samples were performed in different locations in french hospitals. The wiping samples were collected in preparation areas inside Biological Safety Cabinets (BSC), and outside BSC in a first hospital. The surface contamination in administration areas was also explored in different positions such as floor bed patient and nurse gloves in a second french hospital. The levels of extracted contamination from the wipe samples are presented in Table 7. As expected, the percentage of positive samples in preparation area was highest in the pharmacy BSC, but also in administration area on the floor of patient (9/9 versus 3/5). The consequences of these contaminations are not the same depending the considered area. In particular, health workers in pharmacy BSC could be protected with personal protection (gloves, masks....) and also reduced sources of exposure and close systems. However, these levels of contamination are in agreement with many previous works [33]. 5FU, CP and GEM were the main contaminants quantified in our localizations. Experimental design study should be realized to robustly evaluate occupational exposure to cytotoxics, and confirm this first work. Indeed, the analysis of the few surface samples carried out on floor of room (mean \pm SE: 0.211 \pm 0.18 ng/cm² for CP) suggested an increase in the risk of contamination and the need to implement monitoring within 3 to 6 months, as suggested [42]. Conversely, according to [16], robust studies are necessary to define a relevant threshold of contamination and protective measures,. Our method could be used in such an approach.

4 Conclusion

An UPLC-MS/MS method to evaluate surface contamination by cytotoxic drugs, with six molecules as surrogate markers, was developed and validated. Our affordable method was found to be more sensitive, rapid and selective than

1 previously reported methods. Good accuracy and precision were also successfully achieved. This method has been also
2 used to evaluate the level of occupational exposure in few areas of preparation and administration in hospital. This
3 method appears to be a very interested tool to monitor the cytotoxic risk for health workers, in agreement with EU
4 directives concerning carcinogenic compounds, and should be used in large studies to contribute to define
5 recommendations for environmental cytotoxic contamination
6

7 **Acknowledgement:** This work partially supported by Eli Lilly and Company

8 5 References

- 9 [1] V.J. Cogliano, R. Baan, K. Straif, Y. Grosse, B. Lauby-Secretan, F. El Ghissassi, V. Bouvard, L. Benbrahim-Tallaa,
10 N. Guha, C. Freeman, L. Galichet, C.P. Wild, Preventable Exposures Associated With Human Cancers, *JNCI J.*
11 *Natl. Cancer Inst.* 103 (2011) 1827–1839. <https://doi.org/10.1093/jnci/djr483>.
- 12 [2] M. Sorsa, M. Hämeilä, E. Järviluoma, Handling Anticancer Drugs, *Ann. N. Y. Acad. Sci.* 1076 (2006) 628–634.
13 <https://doi.org/10.1196/annals.1371.008>.
- 14 [3] List of classifications, Volumes 1–123 – IARC, (n.d.). [https://monographs.iarc.fr/list-of-classifications-](https://monographs.iarc.fr/list-of-classifications-volumes/)
15 [volumes/](https://monographs.iarc.fr/list-of-classifications-volumes/) (accessed June 26, 2019).
- 16 [4] S. Bessière, La féminisation des professions de santé en France : données de cadrage, (n.d.) 15.
- 17 [5] Environmental and biological monitoring on an oncology ward during a complete working week | Elsevier
18 Enhanced Reader, (n.d.).
19 [https://reader.elsevier.com/reader/sd/pii/S0378427418301772?token=A89DD5C671982FD143C73F7AAEC0](https://reader.elsevier.com/reader/sd/pii/S0378427418301772?token=A89DD5C671982FD143C73F7AAEC00F7F555BFC325A6F3119D5CFE5EC774474C022128361826798C95034F4079265904A)
20 [0F7F555BFC325A6F3119D5CFE5EC774474C022128361826798C95034F4079265904A](https://reader.elsevier.com/reader/sd/pii/S0378427418301772?token=A89DD5C671982FD143C73F7AAEC00F7F555BFC325A6F3119D5CFE5EC774474C022128361826798C95034F4079265904A) (accessed June 27,
21 2019).
- 22 [6] P.J. Sessink, K.A. Boer, A.P. Scheefhals, R.B. Anzion, R.P. Bos, Occupational exposure to antineoplastic agents
23 at several departments in a hospital. Environmental contamination and excretion of cyclophosphamide and
24 ifosfamide in urine of exposed workers, *Int. Arch. Occup. Environ. Health.* 64 (1992) 105–112.
- 25 [7] M. Hedmer, H. Tinnerberg, A. Axmon, B.A.G. Jönsson, Environmental and biological monitoring of
26 antineoplastic drugs in four workplaces in a Swedish hospital, *Int. Arch. Occup. Environ. Health.* 81 (2008)
27 899–911. <https://doi.org/10.1007/s00420-007-0284-y>.
- 28 [8] R. Turci, C. Sottani, G. Spagnoli, C. Minoia, Biological and environmental monitoring of hospital personnel
29 exposed to antineoplastic agents: a review of analytical methods, *J. Chromatogr. B.* 789 (2003) 169–209.
30 [https://doi.org/10.1016/S1570-0232\(03\)00100-4](https://doi.org/10.1016/S1570-0232(03)00100-4).
- 31 [9] S. Ndaw, O. Hanser, V. Kenepikian, M. Vidal, M. Melczer, A. Remy, A. Robert, N. Bakrin, Occupational
32 exposure to platinum drugs during intraperitoneal chemotherapy. *Biomonitoring and surface*
33 *contamination, Toxicol. Lett.* 298 (2018) 171–176. <https://doi.org/10.1016/j.toxlet.2018.05.031>.
- 34 [10] Overall evaluations of carcinogenicity: an updating of IARC Monographs volumes 1 to 42, *IARC Monogr. Eval.*
35 *Carcinog. Risks Hum. Suppl.* 7 (1987) 1–440.
- 36 [11] Guide-BPF_Mai 2019_4.pdf, (n.d.).
- 37 [12] QuapoS-6.pdf, (n.d.). <https://www.sfpo.com/wp-content/uploads/2018/07/QuapoS-6.pdf> (accessed June
38 26, 2019).
- 39 [13] S. Crauste-Manciet, P.J.M. Sessink, S. Ferrari, J.-Y. Jomier, D. Brossard, Environmental contamination with
40 cytotoxic drugs in healthcare using positive air pressure isolators, *Ann. Occup. Hyg.* 49 (2005) 619–628.
41 <https://doi.org/10.1093/annhyg/mei045>.
- 42 [14] N. Simon, M. Vasseur, M. Pinturaud, M. Soichot, C. Richeval, L. Humbert, M. Lebecque, O. Sidikou, C.
43 Barthelemy, P. Bonnabry, D. Allorge, B. Décaudin, P. Odou, Effectiveness of a Closed-System Transfer Device

- 1 in Reducing Surface Contamination in a New Antineoplastic Drug-Compounding Unit: A Prospective,
2 Controlled, Parallel Study, PLOS ONE. 11 (2016) e0159052. <https://doi.org/10.1371/journal.pone.0159052>.
- 3 [15] N. Vyas, D. Yiannakis, A. Turner, G.J. Sewell, Occupational exposure to anti-cancer drugs: A review of effects
4 of new technology, *J. Oncol. Pharm. Pract. Off. Publ. Int. Soc. Oncol. Pharm. Pract.* 20 (2014) 278–287.
5 <https://doi.org/10.1177/1078155213498630>.
- 6 [16] L.M. Best, C. Tanguay, E. Lennan, M. Korva, J. Bussi eres, K.S. Gurusamy, Closed-system drug-transfer devices
7 plus safe handling of hazardous drugs versus safe handling alone for reducing exposure to infusional
8 hazardous drugs in healthcare staff, *Cochrane Database Syst. Rev.* 2018 (2018).
9 <https://doi.org/10.1002/14651858.CD012860.pub2>.
- 10 [17] P. Marie, C. Christophe, R. Manon, M. Marc, B. Charleric, V. Patrice, Environmental monitoring by surface
11 sampling for cytotoxics: a review, *Environ. Monit. Assess.* 189 (2017) 52. [https://doi.org/10.1007/s10661-](https://doi.org/10.1007/s10661-016-5762-9)
12 [016-5762-9](https://doi.org/10.1007/s10661-016-5762-9).
- 13 [18] L. L e, P. Jolivot, H. Sadou Yaye, A. Rieutord, A. Bellanger, D. Pradeau, S. Barbault-Foucher, E. Caudron,
14 Effectiveness of cleaning of workplace cytotoxic surface, *Int. Arch. Occup. Environ. Health.* (n.d.) 1–9.
15 <https://doi.org/10.1007/s00420-012-0769-1>.
- 16 [19] B. Kopp, R. Schierl, D. Nowak, Evaluation of working practices and surface contamination with antineoplastic
17 drugs in outpatient oncology health care settings, *Int. Arch. Occup. Environ. Health.* 86 (2013) 47–55.
18 <https://doi.org/10.1007/s00420-012-0742-z>.
- 19 [20] M. Federici, J. Raffaelli, D. Paolucci, R. Schierl, I. Kr amer, Efficacy of four cleaning solutions for the
20 decontamination of selected cytotoxic drugs on the different surfaces of an automated compounding
21 system, *J. Occup. Environ. Hyg.* 16 (2019) 6–15. <https://doi.org/10.1080/15459624.2018.1526384>.
- 22 [21] S. Nussbaumer, S. Fleury-Souverain, P. Antinori, F. Sadeghipour, D. Hochstrasser, P. Bonnabry, J.-L. Veuthey,
23 L. Geiser, Simultaneous quantification of ten cytotoxic drugs by a validated LC–ESI–MS/MS method, *Anal.*
24 *Bioanal. Chem.* 398 (2010) 3033–3042. <https://doi.org/10.1007/s00216-010-4243-1>.
- 25 [22] L. Florida, A.M. Pietropaolo, M. Tavazzani, F.M. Rubino, A. Colombi, High-performance liquid
26 chromatography of methotrexate for environmental monitoring of surface contamination in hospital
27 departments and assessment of occupational exposure, *J. Chromatogr. B. Biomed. Sci. App.* 726 (1999) 95–
28 103.
- 29 [23] S. Nussbaumer, L. Geiser, F. Sadeghipour, D. Hochstrasser, P. Bonnabry, J.-L. Veuthey, S. Fleury-Souverain,
30 Wipe sampling procedure coupled to LC–MS/MS analysis for the simultaneous determination of 10 cytotoxic
31 drugs on different surfaces, *Anal. Bioanal. Chem.* 402 (2012) 2499–2509. [https://doi.org/10.1007/s00216-](https://doi.org/10.1007/s00216-011-5157-2)
32 [011-5157-2](https://doi.org/10.1007/s00216-011-5157-2).
- 33 [24] C.B.P. da Silva, I.P. Julio, G.E. Donadel, I. Martins, UPLC-MS/MS method for simultaneous determination of
34 cyclophosphamide, docetaxel, doxorubicin and 5-fluorouracil in surface samples, *J. Pharmacol. Toxicol.*
35 *Methods.* 82 (2016) 68–73. <https://doi.org/10.1016/j.vascn.2016.08.004>.
- 36 [25] T.H. Connor, P.J.M. Sessink, B.R. Harrison, J.R. Pretty, B.G. Peters, R.M. Alfaro, A. Bilos, G. Beckmann, M.R.
37 Bing, L.M. Anderson, R. DeChristoforo, Surface contamination of chemotherapy drug vials and evaluation of
38 new vial-cleaning techniques: Results of three studies, *Am. J. Health. Syst. Pharm.* 62 (2005) 475–484.
39 <https://doi.org/10.1093/ajhp/62.5.475>.
- 40 [26] M. Hedmer, A. Georgiadi, E.R. Bremberg, B.A.G. J nsson, S. Eksborg, Surface contamination of
41 cyclophosphamide packaging and surface contamination with antineoplastic drugs in a hospital pharmacy in
42 Sweden, *Ann. Occup. Hyg.* 49 (2005) 629–637. <https://doi.org/10.1093/annhyg/mei042>.
- 43 [27] J.R. Pretty, T.H. Connor, I. Spasojevic, K.S. Kurtz, J.L. McLaurin, C. B’Hymer, D.G. Debord, Sampling and mass
44 spectrometric analytical methods for five antineoplastic drugs in the healthcare environment, *J. Oncol.*
45 *Pharm. Pract. Off. Publ. Int. Soc. Oncol. Pharm. Pract.* 18 (2012) 23–36.
46 <https://doi.org/10.1177/1078155210389215>.
- 47 [28] N. Simon, M. Vasseur, M. Pinturaud, M. Soichot, C. Richeval, L. Humbert, M. Lebecque, O. Sidikou, C.
48 Barthelemy, P. Bonnabry, D. Allorge, B. D caudin, P. Odou, Effectiveness of a Closed-System Transfer Device
49 in Reducing Surface Contamination in a New Antineoplastic Drug-Compounding Unit: A Prospective,
50 Controlled, Parallel Study, *PLoS One.* 11 (2016) e0159052. <https://doi.org/10.1371/journal.pone.0159052>.

- 1 [29] A UHPLC–MS/MS-based method for the simultaneous monitoring of eight antineoplastic drugs in plasma and
2 urine of exposed healthcare workers | Elsevier Enhanced Reader, (n.d.).
3 <https://doi.org/10.1016/j.jpba.2018.03.024>.
- 4 [30] C. Bobin-Dubigeon, M. Amiand, C. Percheron, C. Audeval, S. Rochard, P. Leynia, J.-M. Bard, A new, validated
5 wipe-sampling procedure coupled to LC-MS analysis for the simultaneous determination of 5-fluorouracil,
6 doxorubicin and cyclophosphamide in surface contamination, *J. Anal. Toxicol.* 37 (2013) 433–439.
7 <https://doi.org/10.1093/jat/bkt045>.
- 8 [31] FDA Guidance for Industry: Analytical Procedures and Methods Validation for Drugs and Biologics - ECA
9 Academy, (n.d.). [https://www.gmp-compliance.org/guidelines/gmp-guideline/fda-guidance-for-industry-](https://www.gmp-compliance.org/guidelines/gmp-guideline/fda-guidance-for-industry-analytical-procedures-and-methods-validation-for-drugs-and-biologics)
10 [analytical-procedures-and-methods-validation-for-drugs-and-biologics](https://www.gmp-compliance.org/guidelines/gmp-guideline/fda-guidance-for-industry-analytical-procedures-and-methods-validation-for-drugs-and-biologics) (accessed October 19, 2018).
- 11 [32] Analytical Procedure Development and Revision of Q2(R1) Analytical Validation : ICH, (n.d.).
12 [http://www.ich.org/products/guidelines/quality/quality-single/article/validation-of-analytical-procedures-](http://www.ich.org/products/guidelines/quality/quality-single/article/validation-of-analytical-procedures-text-and-methodology.html)
13 [text-and-methodology.html](http://www.ich.org/products/guidelines/quality/quality-single/article/validation-of-analytical-procedures-text-and-methodology.html) (accessed June 27, 2019).
- 14 [33] S. Santana-Viera, S. Montesdeoca-Esponda, Z. Sosa-Ferrera, J.J. Santana-Rodríguez, Cytostatic drugs in
15 environmental samples: An update on the extraction and determination procedures, *TrAC Trends Anal.*
16 *Chem.* 80 (2016) 373–386. <https://doi.org/10.1016/j.trac.2015.08.016>.
- 17 [34] N. Negreira, N. Mastroianni, M. López de Alda, D. Barceló, Multianalyte determination of 24 cytostatics and
18 metabolites by liquid chromatography-electrospray-tandem mass spectrometry and study of their stability
19 and optimum storage conditions in aqueous solution, *Talanta.* 116 (2013) 290–299.
20 <https://doi.org/10.1016/j.talanta.2013.04.070>.
- 21 [35] P. Marie, C. Christophe, R. Manon, M. Marc, B. Charleric, V. Patrice, Environmental monitoring by surface
22 sampling for cytotoxics: a review, *Environ. Monit. Assess.* 189 (2017). [https://doi.org/10.1007/s10661-016-](https://doi.org/10.1007/s10661-016-5762-9)
23 [5762-9](https://doi.org/10.1007/s10661-016-5762-9).
- 24 [36] S. Negri, E. Oddone, F. Morandi, C. Sottani, F. Gardinali, A. Lillo, O. Pastoris, V. Dacrema, A. Losurdo, E.
25 Grignani, D. Cottica, M. Imbriani, Validation of cleaning procedures used in an Italian Hospital Pharmacy for
26 antineoplastic drug decontamination: a new tool for industrial hygiene, *Med. Lav.* 110 (2019) 93–101.
27 <https://doi.org/10.23749/mdl.v110i2.8001>.
- 28 [37] T.K. Kiffmeyer, J. Tuerk, M. Hahn, H. Stuetzer, C. Hadtstein, A. Heinemann, U. Eickmann, Application and
29 Assessment of a Regular Environmental Monitoring of the Antineoplastic Drug Contamination Level in
30 Pharmacies - The MEWIP Project, *Ann. Occup. Hyg.* 57 (2013) 444–455.
31 <https://doi.org/10.1093/annhyg/mes081>.
- 32 [38] S. Dugheri, A. Bonari, I. Pompilio, P. Boccalon, D. Tognoni, M. Cecchi, M. Ughi, N. Mucci, G. Arcangeli,
33 Analytical strategies for assessing occupational exposure to antineoplastic drugs in healthcare workplaces,
34 *Med. Pr.* 69 (2018) 589–604. <https://doi.org/10.13075/mp.5893.00724>.
- 35 [39] Guidance validation analytical methods FDA, (n.d.).
36 [http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070107.](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070107.pdf)
37 [pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070107.pdf) (accessed May 3, 2012).
- 38 [40] Kiffmeyer et al. - 2013 - Application and Assessment of a Regular Environmen.pdf, (n.d.).
- 39 [41] R. Schierl, A. Böhlant, D. Nowak, Guidance values for surface monitoring of antineoplastic drugs in German
40 pharmacies, *Ann. Occup. Hyg.* 53 (2009) 703–711. <https://doi.org/10.1093/annhyg/mep050>.
- 41 [42] P. Sessink, Biomonitoring great, but do it the right way!, *J. Oncol. Pharm. Pract. Off. Publ. Int. Soc. Oncol.*
42 *Pharm. Pract.* 25 (2019) 246–247. <https://doi.org/10.1177/1078155218761800>.
- 43 [43] C. Bobin-Dubigeon, M. Amiand, C. Percheron, C. Audeval, S. Rochard, P. Leynia, J.-M. Bard, A New, Validated
44 Wipe-Sampling Procedure Coupled to LC–MS Analysis for the Simultaneous Determination of 5-Fluorouracil,
45 Doxorubicin and Cyclophosphamide in Surface Contamination, *J. Anal. Toxicol.* 37 (2013) 433–439.
46 <https://doi.org/10.1093/jat/bkt045>.
- 47 [44] P.J. Sessink, M.C. Van de Kerkhof, R.B. Anzion, J. Noordhoek, R.P. Bos, Environmental contamination and
48 assessment of exposure to antineoplastic agents by determination of cyclophosphamide in urine of exposed
49 pharmacy technicians: is skin absorption an important exposure route?, *Arch. Environ. Health.* 49 (1994)
50 165–169. <https://doi.org/10.1080/00039896.1994.9940377>.
- 51

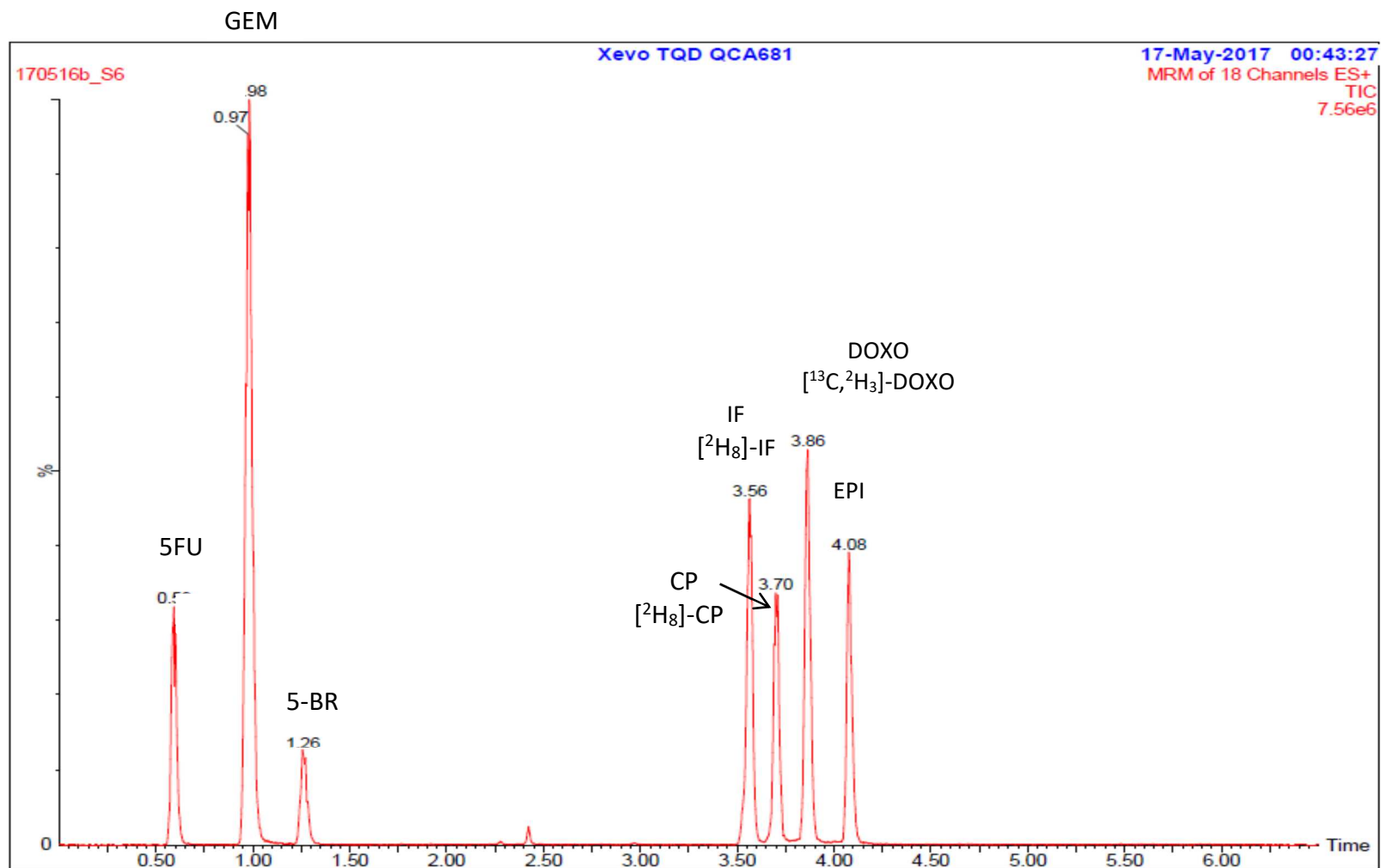
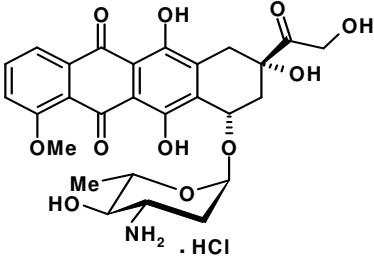
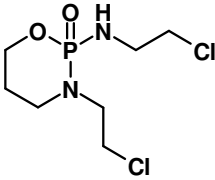
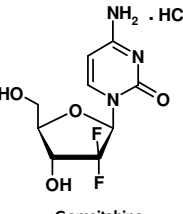
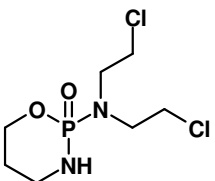
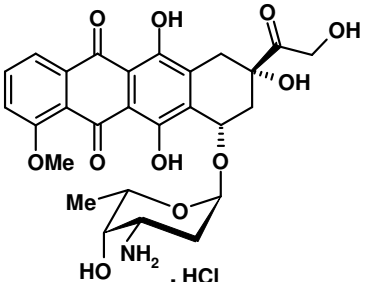


Figure 1

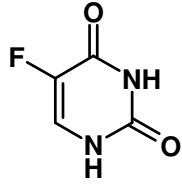
Representative chromatogram spiked filter with cytotoxics : 5FU (200 ng), GEM (40 ng), IF (40 ng), CP (40 ng), DOXO (200 ng) and EPI (200 ng)

Table 1

Structures of studied antineoplastic compounds and References of commercial preparation

	IARC	Main indications	
	Classification		
EPI	 <p style="text-align: center;">Epirubicin</p>	NA	Breast cancer, lung cancer, ovary cancer, stomach cancer, and lymphoma
IF	 <p style="text-align: center;">Ifosfamide</p>	Group 3	lymphomas, sarcoma and advanced forms of solid tumor
GEM	 <p style="text-align: center;">Gemcitabine</p>	NA	Solid tumors
CP	 <p style="text-align: center;">Cyclophosphamide</p>	Group 1	Chronic lymphocytic leukaemia, lymphomas, soft tissue and osteogenic sarcoma, and solid tumours.
DOXO	 <p style="text-align: center;">Doxorubicin</p>	Group 2A	leukaemia, lymphomas, and solid tumours.

5FU



5-Fluorouracil

Group 3

Solid tumours

IARC classification human carcinogenicity Groups: 1 – Carcinogenic to humans; 2A – Probably carcinogenic to humans; 2B – Possibly carcinogenic to humans; 3 - Not classifiable as to its carcinogenicity to humans; and 4 – Probably not carcinogenic to humans.

Abbreviations: NA = not available.

Table 2

Retention times and MS/MS settings for six cytotoxics and internal standards.

Analyte	Retention time (min)	Parent (m/z)	Cone voltage (V)	Daughter (m/z)	Collision energy (eV)	
5FU	0.59	131	35	113.9	<i>Q</i>	15
				57.9	<i>ID</i>	22
GEM	0.98	264	40	112.2	<i>Q</i>	17
				95.2	<i>ID</i>	42
5-Br	1.26	191	40	173.9	<i>Q</i>	18
				117.9	<i>ID</i>	26
CP	3.70	261	45	140.0	<i>Q</i>	22
				105.9	<i>ID</i>	20
IF	3.56	261	40	92.1	<i>Q</i>	27
				153.9	<i>ID</i>	21
IF*	3.56	269	46	93.9	<i>Q</i>	26
				156.0	<i>ID</i>	22
CP*	3.70	269	38	240.8	<i>Q</i>	17
EPI	4.08	544	40	130.1	<i>Q</i>	18
				397.1	<i>ID</i>	14
DOXO	3.86	544	40	397.1	<i>Q</i>	14
				130.1	<i>ID</i>	18
DOXO*	3.86	548	35	401.1	<i>Q</i>	14
				383.0	<i>ID</i>	18

Q: Quantification; *ID*: Identification; *DOXO**: [¹³C,²H₃]-doxorubicin; *CP**: [²H₈]-Cyclophosphamide; *IF**: [²H₈]-Ifosfamide

1 **Table 3**

2 Assayed concentrations of calibration standards of cytotoxics (n= 6 runs)

3

Nominal quantity ng	5FU			DOXO			EPI		
	Assayed concentration			Assayed concentration			Assayed concentration		
	Mean	R.E. (%)	R.S.D. (%)	Mean	R.E. (%)	R.S.D. (%)	Mean	R.E. (%)	R.S.D. (%)
2.5	2.48	-0.7%	1.0%	2.53	1.0%	1.3%	2.51	0.4%	1.5%
12.5	12.90	3.2%	5.2%	11.66	-6.7%	9.4%	12.19	-2.5%	8.2%
25	25.45	1.8%	5.2%	25.31	1.2%	4.7%	25.76	3.0%	5.2%
50	50.11	0.2%	9.3%	48.69	-2.6%	5.3%	46.98	-6.0%	6.8%
100	101.49	1.5%	6.5%	102.28	2.3%	5.2%	102.43	2.4%	5.2%
200	189.61	-5.2%	8.3%	207.37	3.7%	4.7%	205.58	2.8%	6.2%
slope									
r ²									
	CP			IF			GEM		
	Assayed concentration			Assayed concentration			Assayed concentration		
	Mean	R.E. (%)	R.S.D. (%)	Mean	R.E. (%)	R.S.D. (%)	Mean	R.E. (%)	R.S.D. (%)
0.20	0.20	-1.0%	0.8%	0.20	-1.1%	0.7%	0.20	-0.4%	1.1%
1.00	1.04	3.8%	3.9%	1.03	3.3%	4.4%	1.03	2.6%	5.2%
2.50	2.64	5.6%	5.5%	2.60	3.8%	2.6%	2.45	-1.9%	7.6%
5.00	4.97	-0.6%	5.5%	4.98	-0.4%	5.0%	5.01	0.2%	5.6%
20.00	19.82	-0.9%	6.3%	20.12	0.6%	7.7%	20.88	4.4%	5.8%
40.00	37.48	-6.3%	7.3%	37.44	-6.4%	3.8%	38.04	-4.9%	6.9%
slope									
r ²									

4

Table 4

Within-run and between-run precision and accuracy of the quantification 5FU, DOXO, EPI, CP, IF and GEM on wipe samples

	Nominal quantity(ng)	Within-run Imprecision (%)	Between-run Imprecision (%)	Accuracy (%)	95% CI of Inaccuracy (%)
5FU	2.5	16.9	18.1	-0.7	-9.3-6.1
	10	14.3	11.7	2.7	-4.8-5.2
	75	8.3	14.0	-2.1	-4.7-3.8
	150	12.2	11.3	-6.7	-8.9-(-1.3)
DOXO	2.5	11.7	10.6	1.1	-5.0-4.4
	10	8.4	8.8	-10.9	-10.9-(-5.7)
	75	11.1	6.6	-4.6	-7.4-(-1.6)
	150	7.6	9.6	-4.9	-7.6-0.3
EPI	2.5	14.9	14.2	2.9	-4.8-8.1
	10	13.1	14.3	-9.0	-10.8-(0.1)
	75	12.1	10.6	-4.4	-6.9-1.6
	150	11.4	10.9	-1.8	-3.5-4.3
CP	0.22	11.8	19.9	-7.7	-10.7-3.1
	0.88	6.3	11.1	-0.2	-6.7-4.7
	4	10.6	6.9	1.1	-2.0-4.5
	30	9.6	8.8	-2.8	-5.6-3.6
IF	0.22	13.7	16.4	-1.8	-10.6-7.4
	0.88	12.2	8.7	3.9	-1.1-7.6
	4	4.5	4.7	4.5	1.5-5.5
	30	8.7	6.1	-2.5	-5.2-2.8
GEM	0.22	16.5	15.1	-4.8	-8.5-5.3
	0.88	7.3	11.2	1.6	-7.1-1.3
	4	12.5	9.9	1.6	-4.7-3.6
	30	9.6	7.5	-6.3	-7.6-(-1.8)

Table 5Recoveries of analytes expressed as mean \pm standard deviation

Analyte	Extraction recovery %	Ionization recovery %	Process efficiency %
5FU	21 \pm 2 %	98 \pm 8 %	20 \pm 3 %
GEM	54 \pm 8 %	108 \pm 5%	59 \pm 7 %
CP	75 \pm 8 %	105 \pm 4 %	79 \pm 5 %
IF	81 \pm 8 %	103 \pm 4 %	83 \pm 8 %
EPI	14 \pm 2 %	98 \pm 6 %	14 \pm 2 %
DOXO	18 \pm 2 %	98 \pm 5%	18 \pm 2 %

Table 6

Stability of 5FU, DOXO, EPI, CP, IF and GEM on filter after extraction (extracted short term stability) and after Freeze Thaw cycle

Analytes	Nominal quantity (ng)	Extracted short term stability % of residual sample (n =3)	Freeze Thaw cycle stability % of residual sample (n =3)
5FU	10	88	108
	150	90	100
DOXO	10	103	99
	150	95	101
EPI	10	99	91
	150	96	103
CP	0.88	89	102
	30	106	103
IF	0.88	92	91
	30	99	98
GEM	0.88	90	91
	30	99	101

Table 7

Levels of extracted contamination from wipe samples in preparation places and in administration places in two different hospitals

	Contaminated samples	5FU	DOXO	EPI	CP	IF	GEM
Administration places							
Nurse gloves (n=10)	7/10	3.4 ± 5.1	nd	nd	65.1 ± 156.6 0-501.0	0.3 ± 3.9 0-11.3	0.0 ± 0.0 0-0.1
Floor sample beside patient bedroom (n=17)	17/17	1731.0 ± 1678.0 192.0-5336.7	nd	nd	211.7 ± 185.9 14.8-746.2	3.9 ± 3.0 0.36-19.5	106.4 ± 72.3 4.8-1210.9
Preparation places							
Inside BSC (n=9)	9/9	2601.4 ± 7617 0-22913.5	nd	nd	151.3 ± 226.5 0-568.8	64.5 ± 94.8 0-296.1	311.9 ± 535.6 4.2-1430.5
Outside BSC (n=5)	3/5	nd	nd	nd	nd	nd	1.1 ± 1.64 0-3.9

Mean ± SE in pg/cm²; range : min-max; nd= not detected