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Antineoplastic drug concentration levels in the urine of Canadian healthcare workers

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SUBMITTED VERSION

Abstract

Purpose: The purpose of this study was to quantify the urine concentration of non-metabolized cyclophosphamide (CP), a commonly administered antineoplastic drug, among potentially exposed Canadian healthcare workers and to identify factors associated with the drug concentration levels. Methods: Participants were asked to provide two sets of 24-hour urine samples (at two different sampling events) and the level of CP was quantified using high-performance liquid chromatography-tandem mass spectrometry. In addition to demographic information, participants were surveyed regarding their frequency of handling of antineoplastic drugs, safe drug handling training, and known contact with CP on their work shift. Descriptive and inferential statistical analyses were performed. A backward stepwise linear mixed effect model was conducted to identify factors associated with urine concentration levels. Results: We collected 201 urine samples and 55% (n=111) had levels greater than the LOD of 0.05 ng/mL. The mean urinary CP concentration was 0.156 ng/mL, the geometric mean was 0.067 ng/mL, the geometric standard deviation was 3.18, the 75th percentile was 0.129 ng/mL and the range was <LOD to 2.37 ng/mL. All eight job categories evaluated had some urinary concentrations in excess of the LOD with unit clerks having the highest average level. Workers who worked in the drug administration unit but were not responsible for administering the drugs to patients, i.e. volunteers, oncologists, ward aides and dieticians, had the largest proportion of samples exceeding the LOD. We did not find any correlation between the urinary concentration levels and known contact with CP during the work shift. Two factors were found to be significantly associated with urinary CP concentration: (1) workers who had a duty to handle antineoplastic drugs had higher concentration levels; (2) workers who had not received safe drug handling training had higher levels of CP in their urine compared to those who had. Conclusions: The

presence of non-metabolized CP in urine confirms that, despite the existence of control measures, a broad range of healthcare workers are at risk of exposure to antineoplastic drugs. A review of the effectiveness of interventions to reduce exposure is warranted and should apply to all healthcare workers involved in some capacity with the hospital medication system. This study identified two factors that are related to the urine CP concentration levels which can serve as an impetus for reducing exposure.

Key words

Antineoplastic drugs, urinary concentration, healthcare workers, hospital medication system, risk assessment

SUBMITTED VERSION

Introduction

Health risks associated with healthcare workers' exposure to antineoplastic drugs have been known since the 1970's (NIOSH 2004). Associated adverse health outcomes include mutagenicity, reproductive toxic effects and cancer (Dranitsaris et al. 2005; Ritchie et al., 2000; Connor and McDiarmid 2006). The primary route of occupational exposure to antineoplastic drugs has been shown to be through dermal contact (Sessink et al. 1994; Fransman et al. 2005). This can occur either: a) *directly* through handling of the drug vials or intravenous preparations or b) *indirectly* by contacting drug-contaminated surfaces/objects. We previously reported that healthcare workers are at risk of exposure to antineoplastic drugs by confirming the presence of drug contamination on the hands of pharmacy personnel (Hon et al. 2011a). In a more recent study, we demonstrated that an assortment of healthcare job categories throughout the hospital medication system (process flow of drugs within a facility from initial delivery to eventual disposal) have measurable dermal concentration levels (Hon et al. 2014b)

The collection of dermal wipes is practical because they are non-invasive; however, they are only representative of the level of external contamination and do not account for drug that may have been absorbed by an individual. The absorbed dose is important because most antineoplastic drugs, including the marker drug in our study, cyclophosphamide (CP), are initially inactive and do not exhibit cytostatic effects until they are metabolized (de Jonge et al. 2005). Furthermore, dermal wipe samples do not account for other potential routes of occupational exposure such as inhalation or ingestion and, therefore, may not provide a complete measure of exposure. Given this, a number of occupational exposure studies have collected urine samples as a biomarker to estimate the dose of antineoplastic drug as evidenced in reviews conducted by Suspiro and Prista (2011) and Hon et al. (2014a).

The aim of this study was to assess the concentration of non-metabolized CP in the urine of a broad range of Canadian healthcare workers who are potentially exposed to antineoplastic drugs due to their role in the hospital medication system. In addition, we sought to identify individual and workplace factors that may be associated with the concentration of CP in urine.

Methodology

Selection of participants

Ethics approval was obtained prior to study commencement. Six facilities participated in the study – five acute care sites and one cancer treatment centre. Additional characteristics of the participating facilities have been described previously (Hon et al. 2011b) Participants were selected from those who were considered potentially exposed following site observations to identify drug-contaminated surfaces and the job categories that contacted the suspect surfaces. The job categories selected for inclusion were pharmacists, pharmacy receiver, pharmacy technician, nurse, transport staff, unit clerks and others working in drug administration units (volunteers, ward aides, oncologists and dieticians). The participating hospitals' research ethics boards dictated the form of recruitment. Participants were selected either actively through a mailed letter of invitation or passively via the distribution of consent to contact forms at departmental meetings. For each job category, up to three representatives per site were invited to participate.

Upon receiving consent from workers to participate in the study, members of the research team contacted each participant via email or telephone to arrange a mutually convenient time to meet at their place of work to collect samples. Every participant was given a cash honorarium of \$25 for providing a urine sample.

Collection of urine samples

As elimination of CP is almost complete 24 hours after uptake (de Jonge et al. 2005), participants were asked to provide 24-hour urine samples. This same sampling period is recommended by the U.S. Environmental Protection Agency for biological monitoring of toxic substances (US EPA 2011) and is also consistent with other urinary biomarker studies of anticancer agents (Suspiro and Prista 2011; Jakubowski and Trzcinka-Ochocka 2005).

Participants were asked to provide the initial urine sample immediately after the dermal wipe was collected (convenient sampling during the course of a work shift) (Hon et al. 2014b). Every participant was supplied with ten 250 mL polypropylene collection jars (Fisher Scientific, Ottawa, ON) with every void during the 24-hour period collected in a new jar. To prevent potential degradation, participants were asked to keep the urine samples refrigerated whenever practical and, where a refrigerator was unavailable, participants were asked to use the instant cold packs provided to facilitate the maintenance of a colder environment.

Once the 24-hour sampling period was completed, the samples were couriered to the Occupational and Environmental Hygiene laboratory at the University of British Columbia. All urine samples from a participant (typically between 6 and 7 voids in the 24-hour period) were pooled and three 5-mL aliquots of the 24-hr pooled sample were placed into cryogenic tubes and subsequently stored at -80°C until analysis.

A second set of 24-hour urine samples was collected from most participants with at least three weeks' lag between collection times (average of 97 days; range 22 to 188 days). Participants were not made aware of the results from the first collection date before the second sample was collected. Sample collection took place between June 2010 and February 2011.

Urine sample analysis

For every participant's sample, one of the 5 mL aliquots was allowed to thaw. After thawing, contents were transferred to a scintillation vial and an internal standard, 50 µL of D4-CP (0.05 ng/µl) (Toronto Research Chemicals, Toronto, Canada), was added. Ethyl acetate solvent (Sigma Aldrich, Oakville, ON) was added to separate the organic matter from the aqueous layer. This step was repeated three times until virtually all the organic matter was extracted. The culture tube containing organic matter was then allowed to dry under a gentle stream of nitrogen gas. Once dry, the residual was reconstituted in 1.0 mL 0.1M ammonium acetate (Sigma Aldrich, Oakville, ON) and this amount was transferred to liquid chromatography vials. The aliquot was analyzed for CP by high-performance liquid chromatography-tandem mass spectrometry using an Agilent Technologies 6410 Triple Quadrupole LC-MS/MS (Santa Clara, CA). The instrument employed a Zorbax XDB-C18 column (Agilent Technologies, Santa Clara, CA) with a gradient mobile phase of 5 mM Ammonium Acetate:100% Methanol (A:B) (Sigma Aldrich, Oakville, ON) and samples were run at a flow rate of 0.5 mL/min. A 10-point calibration curve was used and, for quality control purposes, a calibration standard was run for every 10 samples. For additional quality control, QC spike samples, urine spike samples and blanks were included in the analysis. Ten percent of the samples in each batch were run in duplicate and a duplicate response that varied by more than 10% was not tolerated¹. The limit of detection (LOD) was 0.05 nanograms per milliliter (ng/mL) and the urinary drug concentrations were reported in ng/mL.

Supplemental data collected

We collected a variety of information from the participants while on-site as well as via a self-administered questionnaire. After the urine sample was collected, all participants were surveyed

¹ If duplicate response varied by more than 10%, the batch was re-analyzed to see if the instrument was an issue or the extraction. Some samples were re-run and the resulting concentrations were used for this study.

by a member of the research team regarding the type and frequency of contact with CP during the current work shift. Types of contact with CP included mixing, administering, starting or disconnecting an IV line, physically caring for a patient on a CP regimen, disposing of body fluids from a patient on CP, touching a container, disposing of drug waste, touching a drug-contaminated surface, and consuming food in an area where antineoplastic drugs are handled.

The self-administered questionnaire asked questions regarding a participant's gender, job title, previous training related to the safe handling of antineoplastic drugs and the usual degree of contact with antineoplastic drugs. The latter included whether the worker had a duty to handle antineoplastic drugs, whether the individual was assigned to work in an area where antineoplastic drugs are handled/prepared and/or administered and the percentage of time spent on a typical work shift handling, preparing and/or administering antineoplastic drugs. In addition, participants were asked a series of questions regarding their knowledge of safe handling procedures within their hospital as well as the risk of occupational exposure to antineoplastic drugs. These seven questions, equally weighted, resulted in a cumulative "knowledge" score (scores ranged from 0 to 7). The knowledge questions are in the study questionnaire (Section C) available from <http://antineoexposure.spph.ubc.ca/healthcare-workers-exposure-antineoplastic-drugs/study-documents>.

In addition, we gathered information regarding hospital characteristics: the hospital type (acute care or cancer treatment); whether the hospital had an isolated drug preparation area (yes or no); and where antineoplastic drugs were initially delivered to the facility (shipping/receiving department or direct to the pharmacy).

Statistical Analysis

Both untransformed and log-transformed (base e) data were used to examine the distribution of the urinary CP concentration levels. When log-transformed, the measurements exhibited more of a normal distribution than the corresponding untransformed data. Summary statistics (arithmetic mean (AM), geometric mean (GM), geometric standard deviation (GSD), 75th percentile, maximum, and proportion greater than LOD) were used to describe the data. Summaries of the urinary CP concentration levels were stratified by various independent variables from the survey instruments. “No” and “don’t know” responses to pertinent questions from either of the two survey tools were combined into one category and compared with “yes” responses to the same question.

The urinary concentrations measured in the same subjects in the repeated sampling rounds were summarized separately and compared using a paired t-test and Pearson correlation coefficient.

To determine which factors were related to the urinary CP concentrations (ln-transformed), while controlling for the repeated measures, linear mixed effect models were performed with subject and hospital as random effects. Initial screening models included only one fixed effect each. The fixed effects included individual characteristics (job title, gender, duty to handle antineoplastic drugs, percentage of time handling antineoplastic drugs, working in an area where antineoplastic drugs are handled, and received safe drug handling training); whether CP was contacted during the work shift; the dermal concentration levels from a previous study of ours (Hon et al. 2014b); the number of types of contact with CP during the work shift; the participants’ knowledge score; and hospital characteristics (hospital type, department, if facility had an isolated preparation room and where antineoplastic drugs are initially delivered). All independent variables (fixed effects) with $p < 0.25$ from the screening analyses were then offered in one linear mixed effects regression and those variables with $p < 0.05$ were retained in the final model. A random effects

only (hospital, subject) model was also run to examine the variance components. All analyses were performed using TIBCO Spotfire S+ 8.2 for Windows (TIBCO Software Inc.).

Data less than the limit of detection

As with the dermal and surface concentration levels reported in our previous studies (Hon et al. 2013; Hon et al. 2014b), a large proportion of urine samples had concentrations less than the laboratory-determined limit of detection (Table 2). To address this, we explored ways to prevent the bias that will occur if samples less than the detection limit are omitted or if inappropriate quantitative values are assigned to them (Helsel 2009). Laboratory-calculated concentrations below the method limit of detection were available to us. Although these data have a lower signal-to-noise ratio than data above the detection limit, they were based on actual measurements rather than substitute values, a technique often used for exposure data below detection limits (Hornung and Reed 1990). As there are biases associated with using a substitute value (Ganser and Hewett 2010), we used the actual analytical data for concentrations below the detection limit in all data analyses.

Results

Study population and urinary CP concentration levels

In total, 103 healthcare workers agreed to participate in the study. It was not possible to calculate a true response rate because of the constraints of the recruitment methods dictated by hospital ethics boards; however, the proportions who participated of those contacted in the six facilities ranged from 55% to 76%.

Of the 103 participants, 98 provided a second sample, for a total of 201 urine samples. Slightly more than half of the samples (55% or n=111) had CP levels greater than the LOD with a maximum reported concentration of 2.37 ng/mL (Table 1). The mean urinary CP concentration

was 0.156 ng/mL, the geometric mean 0.067 ng/mL, the geometric standard deviation 3.18, and the 75th percentile 0.129 ng/mL. The CP concentrations in the two sampling rounds (Table 1) were positively correlated (Pearson $r = 0.145$, $p < 0.01$), but also differed significantly between the two sampling rounds ($p < 0.01$, paired t-test).

Characteristics of the study population and concentration by individual factors

A summary of jobs, genders and other characteristics of the study population can be found in Table 2. Also shown in the table are urinary CP concentrations stratified by these characteristics. The job category with the highest average urinary drug concentration was the unit clerks. The job category with the largest proportion of samples exceeding the LOD were those classified as “others” who work in the drug administration unit but are not responsible for administering the drugs to patients (i.e. volunteers, oncologists, ward aides and dieticians). Every job category examined had sample results above the LOD of 0.05 ng/mL with the maximum reported urinary concentration level originating from a pharmacy technician.

Participants who had a duty to handle antineoplastic drugs and those who handled these agents for more than 25% of their shift had higher GMs as well as a larger proportion of samples above the LOD. Workers who had received safe drug handling training in the past had lower average CP concentrations as well as a lower proportion of samples above the LOD than those who had never received training.

Participants who were not certain if they contacted CP during the shift had a higher proportion of samples above the LOD as well as had a higher average concentration level than those who indicated that they had contacted CP at least once on their shift (Table 2). However, there was no association between urinary CP levels and the number of types of contact with CP on the work shift (Table 3).

Also shown in Table 3, there was no association between a worker's knowledge score and their resulting urinary concentration levels. Further, there was no correlation between the dermal wipe sample results in our previous study (Hon et al. 2014b) and the urinary CP concentrations reported in the current study.

Concentration levels by hospital characteristics

A review of Table 4 indicates that healthcare workers from the cancer centre had a higher proportion of samples above the LOD and a higher average CP concentration compared to their counterparts who work at an acute care setting.

Of the three departments examined, the "other" departments not involved in either drug preparation or drug administration had the highest arithmetic mean urinary concentration level.

Facilities with an isolated drug preparation room had a higher proportion of samples exceeding the LOD and the maximum reported concentration level was from this type of facility. In facilities where the drugs are initially delivered to the shipping/receiving department, as opposed to the pharmacy directly, a higher proportion of samples were above the LOD and the average urinary concentration level was higher.

Linear mixed effects regression

Five independent variables had $p < 0.25$ in the screening analyses: 1) job title, 2) whether the participant had a duty to handle antineoplastic drugs, 3) whether the participant received training, 4) hospital type and 5) department. All other independent variables had $p > 0.25$.

These five independent variables were offered as fixed effects in a linear mixed effects regression (with subject and hospital as random effects) to examine associations with urinary CP concentration. Two fixed effect variables remained in the final model: whether a participant had a duty to handle and whether a participant had ever received training (Table 5). Participants who

had a duty to handle antineoplastic drugs had higher urinary CP concentrations. Participants who never had training regarding safe drug handling had higher CP levels in urine.

The final linear mixed effects regression model was as follows:

$$y_{ijk} = \beta_0 + \beta_1 \text{Duty to handle}_{ijk} + \beta_2 \text{Training}_{ijk} + u_i + v_{ij} + e_{ijk}$$

where y is the ln-transformed CP concentration, u is a random effect for between-hospital variance, v is a random effect for between-subject variance, e is within-subject random error, i is hospital index, j is subject index, and k is measurement index.

In the random effects only model, almost all the variance was within subject (96.9%), a negligible proportion between subject, and a small proportion between hospital (3.1%).

Discussion

Our results demonstrate that Canadian healthcare workers involved in some capacity with the hospital medication system have detectable levels of antineoplastic drug, specifically non-metabolized CP, in their urine. Slightly more than half the samples exceeded the LOD, but the proportion of samples above LOD ranged from 44% to 67% depending on the independent variable examined. All eight job categories examined had a maximum urinary concentration level above the LOD of 0.05 ng/mL.

A review of the literature indicates that there is a great deal of variability with respect to antineoplastic drug concentration levels in the urine of healthcare workers. Some studies have reported little or no CP detected (Hedmer et al. 2008b; Mason et al. 2005; Turci et al. 2010; Sottani et al. 2011; Connor et al. 2010) while one reported that up to 80% of their samples exceeded the LOD (Burgaz et al. 1999). A research team in Italy concluded that there has been a reduction in the percentage of positive urine samples over time (Sottani et al. 2010). As we are

the first to determine CP urine concentration amongst Canadian healthcare workers, future similar studies are suggested to determine any possible trends in exposure levels in our country.

The difference in mean urinary concentration between our two sampling sessions was statistically significant. Our random effects only model demonstrated the high proportion of the variance in urine concentrations was within subjects. These findings are consistent with Sugiura et al.'s observation that urinary concentration levels vary considerably amongst healthcare workers within a study (Sugiura et al. 2011). Differences in urinary CP concentrations within and between studies are likely due to variations in CP use, handling and cleaning practices, personal protective equipment usage as well as variability in metabolic rates amongst individuals (Villarini et al. 2011; Hedmer et al. 2008b).

In the current study, participants from departments where drug preparation and drug administration do not take place (shipping/receiving, transport, nutrition and materials management) had the highest average urinary concentration levels. Similarly, workers who do not work in an area where antineoplastic drugs are regularly handled had the higher mean concentration. Not surprisingly then, when the results were stratified by job title, unit clerks had the highest average urinary CP concentration. This may be novel to some as pharmacists and nurses have long been considered the highest risk job categories for occupational exposure to antineoplastic drugs.(McDiarmid et al. 2010) However, the results of the current study support our previous findings that other workers within the hospital medication system, besides nurses and pharmacy personnel, may be at greater risk of exposure to antineoplastic drugs (Hon et al. 2013).

We found that participants who did not report having contact with CP during their work shift had a higher mean concentration level and a higher proportion of samples exceed the LOD compared

to those who did report CP contact. This is of concern as long-term urinary excretion of CP (i.e. continuously positive urine samples) may signify continuous absorption of CP (Sugiura et al. 2011). This phenomenon may be attributed to the fact that workers could have been exposed through skin contact due to environmental contamination from drug handling activities the day before (Tanimura et al. 2009). Another possibility is the fact that the skin may serve as a reservoir whereby internal exposure may continue despite the cessation of external exposure (Bos et al. 1998). Given this, it is not surprising that we did not find a correlation between the urinary concentration levels and the number of CP contact types that a worker may have had during the shift. This finding is consistent with others who have reported that antineoplastic drug handling activities are not associated with urinary concentration levels (Favier et al. 2003; Pethran et al. 2003; Sessink et al. 1994; Connor et al. 2010).

Participants from facilities in which the drugs were delivered to the shipping/receiving department had a higher mean concentration level as well as a larger proportion of samples above LOD than participants at facilities where drugs by-pass shipping/receiving and are delivered directly to the pharmacy. We observed the same finding for drug concentration levels found on various work surfaces (Hon et al. 2013). It should be noted that the two matrices were collected at different times; albeit at the same participating facilities. To determine if an association exists, it is recommended to collect environmental samples concurrently with urine samples as the former can demonstrate how, where and possibly when contamination occurred while the biological sample indicates if exposure occurred (Turci et al. 2010).

There was no correlation between the dermal concentration levels that we reported previously (Hon et al. 2014b) and urinary concentration levels in the current study. This could be because we collected the hand wipes at a single point in time which is not reflective of a worker's

exposure throughout the shift. It could also suggest that other routes of exposure (e.g., inhalation and accidental ingestion) as well as metabolism may play a role in the body burden of antineoplastic drugs.

We identified two variables that were statistically significant in the linear mixed effects regression model: (1) whether a worker had a duty to handle antineoplastic drugs, and (2) whether the worker had ever received safe drug handling training. Not surprisingly, individuals tasked with handling antineoplastic drugs had higher CP concentrations in their urine. The fact that workers who did not receive training had higher levels of urinary CP concentration lends support that training is an important administrative control to reduce the level of occupational exposure to antineoplastic drugs. However, we also found that one's level of knowledge related to the risks of antineoplastic drugs was not associated with urinary concentration levels. Further evaluation of training and its effectiveness in reducing the risk of exposure is therefore suggested.

With regards to the health risks associated with the urinary concentration levels reported in this study, a no-significant-risk level (NSRL) of 1000 ng/day has been suggested for CP² (Sargent et al. 2002). The NSRL is the level at which no increase in cancer risk and no adverse effects on organ systems or the developing fetus are expected (Sargent et al. 2002). Converting our results to ng/day based on the estimated 24-hr urinary output volume per participant, we found 10 observations (4.5%) had exposure levels which exceeded the NSRL threshold. Of these ten samples greater than 1000 ng/day, four were from nurses, two were from pharmacy technicians, one was from a pharmacist, two were from unit clerks and one was from an individual who worked in a drug administration unit but was not responsible for drug administration. The latter

² Assumed that "day" is equivalent to 24 hours

two job categories reaffirms the notion that other healthcare workers, in addition to nurses and pharmacy personnel, are at risk of occupational exposure to antineoplastic drugs.

Limitations of this study are described here. We collected a hand wipe sample from every participant immediately prior to collecting urine samples. As the skin is a possible reservoir source for the uptake of CP, our results may underestimate the CP concentrations in urine. However, hand wipe sampling is akin to handwashing and virtually all of our participants washed their hands at least once prior to sample collection, so the extent of underestimation of urinary concentrations from the additional wiping via our study is not expected to be large. Housekeepers (cleaners) were not participants in the study because the contract company that employed the housekeepers declined to participate. This cohort is known to be at risk of exposure because they are responsible for removing the antineoplastic drug waste containers from the various departments at each facility as well as cleaning of patient lavatories (Fransman, et al. 2005; Hedmer et al. 2008b). We measured for only one antineoplastic drug, but healthcare workers are potentially exposed to many others. Lastly, several of the independent variables were gathered via self-reports and we cannot confirm their accuracy.

Conclusions

This study confirmed the presence of antineoplastic drug, specifically non-metabolized CP, in the urine of a broad range of healthcare workers who work at Canadian hospitals. This is consistent with the literature with respect to the fact that, despite the implementation of protective guidelines, occupational uptake of antineoplastic drugs is still occurring (Suspiro and Prista 2011). These findings also reaffirm our notion that more healthcare workers than initially believed are potentially exposed to antineoplastic drugs (Hon et al. 2011; Hon et al., 2014b). We identified two factors associated with urinary concentration – if a worker has a duty to

handle antineoplastic drugs and whether a worker received training on safe drug handling. This finding provides a basis for targeting interventions to reduce occupational exposure. To our knowledge, this is the first study based in Canada to identify determinants of urinary CP levels for a broad range of healthcare workers. We therefore suggest that similar occupational exposure studies in the future include all potentially exposed job categories that are involved in the hospital medication system. Furthermore, interventions to minimize the risk of occupational exposure to antineoplastic drugs should be broadly applied and not focussed strictly on pharmacy personnel and nurses.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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Table 1: Urinary concentrations of CP (in ng/mL) overall and in each of the two sampling rounds

Subcategory	Sample Size	% > LOD	AM	GM	GSD	75th %	Max
Overall	201	55	0.156	0.067	3.18	0.129	2.37
Sampling round 1	103	40	0.082	< LOD	2.59	0.086	0.74
Sampling round 2	98	71	0.234	0.095	3.49	0.190	2.37

SUBMITTED VERSION

Table 2: Urinary concentrations of CP (in ng/mL) stratified by individual characteristics and CP contact during shift: summary statistics and p-values for each fixed effect variable in screening^a analyses

Fixed effect variable	Categories	Sample size		% > LOD	AM	GM	GSD	75th %	Max	p-value
		Rnd 1	Rnd 2							
Title	Pharmacist	16	16	44	0.089	< LOD	2.79	0.095	0.67	Reference
	Pharmacy receiver	6	6	58	0.115	0.064	2.79	0.096	0.61	0.46
	Pharmacy technician	21	21	57	0.170	0.065	3.23	0.125	2.37	0.28
	Porter	6	4	50	0.085	0.063	2.25	0.123	0.25	0.35
	Nurse	29	28	56	0.185	0.075	3.45	0.167	1.83	0.08
	Transport	4	4	63	0.134	0.057	3.54	0.079	0.72	0.74
	Unit Clerk	11	10	55	0.197	0.091	3.54	0.261	1.07	0.09
	Other (volunteer, oncologist, ward aide, dietician)	10	9	67	0.182	0.065	3.36	0.095	2.01	0.59
Gender	Female	82	79	55	0.158	0.067	3.25	0.141	2.01	Reference
	Male	21	19	55	0.151	0.064	2.96	0.110	2.37	0.89
Duty to handle?	Yes	82	80	56	0.160	0.069	3.16	0.130	2.37	Reference
	No	21	18	51	0.142	0.056	3.29	0.117	2.01	0.18
Percentage of time handling	< 25%	68	66	54	0.170	0.066	3.39	0.113	1.83	Reference
	> 25%	35	32	57	0.152	0.076	2.95	0.156	2.37	0.47
Work in an area where antineoplastic drugs are handled?	Yes	72	72	56	0.150	0.067	3.09	0.128	2.01	Reference
	No	31	26	54	0.173	0.066	3.45	0.130	2.37	0.93
Received training?	Yes	52	52	47	0.129	0.057	3.01	0.108	1.83	Reference
	No	51	46	64	0.185	0.080	3.30	0.160	2.37	0.06
Contact with CP on this shift?	No/Don't know	73	71	58	0.181	0.071	3.37	0.133	2.37	Reference
	Yes	30	27	49	0.095	0.057	2.70	0.118	0.55	0.27

^a Linear mixed effects models of ln-transformed urinary CP concentration, each model with a single fixed effect variable and hospital and subject as random effects

Table 3: Linear mixed effect models of urinary CP concentration levels (ln-transformed) in screening^a analyses of various continuous independent variables

Fixed effect variable	Intercept	Coefficient	SE	p-value ^a
Dermal concentration ^b	-2.697	-0.018	0.032	0.57
Number of types of CP contact on shift ^c	-2.660	-0.066	0.062	0.29
Knowledge score ^d	-2.565	-0.024	0.043	0.58

^a Each model with a single fixed effect variable and hospital and subject as random effect

^b Mean = 0.36 ng/wipe; range < 0.36 to 22.8 ng/wipe

^c Mean = 2; range 0 to 7

^d Mean = 5.8; range 0 to 7 (perfect)

Table 4: Urinary concentration levels of CP (in ng/mL) stratified by hospital characteristics: summary statistics and p-values for each fixed effect variable in screening^a analyses

Fixed effect variable	Categories	Sample Size		% > LOD	AM	GM	GSD	75th %	Max	p-value
		Rnd 1	Rnd 2							
Type	Acute Care	82	77	52	0.137	0.060	3.03	0.113	2.01	Reference
	Cancer Centre	21	21	67	0.228	0.097	3.58	0.212	2.37	0.12
Department	Drug administration	49	46	59	0.169	0.076	3.23	0.167	1.83	Reference
	Other ^b	11	9	55	0.184	0.064	3.50	0.112	2.01	0.68
	Pharmacy	43	43	51	0.134	0.058	3.04	0.106	2.37	0.16
Isolated preparation room	No	22	19	49	0.157	0.062	3.37	0.107	1.83	Reference
	Yes	81	79	57	0.156	0.068	3.15	0.129	2.37	0.78
Where drugs are initially delivered	Pharmacy	45	42	52	0.133	0.061	3.15	0.131	1.83	Reference
	Shipping/receiving	58	46	58	0.174	0.071	3.21	0.125	2.37	0.53

^a Linear mixed effects models of ln-transformed urinary CP concentration, each model with a single fixed effect variable and hospital and subject as random effects

^b Includes shipping/receiving, transport, nutrition and materials management

Table 5: Coefficients, standard errors and p-values for final linear mixed effect regression model^a showing the factors related to urinary CP concentration (ln-transformed)

Fixed effects variables	Coefficients	Standard Error	p-value
Intercept	-2.813	0.143	<0.0001
Duty to handle – Yes	Reference		
Duty to handle - No	-0.442	0.218	0.045
Received training - Yes	Reference		
Received training - No	0.414	0.172	0.018

^a Linear mixed effects model of ln-transformed urinary CP concentration, with all fixed effect variables together and hospital and subject as random effects