Environmental and Biological Monitoring of Platinum-Containing Drugs in Two Hospital Pharmacies Using Positive Air Pressure Isolators

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Environmental and biological monitoring of platinum containing drugs was implemented in two French hospital pharmacies using positive air pressure isolators and having similar working procedures when preparing antineoplastic drugs. Wipe sampling of surfaces, gloves, and vials was performed in the preparation room and in storage areas. All employees involved in the preparation of antineoplastic drugs were tested for urinary platinum on Monday before work and Friday after shift. Only traces of platinum were detected on surfaces in the preparation room outside the isolators (less than 1.61 pg cm⁻²). However, in one center, significant contamination was found in the storage area of the drug vials, which can most likely be linked to the rupture of a platinum vial and due to inefficient cleaning procedures. Surfaces inside the isolators were found to be contaminated (maximum: 198.4 pg cm⁻²). A higher level of contamination was detected in one pharmacy and could be explained by the lack of overgloving with regular changes during the preparation process. Nitrile gloves used during drug handling outside the isolator showed the highest platinum concentration (maximum: 5.86 ng per pair).

With regards to platinum urine concentration, no significant difference was found between exposed and unexposed pharmacy personnel. Isolator technology combined with individual protective measures seems to be efficient to protect workers from occupational exposure to antineoplastic drugs, whereas specific individual protective procedures implemented were focussing on the risk of handling vials outside the isolator (e.g. high frequency of glove changing). Moreover, overgloving inside the isolator would contribute to substantially decrease inner surface contamination and should be recommended in order to limit the transfer of chemical contamination to the end products.

Keywords: biological monitoring; environmental monitoring; exposure assessment; hospital pharmacy; Isolator; personal protective clothing; platinum

INTRODUCTION

Most antineoplastic drugs are classified as carcinogenic, mutagenic, or teratogenic for humans (IARC, 2012). Despite the implementation of detailed
guidelines and regulations for the safe handling of cytotoxic drugs, many studies showed that nurses and pharmacy personnel are still being exposed to these substances (Pethran et al., 2003; Kopjar et al., 2009; Mader et al., 2009; Boughattas et al., 2010; Connor et al., 2010; McDiarmid et al., 2010). An important step taken to protect healthcare workers from contamination of antineoplastic drug was to centralize the preparation in specialized pharmacies. In addition to quality and economic benefits, the centralization of preparations offers better safety and occupational health. This was achieved by specially trained staff and ensuring a high technical standard, including safety measures such as isolators, biological safety cabinets (BSC), and personal protective equipment.

Dermal exposure represents the most significant absorption into the body (Kromhout et al., 2000; Fransman et al., 2005). It can therefore be assumed that exposure levels are lower if little or no surface contamination could be measured. Surface wipe sampling is an appropriate and established method to evaluate the magnitude of surface contamination in the workplace environment. Recent studies showed that there is still high and widespread surface contamination in pharmacies preparing antineoplastic drugs (Bussieres et al., 2007; Schierl et al., 2009; Touzin et al., 2009; Sottani et al., 2010). In many countries, preparation of antineoplastic drugs occurs predominately in BSC. In France, a protective measure focuses on the use of a specific isolator technology (Larroueturou et al., 1992; Cazin and Gosselin, 1999). Up to now, little data have been collected in pharmacies working with isolator technology. One study described the contamination level with cyclophosphamide, ifosfamide, 5-fluorouracil (5-FU), and methotrexate in two French pharmacies (Crauste-Manciet et al., 2005). Contamination was routinely found inside the isolators but rarely outside. However, contamination was also detected on the outer surface of cytotoxic drug vials and on gloves of staff handling drug vials and final products. Based on these findings, the authors concluded that pharmacy technicians are at risk of occupational exposure with antineoplastic drugs.

The actual investigation, conducted in the same facilities, was implemented to assess if individual protective measures added to the collective equipment were sufficient to prevent biological uptake of antineoplastic drugs. Therefore, exposure to platinum (Pt) was chosen as a marker for occupational monitoring because Pt-containing drugs (cisplatin, carboplatin, and oxaliplatin) were frequently used in French hospitals, and sensitive analytical techniques are available (Ensslin et al., 1994; Schmaus et al., 2002). Urine sampling and wipe sampling was carried out to assess exposure of the pharmacy personnel and surface contamination of the workplace environment.

### METHODS

#### Study sites

**Characteristics of the study centers.** The study was conducted in two French hospital pharmacies selected for having the same isolator design, similar workloads, and working practices. The characteristics of the Centers are shown in **Table 1**.

**Isolator design.** The design of the isolators (Isoconcept®, A.R.F.L., Neuilly sur Marne, France) is defined in the previous publication (Crauste-Manciet et al., 2005). In summary, isolators are soft walled, totally enclosed, gas-sterilized isolators, vented outside the building and run positive air pressure (+35 Pa), and inlet and outlet air are filtered without any recirculation through high efficiency particulate air filters. Isolators’ wall is fitted with interlocking doors (Biosafe® door, IDC, Lourdes, France), which are leak tight connected to disposable sterile Biosafe® containers. These transfer systems ensure containment of end products and wastes. In both Centers, the isolators are located in dedicated rooms.

**Working procedures.** For both Centers, the working procedures are similar. The descriptions of tasks performed by the pharmacy personnel and the appropriate glove use are given in **Table 2**.

**Personnel characteristics.** For biological evaluation, the whole team involved in cytotoxic drug preparation was clearly informed about the goal of the study and each operator was asked for consent for contribution to the study. In total, nine employees in Center 1 and three employees in center 2 were investigated of urinary platinum contamination. The mean amount of time spent by operators in the cytotoxic working room was 20 h, with a minimum of 7 h and a maximum of 30 h. An average of 50 preparations with platinum drugs was prepared during the week in both pharmacies.

In addition, a control group, consisted of three people from center 1 and two people from center 2, was also investigated. They did not handle antineoplastic drugs and were working outside the drug preparation room (e.g. supervisors). Since the main source of low-level platinum excretion in occupationally unexposed population is caused from dental gold alloys (Schierl, 2001), all study participants...
were asked about this with the result that none of the persons investigated were subjected to dental gold restorative work.

**Sampling strategy**

*Wipe sampling.* Wipe sampling was performed according to a procedure previously published by Schmaus *et al.* (2002). Sampling was performed by trained field workers of each facility. Sampling tests were carried out on Monday morning before starting work and Friday at the end of the working day. Comparable locations were wiped in both pharmacies. Typically, an area of 400 cm² (20 × 20 cm) was sampled; hydrochloric acid (0.1%) was used as solvent to moisten the wipe filters. Sampling locations were selected in that way that the entire workflow ranging from the receiving and storage of the drug vials, the preparation, inspection of the finals

### Table 1. Characteristics of the pharmacy services studied.

<table>
<thead>
<tr>
<th></th>
<th>Center 1</th>
<th>Center 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of doses prepared per year (n)</td>
<td>9000</td>
<td>11,000</td>
</tr>
<tr>
<td>Platinum drug use per year (g)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cisplatin</td>
<td>30</td>
<td>49</td>
</tr>
<tr>
<td>carboplatin</td>
<td>102</td>
<td>111</td>
</tr>
<tr>
<td>oxaliplatin</td>
<td>50</td>
<td>40</td>
</tr>
<tr>
<td>Isolator</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number year in service</td>
<td>15</td>
<td>11</td>
</tr>
<tr>
<td>Neoprene gloves–number of days in service</td>
<td>7</td>
<td>7</td>
</tr>
</tbody>
</table>

### Cleaning procedures

**Inside isolator**
- Surfaces (beginning and end of work shift and whenever needed in case of spill): Isopropanol 50%
- Surfaces and air sterilisation (monthly): Peracetic acid vaporization

**Outside isolator**
- Surfaces (before and after work shift and whenever needed in case of spill): Isopropanol 50%
- Floors (daily), shelves-storage boxes (weekly): Surface detergent–disinfectant

### Table 2. Description of tasks performed by the operators in both centers.

<table>
<thead>
<tr>
<th>Task</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug vials handling</td>
<td>All cytotoxic drugs were stored in a specific storage area. Before entering the working isolator, vials were introduced directly inside isolator’s pass through hatch to be further sterilised by gas vaporization using peracetic acid (Soproper®). Flip-off caps of the vials were not removed prior entering, and vials were not submitted to any decontamination treatment of the external surfaces, i.e. alcohol spraying. Operators wore disposable nitrile gloves that were systematically discarded at the end of the task, followed by hand washing.</td>
</tr>
<tr>
<td>Drug preparation</td>
<td>Preparations of platinum drug were performed following individual prescription and corresponds to the transfer of liquid drug solution from manufactured vials to a final container (i.e. plastic bags) using syringe and vented needle. Operators wear undergloves (disposable nitrile gloves) which are changed on regular basis (at least each hour) before entering isolator gloves. In center 2, overgloves (disposable sterile latex gloves) were worn over the isolator gloves and were changed on a regular basis at least each 30 minutes.</td>
</tr>
<tr>
<td>End product wrapping</td>
<td>At the end of preparation, each preparation is individually wrapped and simultaneously sealed in a unique operation inside a sterile plastic container (Biosafe®) directly connected to the isolator wall using double interlocking door (Biosafe®). Operators wore disposable nitrile gloves to perform this task, which were changed on a regular basis and at least each hour.</td>
</tr>
<tr>
<td>End product control</td>
<td>Without opening the sealed container, operators were checking the concordance of end-product and preparation sheet with the original prescription, labelling conformity, and organoleptic aspects (e.g. lack of unusual coloration or precipitation). Operators wore disposable nitrile gloves to perform this task, which were changed on a regular basis and at least each hour.</td>
</tr>
<tr>
<td>Supervision</td>
<td>Pharmacist supervised the good operating procedures in preparation room. He was not directly involved in the preparation and handling task but was physically present in preparation room.</td>
</tr>
</tbody>
</table>
products, and waste disposal. For example, wipe samples were collected in the preparation room inside the isolator (work station), outside the isolator on the floor, and on surfaces such as desks, work benches, the waste bin, and the phone. Samples were also taken from the floor and desk in the end-product control room and from the floor and shelves in the drug vial storage rooms.

Glove sampling. Additionally, gloves were sampled after performing different tasks such as drug preparation inside the isolator, handling final products, handling vials during reception, and storage or during transfer into the isolator. Sampling occurred at that time where the workers were going to change or remove their gloves. In case of isolator gloves (neoprene gloves), the inner surface that contacts the nitrile glove of the operator was sampled. When sampling nitrile gloves used for tasks performed outside theisolator, samples were taken from the outer surface of the gloves. In addition, control samples were taken from gloves before starting any handling of antineoplastic drugs.

Vial sampling. The outer surface of drug vials (three vials as one sample) containing carboplatin (Carboplatin 450 mg 450 ml−1; Faulding, France) (n = 15), cisplatin (cisplatin 50 mg 50 ml−1; Merck, France) (n = 18), and oxaliplatin (Eloxatine 100 mg 20 ml−1; Sanofi Aventis, France) (n = 18) were analyzed for the presence of drug contamination.

Urine sampling. Parallel to environmental monitoring, employees were requested to give spontaneous urine samples on Mondays and Fridays before starting work, as well as an additional sample on Fridays after work. Samples were collected in cleaned PP-bottles. In order to minimize the risk of contamination, during sampling all participants removed their protective clothing and washed their hands prior to urine collection. Samples were stored at −20°C until they were transferred to the Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine in Munich for analysis.

Sample analysis/analytical procedure

The procedure for sample preparation and analysis was carried out according the method previously described in detail by Ensslin et al. (1994). After the addition of 0.5 N hydrochloric acid, the samples were processed using ultraviolet radiation, and the total amount of platinum was determined by voltammetry. Precision within and between series (n = 10) is between 5 and 10%. Blanc values for platinum are 0.66±0.25 pg (n = 10), giving an absolute Limit of Quantification (LOQ) of 2 pg per determination. For wipe samples (400 cm²), the LOQ is 0.05 pg cm⁻² and for urine samples 2 ng/l. Internal and external quality schemes were followed successfully. For a homogenous presentation of the wipe sampling results, the size of the area sampled was included and the measurements are presented in the unit pg cm⁻².

RESULTS

Statistical analysis

The statistical analysis was performed using SPSS Statistics Version 19. Since the data for wipe sampling were not normally distributed, the 50th, 75th, and 100th percentiles were presented. For urine samples, mean and standard deviation (SD) were calculated. For differences between Monday and Friday samples, the Wilcoxon matched pair signed rank test was taken.

Surface wipe samples

A total of 70 wipe samples were taken in both pharmacies, 35 on Monday before start of work and 35 on Friday at the end of the working day. Platinum was detectable in all samples (Table 3).

Surface contamination in the preparation room ranged between 0.38 and 198.4 pg cm⁻² inside the isolator and 0.03 and 1.61 pg cm⁻² outside the isolator (Table 4). In center 1, contamination inside the isolator was found to be at very high level with a maximum of 198.4 pg cm⁻² in comparison of center 2 with a maximum of 7.85 pg cm⁻². In center 2, all samples from the preparation room outside the isolator, as well as the samples from the end-product control room and the storage area, contained only traces of platinum (maximum: 0.26 pg cm⁻²). In center 1, the highest surface contamination in the preparation room outside the isolator was detected on the floor in front of the isolator (1.61 pg cm⁻² Pt). However, one critical instance of contamination outside the preparation room had been located on the floor in the storage area (68.53 and 27.88 pg cm⁻² Pt).

Comparing the wipe sample results of the two sampling times (Monday morning before starting work and Friday at the end of the working day) using Wilcoxon matched pair signed rank test resulted in no significant differences in the amount of surface contamination, and no trend could be observed that showed lower surfaces contamination levels on Monday than on Friday.
Glove samples

Overall, 33 samples were taken from gloves. Most glove samples showed insignificant levels and did not differ from controls, which were taken from gloves before starting any activity. However, six gloves had detectable amounts of platinum (more than 0.1 ng per pair). Samples from the outer surface of working nitrile gloves after handling drug vials outside the isolator showed the highest platinum concentration of 5.86 and 3.32 ng per pair. On the outer surface of undergloves, which were worn during drug preparation, we measured 0.38 ng platinum per pair for one sample (Table 4).

Vial samples

In total, the results for cisplatin (6 samples from 18 vials), oxaliplatin (6 samples from 18), and carboplatin (5 samples from 15 vials) showed a consistently external contamination. The platinum concentration ranged between 0.03 and 190.3 ng per three vials (Table 4).

Urine samples

In total, 37 urine samples were analyzed for platinum, including 30 samples from exposed individuals and seven from control individuals. All samples contained measurable amounts of platinum (range 0.8–4.6 ng l⁻¹), but not a single value was increased (Table 5). There was no statistical difference between the platinum concentration in the urines taken from exposed or nonexposed pharmacy personnel, from individuals of center 1 or center 2 or between the three sampling times (Monday/Friday, and preshift/postshift).

DISCUSSION

Environmental and biological monitoring were carried out in two French pharmacies using isolator technology preparing antineoplastic drugs, to investigate whether the implemented safety measures were sufficient to effectively protect workers from occupational exposure to antineoplastic drugs. Platinum was chosen as an indicator due to well-established and sensitive analytical procedures in wipe sampling and urine sampling and because platinum drugs are frequently used in cancer therapy. In addition, platinum has been applied in earlier studies monitoring occupational exposure with antineoplastic drugs and hence comparable data are available. In both locations, surface contamination was detected,

Table 3. Platinum wipe sampling results (pg cm⁻²)

<table>
<thead>
<tr>
<th></th>
<th>Center 1 (Monday preshift)</th>
<th>Center 1 (Friday postshift)</th>
<th>Center 2 (Monday preshift)</th>
<th>Center 2 (Friday postshift)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inside preparation room pg cm⁻²</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inside isolator</td>
<td>Work station right</td>
<td>66.53</td>
<td>107.50</td>
<td>0.68</td>
</tr>
<tr>
<td></td>
<td>Work station left</td>
<td>198.41</td>
<td>74.71</td>
<td>1.45</td>
</tr>
<tr>
<td>Outside isolator</td>
<td>Floor in front of isolator</td>
<td>1.21</td>
<td>1.61</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>Floor middle room</td>
<td>0.93</td>
<td>1.25</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>Floor entry</td>
<td>0.60</td>
<td>0.79</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>Desk</td>
<td>0.06</td>
<td>0.06</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>Work bench</td>
<td>0.06</td>
<td>0.06</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>Worktop (vials)</td>
<td>0.57</td>
<td>0.74</td>
<td>0.16</td>
</tr>
<tr>
<td></td>
<td>Worktop (Biosafe® container)</td>
<td>0.44</td>
<td>0.26</td>
<td>0.26</td>
</tr>
<tr>
<td></td>
<td>Phone</td>
<td>0.07</td>
<td>0.14</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>Waste bin</td>
<td>0.04</td>
<td>0.04</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Outside preparation room pg cm⁻²</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End-product control room</td>
<td>Floor</td>
<td>0.14</td>
<td>0.06</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>Desk 1</td>
<td>0.21</td>
<td>0.15</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>Desk 2</td>
<td>0.06</td>
<td>0.06</td>
<td>—</td>
</tr>
<tr>
<td>Storage room</td>
<td>Floor in (front of the shelves)</td>
<td>68.53</td>
<td>27.88</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>Shelves 1</td>
<td>1.05</td>
<td>0.92</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>Shelves 2</td>
<td>0.94</td>
<td>0.68</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>Shelves 3</td>
<td>0.05</td>
<td>0.03</td>
<td>0.22</td>
</tr>
</tbody>
</table>
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...predominantly inside the isolator and in the storage area. Platinum also was measurable in gloves samples and on the outer surface of drug vials. However, none of the employee urine samples contained an increased amount of platinum.

Wipe sampling

Various studies dealing with environmental contamination (Nygren and Lundgren, 1997; Leboucher et al., 2002; Brouwers et al., 2006; Schierl et al., 2009) documented higher levels of platinum surface contamination in the drug preparation area of pharmacies using BSC than the results of this study. For example, Brouwers et al. (2006) reported about a maximum value of 2.2 ng cm$^{-2}$, Schierl et al. (2009) even found surface loads up to 2.7 ng cm$^{-2}$ in the preparation room outside the BSC. The results of Mason et al., 2005, who investigated two pharmacy units in the UK working with isolator technology, had shown more comparable surface contamination than our findings. The platinum concentration was between 0.5–13 pg cm$^{-2}$, whereas the pharmacy with the positive pressure isolator (analogous to this study) had a maximum value of only 1.3 pg cm$^{-2}$. These results suggest that platinum contamination is far lower if isolator technology was used, as opposed to BSC. But this statement is based on the investigation of only four pharmacies (Mason et al., 2005), while significantly more pharmacies using BSC were tested.

Outside the preparation room, one important instance of contamination was found on the floor in...
the storage area of center 1. Due to the higher level found in comparison to other surfaces, a possible breakage of a platinum vial combined with insufficient cleaning procedure could explain this result, showing the need for improving cleaning procedure of this area. This could also encourage developing containment systems for vial storage and the use of unbreakable vials.

Inside the isolator, unsurprisingly, significant contamination with platinum was found. Comparable data were previously published for other markers (5-FU, CP, and IP) (Crauste-Manciet et al., 2005). Higher levels were found in center 1 in comparison to center 2. The main explanation that can be given is the different practice between the pharmacy units with regards to the use of overgloves. In center 2, sterile latex overgloves were used during drug preparation, which were changed on a regular basis (30 minutes), whereas in center 1, overgloves were not worn. The use of disposable overgloves, which are changed on a regular basis could be an efficient measure limiting the widespread of contamination inside isolator. Moreover, it appeared there were no differences between inside contamination levels on Monday and Friday showing poor efficiency of the cleaning methods in center 1, which should be improved by reeducation of the operators on cleaning procedures. Some other measures, such as closed system devices (Favier et al., 2012), could also be able to reduce surface contamination on the worktop inside the isolator.

All in all, overall surface contamination in both centers is quite low in comparison to other studies performed where the level of contamination is usually found in the ng scale range.

Vial contamination

It has been repeatedly shown that the exteriors of vials containing cytotoxic drugs supplied by manufacturers were contaminated, some of which to a high degree (Nygren et al., 2002; Favier et al., 2003; Mason et al., 2005; Connor et al., 2005; Touzin et al., 2008; Schierl et al., 2010; Osawa et al., 2011). Our results confirm this data as all vials tested contained traces of cytotoxic drugs in a range from 0.03 to 190.3 ng per three vials. Besides handling errors, external contamination of drug vials are an important factor in the contribution of environmental surface contamination (e.g. worktop inside the isolator, floor in front of the isolator, and floor and shelves in the storage area).

Because of the small number of vials sampled, it is not possible to derive a general statement about a correlation between external vial contamination and environmental contamination. In fact, the extend of contamination on the outside of drug vials depend on the manufacturer, on the batch, and on the use of additional safety sheeting systems such as shrink-wraps or plastic containers (Connor et al., 2005; Schierl et al., 2010). Thus, low surface contamination is rather an indicator for good work practices than of low drug vial contamination. These results confirmed that external drug vial contamination is common and protective measures are necessary to protect pharmacy staff from biological uptake of cytotoxic drugs. Gloves are of special importance when unpacking the drug vials delivered from manufactures since not only the vials themselves may be contaminated but also their outer shipping packaging (Favier et al., 2003).

Glove sampling

Six of the 33 gloves sampled contained increased platinum concentrations (more than 0.1 ng per pair). The highest level detected was 5.86 ng per pair. The extent of platinum measured on gloves was lower than in other studies. Ziegler et al. (2002) and Mason et al. (2005) previously reported about platinum concentration in the range of 0.4–36 and 12–102 ng per pair, respectively. These findings were consistent with the results of other authors, who examined the gloves of pharmacy technicians and nurses during their daily work on residues of various cytotoxic drugs (Fransman et al., 2004, 2005, 2007; Funck and Schierl., 2004).

Glove contamination was detected on several samples when handling vials which can be attributed to external contamination of cytotoxic drug vials. This supports the recommendation for using disposable gloves when handling vials and changing them at the end of this task.

In a single case, a nitrile underglove worn inside the neoprene isolator glove was contaminated. Possible explanations for this drug contamination can either be a carryover of contamination from the nitrile gloves of the operator or a drug penetration through the isolator neoprene gloves. Permeation is related to a variety of factors, such as glove composition, glove thickness, exposure period, and the physical characteristics of the agents (Slevin et al., 1984; Stoikes et al., 1987; Klein et al., 2003). Due to the large number of antineoplastic drugs and different kinds of gloves that are available on the market, only limited data about drug permeation are available. Nevertheless, previous investigation with the same isolators reported absence of 5 fluorouracile, cyclophosphamide, Ifospham ide, and Methotrexate on the inner side of the isolator neoprene gloves.
changed twice a month (Crauste-Manzi et al., 2005). The most probable source of contamination would be the possibility that the operator forgot the change of his nitrile gloves before entering the neoprene gloves. Nevertheless, a possible failure of neoprene glove such as micro hole facilitating permeation through gloves cannot be totally ruled out. Therefore, it is important that pharmacy personnel handling antineoplastic drugs always wear under-gloves and change them on a regular basis.

**Urine sampling**

Despite the detection of surface and glove contamination in both pharmacies, none of the urine samples contained increased amounts of platinum (range 0.8–4.6 ng l\(^{-1}\)). But it has to be kept in mind that our sampling strategy with pre- and postshift samples can not exclude a moderate drug uptake during the week. However, such stochastic events are difficult to detect anyway. The urine data in this study lead to the conclusion that there was no uptake on Friday and no high incorporation of platinum drugs during the monitored week. Moreover, the platinum concentrations in our study are in the range that has been reported from authors studying platinum reference values in the general population. For example, Spezia et al. (2005) reported that the increasing use of platinum in medical and industrial applications (e.g., exhaust catalytic converters and cancer therapy) has caused a growing spread in the environment and they measured a median reference values in the general Italian population of 4.13 ng l\(^{-1}\). Wilhelm et al. (2004) obtained a reference value of 10 ng l\(^{-1}\) and gave a urinary range of 0.9–6.6 ng l\(^{-1}\) in subjects not having any dental gold.

Several studies have verified occupational exposure to antineoplastic drugs in nurses and pharmacy personnel using urine sampling (Pethran et al., 2003; Fransman et al., 2007; Connor et al., 2010; Ndaw et al., 2010; Sugiura et al., 2011). Some of them also determined urinary platinum and obtained platinum concentration in the urine, for example, between 3.5–34.4 µg l\(^{-1}\) (Ensslin et al., 1994) or 0.92–1.3 µg l\(^{-1}\) (Turci et al., 2002). The recently published study of Mason et al. (2005) suggests that workers are still exposed to cytotoxic drugs at very low levels (10.4–142.5 ng Pt g\(^{-1}\) creatinine) despite the use of isolator technology when preparing antineoplastic drugs. The authors found a significant difference in urine contamination when using negative pressure isolator in comparison with positive pressure isolator (as used in our study). Explanation seems to be linked to a different risk of dermal exposure of the operators outside isolators. Using negative pressure isolators, which are not gas sterilized, the vials need to be sprayed with alcohol by the operators before entering isolators to reduce microbial contamination risk. This spraying can facilitate permeation of contamination from vials through gloves. In positive pressure isolators, this procedure is not required because the vials are directly gas sterilized in specific isolator’s hatch. It seems that avoiding operations favoring contact with contaminants outside the isolator is the main issue to be considered.

In our study, the very low levels of surface contamination in the isolator’s surrounding contributed to limit risk of dermal exposure of operators and at the end, the biological exposure. Moreover, the very low contamination that may have been in dermal contact could not be detectable anyway in the urine taking into account the limitation of urine sampling procedure as previously discussed. The combination of organizational, technical, and personal protective equipment in both pharmacy units seems to be sufficient to protect workers effectively from occupational exposure of antineoplastic drugs.

**CONCLUSION**

This study shows the efficiency of the physical barrier given by the isolator against the exposure of the handlers. Whereas, personal protective measures have to be implemented in addition, especially strict gloving procedure with high frequency for changing when vials are handled outside the isolator. Moreover, overgloving inside the isolator would contribute to substantial decrease inside surface contamination and should be recommended in order to limit the transfer of chemical contamination to the end products.

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**REFERENCES**


