Evaluation of Occupational Exposure to Antiblastic Drugs in an Italian Hospital Oncological Department

Loredana CASTIGLIA 1, Nadia MIRAGLIA 1, 2, Maria PIERI 1, 2, Angela SIMONELLI 2, Pascale BASILICATA 2, Giuliana GENOVESE 2, Rossella GUADAGNI 2, Antonio ACAMPORA 1, Nicola SANNOLO 2 and Maria Virginia SACAFARTO 3

1Department of Public Medicine and Social Health, University of Naples “Federico II”, 2Department of Experimental Medicine–Labour, Hygiene and Industrial Toxicology Section, Second University of Naples and 3University of Naples “Federico II”–Sanitary Direction, Italy

Abstract: Evaluation of Occupational Exposure to Antiblastic Drugs in an Italian Hospital Oncological Department: Loredana CASTIGLIA, et al. Department of Public Medicine and Social Health, University of Naples “Federico II”, Italy—The determination of the current antiblastic drug contamination levels in an Italian hospital oncology ward was carried out. Statistical evaluation of data aiming to identify potential exposure causes was performed. Cyclophosphamide (CP), ifosfamide (IF) and 5-fluorouracil (5-FU) were determined by wipe tests, extracted with diatomaceous earths and quantified by GC/MSMS or HPLC/UV. Data were analysed with respect to the potential contamination levels of sampled surfaces, and various amounts of handled analyte. χ² tests and Spearman correlation coefficients were calculated. Median concentration levels of 0.086, 0.071, 2.363 µg/dm² were obtained, (CP, IF, 5-FU, respectively). 3.8 and 13.5% of investigated surfaces showed CP and IF concentrations higher than 1 µg/dm² (up to 26.96 µg/dm²) and 13.4% of samples contained 5-FU concentrations in the range 20–208.9 µg/dm². Analytes’ concentration levels were dependent on sampling sites, with significant correlations showing a progressive contamination decrement going from workbenches, floor, hood planes and other surfaces. A diffuse contamination (traces of all the three analytes) was found on all investigated surfaces, even when analytes had not been used during the sampling days. A significant correlation (p=0.303, p=0.001) between the measured analyte concentration and the analyte handled amount was found only in the case of IF. The risk management strategy should be improved, as suggested by the measured and widespread levels of contamination. Since contamination also depends on other factors attributable to working modalities and cleaning procedures, the obtained results suggest that performance of specific training courses as well as scheduling environmental monitoring plans to achieve an actual decrement of the observed contamination levels should be implemented.

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Key words: Occupational exposure, Cyclophosphamide, Ifosfamide, 5-fluorouracil, Statistical evaluation

Many cytostatic drugs commonly used in anticancer therapies display cytotoxic activity and are classified as potentially carcinogenic, mutagenic or teratogenic to humans. The existence of secondary tumour risks due to treatments with these drugs has been confirmed by several studies. Despite different mechanisms of action, antiblastic drugs show a certain grade of cytotoxicity. For instance, cyclophosphamide (CP), can induce primary tumours in healthy subjects handing them, since CP is metabolised to nitrogen mustard, which is responsible for both pharmacological and toxic activities due to its lack of specificity towards tumoral cells. While the appearance of toxic effects is considered “acceptable” in patients in view of possible therapeutic effects, the occurrence of primary tumours in healthy subjects cannot be acceptable. At the end of 1970s Falck et al. first evidenced the occurrence of primary tumours for nurses working without protective measures. While the possible long-term risk for personnel handling antineoplastic drugs has been investigated and mutagenic (micronuclei and chromosomic aberrations) and carcinogenic effects (leukemia and non-Hodgking
lymphoma) have been confirmed, together with damage to the reproductive organs of female nurses (increased risk for spontaneous miscarriage, extraterine pregnancy, congenital defects, infertility, menstrual cycle dysfunctions). Some studies have evidenced a reduced risk when effective protective measures were adopted, so in the last few years the interest of occupational medicine in preventing workers’ health risks related to antiblastic drugs exposure has been increasing and worldwide attempts have been made to prevent exposure. In particular, recent attention has also focused on nursing staff handling antiblastic drugs that have to be administered to patients, and many European Directives (and related National Legislative Decrees and Guidelines) have been issued, aiming to protect nursing personnel potentially exposed to high amounts of various antiblastic drugs on a daily basis. In addition, the need for research on the effectiveness of current control measures on oncology wards and the influence of the levels of training in health and safety measures have been highlighted.

This study aimed to determine the antiblastic drugs concentration levels on surfaces of a drug preparation room of an Italian hospital oncology ward, in order to: i) give researchers dealing with occupational exposure a case study of actual antiblastic drug concentration levels that could be found on workplaces surfaces; and ii) investigate the potential exposure to cytotoxic drugs of oncology ward staff in Italian hospitals, in comparison with concentration levels reported in the literature, which reflect the current pollution levels commonly found internationally.

This study is the first part of a wider project which aims to investigate the effectiveness of organizational measures and training courses on workplace surface contamination on a statistical base. The first part consisted of: a) the definition of the current pollution conditions through the environmental monitoring of workplace surfaces; b) the inferential analysis of the obtained results; and c) information collection about protection equipment, work modalities and training courses attended by nurses. The results of points b) and c) were used to identify potential causes of contamination. The second part of the project is being based on the development of training courses aiming to prevent surface contamination, by submitting in evidence and reducing/removing the pollution causes highlighted by the first part of the project. The third part of the project will involve a new environmental monitoring scheme together with biological monitoring plans in order to verify if better working conditions are achieved.

The monitoring strategy reported here consisted, first of all, in making an on-the-spot inspection of the investigated antiblastic drug preparation room, with two purposes: a) pointing out eventual structural and/or organizational deficiencies; and b) identifying a suitable number of sampling sites that could be representative of the general pollution conditions. Then, data about the amount of each antiblastic drug daily handled were collected, in order to establish which substance could be adopted as a representative exposure marker among the large number of the antiblastic drugs used in the examined oncology ward. Cyclophosphamide (CP), Ifosfamide (IF) and 5-fluorouracil (5-FU) were chosen as representative markers and their concentrations on workplace surfaces were determined by wipe-tests (sampling), GC/MSMS (CP, IF) and HPLC/UV (5-FU) analysis.

Data were elaborated on a statistical basis. The descriptive analysis (concentration ranges, median or mean, dispersion indices etc.) aimed to give a global view of the pollution situation of the examined drug preparation room. Results from the inferential analysis were adopted to evaluate the correctness of working and cleaning modalities, i.e. the effectiveness of formation/information training courses, as well as the actual application of national/international directives about antiblastic drug handling.

Methods

Sampling strategy

General information about protection equipments, working modalities and training courses were obtained by questionnaires given to nurses. The investigated items are reported in Table 1.

The sampling strategy was based on three steps: a) identification of sampling sites representative of contamination through an on-the-spot investigation of the drug preparation room; b) selection of representative markers among the antiblastic drugs commonly used in the examined ward by collecting data about which drugs (type, amount and frequency of preparation) were used each day in a month (March 2006); and c) wipe test sampling from March 30th to April 20th, 2006, of the previously identified surfaces.

1) Sampling sites identification

The on-the-spot investigation found evidence of general disorder in the drug preparation room, that contained various recycle bins and shelves as well as boxes, the surfaces of which were considered. Twenty-three potentially contaminated surfaces were identified and divided into four classes: I, Workbench; II, Floor (in front of the hood); III, Hood Planes (inside the hood); IV, Others (i.e. surfaces such as door handles, storage shelves, transport bin, interphone, boxes, sink). In view of the whole project mentioned above (first part: detailed environmental monitoring; second part: training courses; third part: repetition of environmental monitoring) 5 different sampling sites were identified for classes I, II, and III and 8 surfaces for class IV, so that: a) the global
contamination state of each class could be determined (first project part); and b) the comparison among contamination levels found on different surfaces inside the same class could be used later in order to focus training courses (second part) on correct working modalities (e.g. according to which surface of the workbench and/or the floor was the most contaminated one) and to choose only 1 or 2 sampling sites (among the most contaminated ones) for each class so that routine environmental monitoring strategy could be based on a lesser number of analyses (with cost and time savings).

2) Representative markers
In the investigated ward, the number of daily handled drugs ranged from 1 to 13 (7 different drugs, median value). Among these, cyclophosphamide (CP), ifosfamide (IF) and 5-fluorouracil (5-FU) were chosen as representative markers, following three criteria: carcinogenicity, according to the International Agency of Research on Cancer, IARC\(^4\); daily handled amount; and daily percentage of the handled amount in the total amount of antiblastic drugs used and frequency of use. Table 2 reports data collected over one month, relating to the chosen drugs.

CP is a carcinogenic agent, and its concentrations on workplace surfaces should be as low as possible. However, its use was irregular (7 d out of 31), and consequently, IF and 5-FU, even though they are toxic substances but not carcinogenic ones, were chosen as suitable exposure markers owing to their frequent use in high amounts.

3) Sampling
The sampling procedure (wipe tests) was performed after shift on 15 consecutive working days. Also during the sampling period, data about which drugs were handled were collected. Sampling sites relating to the workbench, hood planes and floor were always sampled, while the

<table>
<thead>
<tr>
<th>Drug</th>
<th>IARC classification</th>
<th>Daily handled amount (median), mg</th>
<th>Daily percentage amount* (median),%</th>
<th>Frequency %#</th>
</tr>
</thead>
<tbody>
<tr>
<td>CP</td>
<td>Group 1: Carcinogenic to humans</td>
<td>1,000</td>
<td>14.3</td>
<td>22.6</td>
</tr>
<tr>
<td>IF</td>
<td>Group 3: Not classifiable as to carcinogenicity in humans</td>
<td>3,000</td>
<td>21.0</td>
<td>41.9</td>
</tr>
<tr>
<td>5-FU</td>
<td>5,000</td>
<td>41.7</td>
<td>77.4</td>
<td></td>
</tr>
</tbody>
</table>

*Percentage of the analyte handled amount with respect to the total amount of antiblastic drugs used. #Frequency: percentage of days in which drugs were used in a month.

Table 1. Summary of information about working practices adopted with respect to Italian Guidelines statements

<table>
<thead>
<tr>
<th>Hospital practices</th>
<th>Italian Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of nurses employed in drug preparation</td>
<td>10</td>
</tr>
<tr>
<td>No. of drug preparations for each nurse</td>
<td>10–20/d</td>
</tr>
</tbody>
</table>

Specific training courses
2 nurses out of 10 employed

Drug transfer to wards
By tray or hand

Hood
Vertical laminar flow

Workbench cleaning frequency and detergents used
Before and after each preparation with water or alcohol

Drug preparation modality
No Luer Lock device was used and needles were not protected during handling

Floor and furniture cleaning:
frequency and detergents used
Before work shift with generic detergents

Individual protective measures
Nurses used powder free latex gloves, specific for antineoplastics (double thickness), without changing them during the work shift; wrapping the needle with sterile gauze

Table 2. Cyclophosphamide, ifosfamide and 5-fluorouracil: carcinogenicity, absolute and relative daily handled amounts, and handling frequencies. Data collected over a month
was dissolved in 100 µl of diethyl ether and CP and IF were derivatized by adding 100 µl of heptafluorobutyric anhydride (Supelco, Bellefonte, PA-USA). After 20 min at 70°C, the solvent was evaporated under a nitrogen stream and the residue was dissolved in 100 µl of isooctane. The other aliquot was solved in 100 µl of the 0.05 M HCOOH utilized for the following quantification of 5-FU by HPLC/UV.

2) Analytes detection and quantification

CP and IF (TP as internal standard) were determined by Gas Chromatography/Tandem Mass Spectrometry (GC/MSMS), by using a TraceGC/PolarisQ and the Xcalibur software, version 1.2 (Thermo, San José, CA, USA). Chromatographic and instrumental conditions were described previously in detail[30].

5-FU (5-CIU as internal standard) was quantified by using a chromatographic column Jupiter C18 (250 x 4.60 mm, 5 µ, 300Å) provided from Phenomenex (St. Torrance, CA, USA) and a modular HPLC/UV system 1100 series (Agilent; Palo Alto, CA, USA), with the following conditions: 0.05 M HCOOH: methanol; flow, 1 ml/min; methanol concentration gradient, 3 min at 0 %, 0–100% in 5 min, 100% for 3 min; absorption wavelength, 265 nm.

Quantitative analyses were based on standard curves obtained by analyzing seven calibration standard samples, prepared as follows. Known amounts of aqueous solutions of cyclophosphamide, ifosfamide (from Baxter, Germany; purity, 95%) and 5-fluorouracil (Sigma-Aldrich, Italy) were added to 1 dm² surfaces of a chemical hood previously cleaned with sodium hypochlorite 5%, in order to have seven analytes concentrations in the range 0.156–10.0 µg/dm², for CP, IF and 0.78 to 50.0 µg/dm² for 5-FU. Then the surfaces were wiped and the samples were processed as described above. Blank wipe samples (without the addition of any analytes) and zero-point samples (prepared by adding internal standards only) were used to evaluate the specificity and the limits of detection and quantification of the methods. Calibration curves, blank wipe samples and zero-point samples were prepared at least three times and were also used to evaluate the accuracy and the precision of the method.

Statistical analysis

Statistical analyses were carried out by using the SPSS software, version 12.0.1 for windows (SPSS ITALIA s.r.l. Bologna, Italy). The normality of the frequency distribution of the collected data (surface concentrations of CP, IF and 5-FU) was evaluated by Kolmogorov-Smirnov tests. For the inferential analysis, the dependence and the correlation between the surface class and contamination levels were evaluated by the χ²-test and the Spearman coefficient, respectively, by the asymptotic method and the Monte Carlo exact test.

Concentration data were divided into subdistributions defined by either class of sampling site or amount of handled drugs. Normality tests were again applied by the Kolmogorov-Smirnov test if the number of data in the examined sub-distribution was higher than 30, otherwise by the Shapiro-Wilk test. Since normality was achieved in neither distributions nor sub-distributions (even when logarithmic transformations were applied), quantitative statistical analyses were not performed.

Results

General information

Information on working practices is shown in Table 1, together with Italian guidelines statements[25]. The actual working practices differed from the guideline statements from various points of view: the number of nurses employed in drug preparation was higher and each nurse attended more preparations per day; the latest training course was attended five years ago (it should be yearly), and the cleaning modalities were inappropriate.

Analytical method parameters

Wipe tests, extraction of analytes from gauze and analyte detection were carried out following procedures set up both in our and in other laboratories and reported in the literature[32–34]. Nevertheless, owing to slight differences that were introduced in the procedure, some
Method validation parameters were evaluated according to the experiments and the acceptance criteria reported in literature. All data are reported in Table 3.

Blank wipe samples were used to verify that no quantifiable interfering peaks were present at the retention time of the analytes.

The limit of detection (LOD) and the lower limit of quantification (LLOQ) were determined by analyzing three zero-point samples. LOD and LLOQ were defined as three and five times the standard deviation of the peak areas (noise, in the case of MSMS analyses) detected at the retention time of the analytes of interest.

Accuracy and precision were evaluated by using calibration samples from different preparations as quality control samples; i.e., samples prepared for the construction of the second calibration curve were quantified with the first calibration curve and so on. Table 3 reports the bias of the mean value and of the coefficient of variation (CV) calculated by analyzing seven levels of concentrations for three times (from three different preparations). Both accuracy and precision respected the acceptance criteria for method validation; i.e., the mean value was within 15% of the nominal value and the CV did not exceed 15%.

Analytes recovery and stability data, necessary for the full validation of the analytical methodology, are not reported here, nevertheless their effects were taken into account in the quantification strategy planning, because the quantification of analytes was carried out: i) by adding the internal standards immediately after the wiping (before storing samples); ii) by preparing calibration curve samples in the examined environmental matrix and by treating them in the same way as unknown samples; i.e. they followed the same freezing/thawing cycle when stored and were stored for the same time as unknown samples before analysis; and iii) by reporting analytes responses as relative area with respect to the internal standard. In this way calibration curve samples used for the quantification of analytes present in the unknown samples underwent the same matrix effect. Also the determined amount of analytes did not have to be normalized for recovery and/or stability percentage.

Descriptive analysis: concentrations of cyclophosphamide, ifosfamide and 5-fluorouracil

Distribution functions were not normal even when data were transformed to the logarithmic scale. The 25th percentile (µg/dm²) of analysed samples were traces, absent and traces for CP, IF and 5-FU, respectively. The 50th percentile (µg/dm²) of analysed sampled were 0.086, 0.100 and 2.363 for CP, IF and 5-FU, respectively. The 75th percentile (µg/dm²) of analysed sampled were 0.156, 0.973 and 8.215 for CP, IF and 5-FU, respectively.

A better comprehension of the contamination state of the investigated surfaces is given by dividing concentration ranges into various levels. Different concentration levels were defined according to each analyte because, within the 249 analyzed samples, the obtained analyte concentrations were lower for CP, slightly higher for IF and distinctly higher in the case of 5-FU. Table 4 reports the percentages of samples for each concentration level.

Inferential analysis

Inferential analysis was divided into two parts: i) identification of surfaces with higher levels of contamination; and ii) correlations between handled amount of analytes and contamination. Even if the measured analytes’ concentrations represented continuous variables, they were considered categorical ones by using the qualitative variables “concentration levels”, the values of which are defined in Table 4 for each analyte.

It was tested whether analytes’ concentration values were related with: i) the qualitative variable “site class” (whose values are reported in the Methods section); or ii) the qualitative variable “used analytes’ amount” (defined below).

1) Identification of surfaces with higher levels of contamination (i)

Figure 1 shows sample percentage of the variable “concentration levels” with respect to “site classes”. For each panel, the values of the first variable are defined by sectors, while each column represents a site class.

For CP and IF the workbench was the most contaminated, followed by the floor in front of the hood, the hood planes and the other investigated surfaces. At...
the same time, the contamination level decrement was
confirmed by the absence of analytes. The analytes were
mainly not found on other surfaces, and the “not detected”
sector area decreased from others to workbench (Fig. 1,
top and middle panels). High contamination levels of 5-
FU were found in all site classes, above all on the
workbench, where concentrations exceed 50 µg/dm² (Fig.
1, bottom panel, last sector). In contrast with the other
two drugs, contamination levels of other surfaces were
considerably high (last two sectors). Finally, all three
analytes were detected as traces on all surfaces, suggesting
a widespread and constant contamination.

Table 5 reports the χ²-test results (Chi) and the
Spearman correlation coefficient (ρs) calculated for the
qualitative variables.

Chi-statistics values indicate the dependency of sample
percentage of contamination level by site class and a
significant dependency for all the three analytes was
found. Despite significant p values being obtained for
all the three investigated analytes, in the case of CP the
strength of correlation was too low for further speculation.
In contrast, Spearman coefficients obtained for IF and 5-
FU made it possible to define a trend of contamination
going from the workbench towards the other surfaces.
The negative coefficient values confirm the inverse
correlation graphically described above. It must be noted
that the strength (and the significance) of correlation
strictly depends on the ordination of the levels of the
“site classes” variable. The order reported here (i.e. the
definition of workbenches as the first level, floor as the
second one and so on) gave the strongest correlations.

2) Correlation between handled amount of analytes and
contamination (ii)

The amount of each analyte handled during the
sampling period was recorded. The amount (mg) of 5-
FU handled in 15 d varied in a wide range, whereas the
quantities of CP and IF used in therapy were always the

Table 4. Analytes concentrations levels on workplace surfaces

<table>
<thead>
<tr>
<th>Levels</th>
<th>CP</th>
<th>IF</th>
<th>5-FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conc. ranges µg/dm²</td>
<td>Samples %</td>
<td>Conc. ranges µg/dm²</td>
<td>Samples %</td>
</tr>
<tr>
<td>0*</td>
<td>0</td>
<td>15.2</td>
<td>0</td>
</tr>
<tr>
<td>1†</td>
<td>traces</td>
<td>5.5</td>
<td>traces</td>
</tr>
<tr>
<td>0.02–0.2</td>
<td>55.7</td>
<td>0.10–0.5</td>
<td>11.0</td>
</tr>
<tr>
<td>0.2–0.5</td>
<td>14.3</td>
<td>0.5–1</td>
<td>5.1</td>
</tr>
<tr>
<td>0.5–1.0</td>
<td>5.5</td>
<td>1–5</td>
<td>8.4</td>
</tr>
<tr>
<td>&gt;1</td>
<td>3.8</td>
<td>5–10</td>
<td>1.3</td>
</tr>
<tr>
<td>&gt;10</td>
<td>3.8</td>
<td>&gt;50</td>
<td>5.6</td>
</tr>
</tbody>
</table>

* not detected: analytes were either absent or below the LOD; † analytes concentrations were below the LLOQ; ‡ the
lower limits correspond to analytes LLOQ.

Fig. 1. Inferential analysis: cyclophosphamide (top panel), ifosfamide (middle panel) and 5-fluorouracil (bottom
panel) concentration levels with respect to Site Classes.
same (only three different amounts for various therapeutic protocols). Hence the variable “used analytes amount” was described as a qualitative ordinal variable, characterized by 4 levels for CP and IF (0, 1,000, 1,500, 2,000 mg and 0, 400, 3,000, 4,000 mg, respectively) and 5 levels (each one representing a range of the handled quantities) for 5-FU (0, 0.3–4,000, 4,000–8,000, 8,000–12,000, >12,000 mg).

Even if χ²-tests showed a dependency of concentration levels by used analyte amount (chi: 46.704, 109.375 and 55.166 respectively, with equal p values of 0.001) a significant correlation between the handled analyte amount and the contamination levels detected on surfaces was found only in the case of IF (ρs=0.363, p=0.001). This apparent contradiction is explained by the fact that analytes were found on the examined surfaces even when they had not been handled during the sampling day, suggesting that the contamination of surfaces does not depend only on the handled amount but also on other factors.

**Discussion**

Determination of the current antiblastic drug contamination levels in an Italian hospital oncology ward was carried out. Statistical evaluation of the data aiming to identify potential exposure causes was performed. Cyclophosphamide (CP), ifosfamide (IF) and 5-fluorouracil (5-FU) were determined by wipe tests, extracted with diatomaceous earths and quantified by GC/MSMS or HPLC/UV. Data were analysed with respect to the potential contamination level of the sampled surfaces, and the various amounts of the handled analytes. χ² tests, and Spearman correlation coefficients were calculated. The measured analyte concentrations showed wide ranges of values. CP, IF and 5-FU concentrations varied respectively in the ranges: <0.020–18.83 µg/dm² (median, 0.086 µg/dm²); <0.100–26.96 µg/dm² (median, 0.100 µg/dm²); and <0.740–208.9 µg/dm² (median, 2.363 µg/dm²).

It is noteworthy that 9.3% of CP determinations (levels 4–5) showed high concentration levels with respect to those found in the literature (in the range 0.016–0.655 µg/dm²)\textsuperscript{34}. Analogous considerations can be made about IF, with a median literature\textsuperscript{36,37} concentration range of 0.003–0.035 µg/dm². In the case of 5-FU, 21.6% of samples (levels 4–6) presented concentrations higher than 10 µg/dm² up to a maximum of 208.9 µg/dm²: values decidedly high with respect to other reported data (0.973–8.376 µg/dm²)\textsuperscript{38}. Contamination levels measured on surfaces of the examined ward agree with levels found about seven years ago\textsuperscript{38,39}, before Guidelines on antiblastic drugs were issued\textsuperscript{35}. Currently, levels reported in the literature are nearly 1,000 times lower (in the range of ng/dm²)\textsuperscript{30,31,36,40}.

Diffuse contamination throughout the drug preparation room was found. It depended both on how close the sampled sites were to the place where drugs were handled and on the amount of the used drug.

Nevertheless, the obtained results showed that surface contamination might also be influenced by two potential factors. One is the presence of analytes, even if in traces, found on days when analytes were not used at all, could be related to incorrect cleaning procedures. In fact, as evidenced from the questionnaire, both the frequency and the detergents used in cleaning procedures were not appropriate\textsuperscript{25}. Another factor is contamination detected on surfaces (such as floor, interphone, door handles, boxes, shelves etc.) that are not strictly related to the preparation of the drugs (as the hood, waste bin and transport box) Together with inadequate room cleaning, it demonstrates incorrect working modalities. For instance, gloves could not be taken off immediately after the handling of the drugs, leading to the contamination of various surfaces unintentionally touched.

The observed decrement of contamination was expected, because both workbenches and the floor in front of the hood are the surfaces closest to the place where the analytes were handled. Nevertheless, these sites are also the surfaces that in theory should be cleaned soon after the drug preparation by nursing personnel (workbenches) and cleaning staff (floors). As a consequence, if cleaning procedures were correctly performed no correlations between site classes and contamination levels should be found.

Because there are no occupational threshold limits for antiblastic drugs classified as carcinogenic for human\textsuperscript{25}, in theory, they should all be absent from workplaces, implying the necessity of reducing as much as possible any contamination phenomena. Since risk management strategies should be based on each particular situation, the findings reported here suggest that a decrement of contamination levels could be achieved by: 1) a new training course focused on a) improving the awareness of nursing personnel about antiblastic drugs’ toxicity and

| Table 5. χ²-tests and Spearman coefficients of cyclophosphamide, ifosfamide and 5-fluorouracil Concentrations Levels with respect to sampling Site Classes |
|----------------|----------------|-----------|
| Variable | Value | p |
| CP | Chi | 42.264 | 0.000 |
| | ρs* | -0.035 | 0.000 |
| IP | Chi | 30.629 | 0.032 |
| | ρs* | -0.205 | 0.001 |
| 5-FU | Chi | 85.256 | 0.000 |
| | ρs* | -0.380 | 0.000 |

* 0.060
potential health consequences for subjects in charge of their preparation and administration, and b) improving working practices and cleaning procedures with regard to the use of specific products, such as sodium hypochlorite; and 2) environmental and biological monitoring plans, scheduled on annual basis, that allow the checking of the efficacy of performed training courses and of the risk management strategy adopted for decreasing the occupational exposure to antibiotic drugs.

References

29) Health & Safety Executive. Workshop on cytotoxic


