HEALTHCARE WORKERS AND ANTINEOPLASTIC DRUGS: EVALUATING THE RISKS AND IDENTIFYING DETERMINANTS OF EXPOSURE

by

Chun-Yip Hon

B.Sc., McMaster University, 1994

B.A.Sc., Ryerson University, 1996

M.Sc.(A), McGill University, 1997

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ABSTRACT

Healthcare workers' exposure to antineoplastic drugs may occur through handling of the drugs and/or via contact with drug-contaminated surfaces. However, studies have been limited to select departments and/or certain job titles. This may lead to an underestimate of the risk as the drugs circulate within a facility known as the hospital medication system (process flow of drugs).

This study aimed to answer the following questions related to antineoplastic drugs and the hospital medication system: 1) is contamination found on surfaces located throughout, 2) are workers throughout occupationally exposed (dermal and urinary contamination), and 3) what factors are associated with surface contamination and occupational exposure?

Site observations were conducted to identify which surfaces may be contaminated and the job categories that may contact these surfaces. Wipe samples were collected from potentially-contaminated surfaces and the hands of at-risk healthcare workers. Urine samples were collected from these same workers. Participants were asked to complete a questionnaire regarding their knowledge and usual protective habits regarding antineoplastic drugs and surveyed about contact with these agents on their work shift.

Drug residual was measurable on surfaces located throughout the hospital medication system. Determinants associated with increased surface contamination were the drug preparation and drug administration stages of the medication system as well as having more job categories responsible for drug transport. Up to 11 job categories per facility may have an exposure risk and the maximum dermal contamination levels for every job category exceeded the limit of detection. Factors associated with increased dermal contamination were working in acute care hospitals, female personnel, working as a porter, nurse, transport, unit clerk or other roles in the drug administration unit and having a duty to handle antineoplastic drugs. Urinary drug

contamination of participants was higher than in non-hospital controls confirming that exposure is occurring in the workplace. Being a pharmacy receiver, pharmacy technician, porter, nurse, or unit clerk and a facility having more job categories responsible for drug transport were associated with increased urinary contamination.

This is believed to be the first study examining environmental contamination and occupational exposure to antineoplastic drugs across the entire hospital medication system.

PREFACE

This dissertation consists of a total of six chapters. There are four research chapters (Chapters 2 to 5) bookended by an introductory and concluding chapter. Chapter 2 has already been published and Chapter 3 has been submitted for publication. Chapters 4 and 5 will be modified to meet journal formatting requirements and submitted in the coming months. I am/will be listed as primary author on each of these journal submissions. In this section, details of my role in the current study are provided as well as the contributions of others to each of the research chapters.

I designed the study and served in the capacity as principal author on the grant application to secure funding for the project. An operating grant was awarded by the WorkSafeBC Research Secretariat [RS2008-OG011] with a research budget of $263,325.70.

Operationally, I was the coordinator of the project responsible for the following duties: ethics applications and renewals (see below), participant recruitment, development of operating procedures for the various tasks related to data collection and field work, development of all study documents and pilot-testing of the questionnaire, hiring and managing research assistants, purchasing supplies, overseeing all sample collection, and management of the results database as well as the budget.

Recruitment of participants, study documents and sample collection methods for the study were approved by the University of British Columbia's Clinical Research Ethics Board (CREB certificate #H08-01167), as well as by the ethics boards of other participating research sites.

The Occupational and Environmental Hygiene laboratory located at the University of British Columbia performed all laboratory analyses. I conducted all the statistical analyses indicated and wrote the body of work presented in this dissertation.

Chapter 2: Identification of surfaces contaminated and job categories exposed throughout the hospital medication system

As repeated site observations were necessary, several research assistants, besides myself, were involved in the data collection - Claire Pitcher, Jennifer Shum and Pearl Signaporia.

I conducted all data analyses and wrote a majority of the manuscript. Feedback was provided by Kay Teschke, Prescillia Chua, Scott Venners and Lynne Nakashima. My overall contribution: 95%.

A version of Chapter 2 has been published: Hon C-Y, Teschke K, Chua P, Venners P and Nakashima L (2011). Occupational exposure to antineoplastic drugs: Identification of job categories potentially exposed throughout the hospital medication system. Safety and Health at Work 2(3): 273-281. http://dx.doi.org/10.5491/SHAW.2011.2.3.273. Copyright permission has been granted from the journal through Creative Commons Attribution Non-Commercial License to include excerpts of the article in this dissertation.

Chapter 3: Identification of surface contamination throughout the hospital medication system and identification of determinants of such contamination

In addition to myself, several research assistants were responsible for collecting surface wipe samples at the participating facilities: Jennifer Shum, Alexandra Barzan, Louise Hughes-Rhodes, Pearl Siganporia and Sarah Chiarello. I conducted all statistical analyses and wrote most of the chapter. Kay Teschke lent guidance regarding data analysis and provided the majority of feedback about the chapter. Winnie Chu led the team responsible for the laboratory analyses of the wipe samples (with Cris Barzan as the lead chemist) and reviewed the Methods section

describing the laboratory analyses. Both Paul Demers and George Astrakianiakis provided feedback comments on the chapter. My contribution: 90%.

A version of this chapter will be submitted for publication in the next few months.

Chapter 4: Evaluation of healthcare workers' dermal exposure throughout the hospital medication system and identification of determinants of such exposure

As in the previous chapter, I had assistance with sample collection. Research assistants involved with dermal wipe sample collection were Jennifer Shum, Pearl Siganporia and Sarah Chiarello.

I conducted all statistical analyses and wrote most of the chapter. Kay Teschke provided guidance regarding data analysis, feedback on the questionnaire, and the majority of feedback about the chapter. Winnie Chu led the team responsible for the laboratory analyses of the wipe samples (with Cris Barzan as the lead chemist) and reviewed the Methods section describing the laboratory analyses. Both Scott Venners and Paul Demers provided feedback on the chapter. My contribution: 90%.

A version of this chapter will be submitted for publication in the next few months.

Chapter 5: Evaluation of healthcare workers' urinary contamination throughout the hospital medication system and identification of determinants of such exposure

The same research assistants involved with dermal wipe sample collection were also involved with urine sample collection: Jennifer Shum, Pearl Siganporia and Sarah Chiarello. Alexandra Barzan helped to dispense the samples as well as document some basic lab measurements e.g. volume of urine, pH and extract temperature readings from probes.

I conducted all statistical analyses and wrote most of the chapter. Scott Venners assisted with the handling and interpretation of urinary contamination results as well as provided feedback

comments regarding the chapter. Kay Teschke provided guidance regarding data analysis and feedback of the chapter. Winnie Chu led the team responsible for the laboratory analyses of the urine samples (with Cris Barzan as the lead chemist) and reviewed the Methods section describing the laboratory analyses. Paul Demers provided constructive comments regarding the chapter as well. My contribution: 85%.

A version of this chapter will be submitted for publication in the next few months.

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4-keto	4-ketocyclophosphamide
AM	Arithmetic mean
BC	British Columbia
BSC	Biological safety cabinet
Carboxy	Carboxyphosphamide
CP	Cyclophosphamide
DNA	Deoxyribonucleic acid
Ethyl-CP	N-dechloroethylcyclophosphamide
GM	Geometric mean
GSD	Geometric standard deviation
HPLC-MS/MS	High-performance liquid chromatograph- tandem mass spectrometry
IV	Intravenous
LOD	Limit of detection
NIOSH	National Institute for Safety and Health

ACKNOWLEDGEMENTS

Numerous people and agencies need to be recognized for their efforts in providing guidance and support to complete this project. I would like to initially thank all the participants and their respective departments/facilities for agreeing to be part of this study – without their consent, there would be no data.

I would like to thank my Thesis Committee members for their guidance and advice throughout the project. Specifically, Kay Teschke for her patience, attention to detail, constructive commentary and positive attitude. To Scott Venners for his insight on biomarkers and for providing a much needed "non-hygiene" perspective. Lastly, to Paul Demers for his knowledge of workplace carcinogens and his understanding as to how the current project relates to the grand scheme of things.

Many thanks to the invaluable contributions made by the various research assistants that were involved in some capacity on this project. They were: Claire Pitcher, Jennifer Shum, Alexandra Barzan, Louise Hughes-Rhodes, Pearl Siganporia and Sarah Chiarello.

I also need to recognize the following healthcare organizations for lending their support to the project: British Columbia Nurses' Union (BCNU), Hospital Employees' Union (HEU), Health Sciences Association of British (HSA) Columbia and Health Employers Association of British Columbia (HEABC).

In addition, many individuals contributed to this study so that it could be successfully completed. These key individuals and their role in the study are summarized in the table that follows:

Name and organization	Contribution
Dr. Winnie Chu and analytical laboratory staff, SPPH	Laboratory analyses of samples.
Dr. George Astrakianakis, SPPH	Assisted with securing union support and reviewed grant application.
Prescillia Chua, Fraser Health	Study liaison at one of the participating health authorities.
Dr. Hui Shen and Hind Sbihi, SPPH	Provided guidance with respect to statistical analyses.
Dr. Robin Ensom, PHSA	Initial support of study and reviewed grant application.
Dr. Lynne Nakashima, BC Cancer Agency	Study liaison and provided insights into pharmacy operations.
Christie Hurrell, SPPH	Designed the study's website
Dr. Karen Bartlett, SPPH	Lent sampling supplies and laboratory space.
Miscellaneous healthcare workers	Pre-tested study documents.

Of course, this work could not be completed without operational funding provided by the WorkSafeBC Research Secretariat (RS2008-OG01). Scholarship support by The Canadian Institutes of Health Research (Doctoral Award), Michael Smith Foundation for Health Research (Junior Graduate Scholarship), WorkSafeBC Research Secretariat (Research Trainee), American Industrial Hygiene Foundation (Robert L. Harris Scholarship and Los Alamos Scholarship), Canadian Centre for Occupational Health and Safety (Dick Martin Scholarship Award) and others were greatly appreciated.

Lastly, I would like to thank my fellow colleagues at the School of Population and Public Health (Occupational and Environmental Hygiene Theme) for their support in keeping my spirits positive through the trials and tribulations of pursuing a doctorate degree. In particular, I would like to acknowledge Imelda Wong, Hind Sbihi and Tracy Kirkham.

DEDICATION

Although my love for knowledge has motivated me to pursue this project,
I could not have completed the journey without the two greatest loves in my life,
Sonca and Sasha. I therefore dedicate this to the two of you.

1 INTRODUCTION

1.1 Background

The term *antineoplastic* is defined as “destroying, inhibiting, or preventing the growth or spread of neoplasms or tumours”.(1) Given these properties, antineoplastic drugs, also referred to as cytotoxic, cytostatic, anticancer or chemotherapy drugs, are primarily utilized for the treatment of cancer. Many of these drugs act by interfering directly with the deoxyribonucleic acid (DNA) or the DNA synthesis of tumour cells and, consequently, the proliferation of these cells decreases. However, because antineoplastic drugs are non-selective in nature, normal healthy cells may also be affected.(2) This results in potential side effects experienced by cancer patients, such as nausea and hair loss(3), but is tolerated because of the therapeutic benefits offered by antineoplastic drugs. The same cannot be said for healthcare workers tasked with providing care and treatment to those undergoing chemotherapy. As such, there is a risk potential to healthcare workers who contact these hazardous agents. Circumstances whereby work-related contact may occur include, but are not limited to, drug preparation, drug administration, and disposal of drug waste.

The first study to demonstrate an occupational exposure risk of healthcare workers to antineoplastic drugs was in 1979; it reported elevated frequencies of mutagenicity in urine samples from oncology nurses.(4) Since then, numerous studies have provided evidence that healthcare personnel experience various health impacts, both acute and long-term, due to occupational exposure to antineoplastic drugs. Documented adverse health outcomes amongst exposed healthcare workers include alterations to genetic material (known as mutagenicity), reproductive toxic effects, and cancer.(5)(6)(7)

1.1.1 Release date of safe drug handling guidelines

In response, a number of agencies have developed safe drug handling guidelines(8)(9)(10) to be used in healthcare facilities to minimize occupational exposure to antineoplastic drugs. One of the most often cited guidelines is the "Alert: Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings" produced by the National Institute for Occupational Safety and Health (NIOSH) in the United States.(9) The NIOSH Alert was introduced in 2004 and included recommendations to minimize occupational exposure through the use of engineering controls (e.g. biological safety cabinets) during drug preparation, personal protective equipment (e.g. gloves and gowns) when handling antineoplastic drugs, and drug decontamination protocols.

Many healthcare facilities, including those in Metro Vancouver, have adopted elements of the NIOSH Alert. Research published prior to 2004 would not reflect the changes in practices and procedures outlined in the NIOSH Alert. The ensuing literature review will therefore primarily refer to findings from articles published from 2004 onwards; however, certain landmark papers released prior to this will still be discussed.

1.1.2 Use of cyclophosphamide as marker drug

Almost all studies examining environmental contamination and/or occupational exposure to antineoplastic drugs have measured a small number (usually fewer than five) marker drugs that act as surrogates to represent contamination to all antineoplastic drugs used in the facility. Although there are numerous antineoplastic drugs commercially available to which workers may be exposed, it is not feasible to measure every drug in assessments. Therefore, marker drugs are utilized. The criteria for selecting an appropriate marker drug are based on three factors: 1) the

toxicity of the drug, 2) the frequency of use of a drug, and 3) the sensitivity of the available analytical methods.(11)

The marker drug most often employed is cyclophosphamide (CP) (Figure 1-1).(12) The reasons for selecting CP as a surrogate are as follows. First, CP is an alkylating drug that forms cross-links with DNA(13) and it has been shown to cause the following malignancies in patients following administration: bladder cancer, acute myeloid leukemia and skin cancer.(14) This lends sufficient evidence that CP is carcinogenic in humans and it is therefore categorized as a known human carcinogen, or Group 1 agent, by the International Agency for Research in Cancer.(15)

Secondly, although first introduced almost 50 years ago, CP remains today as one of the most frequently administered chemotherapeutic agents for the treatment of various cancers, including breast, lymphoid and pediatric malignancies. In addition, CP is also employed in bone marrow transplants and for the treatment of different autoimmune conditions.(14) Data indicate that CP was the most widely prescribed antineoplastic drug in the province of British Columbia (BC) in 2009.(16) Its high frequency of use has been noted in other countries as well.(17)(18)(19)(20)

Lastly, not only is CP an analyte measured in almost all laboratory methods developed for exposure assessments(21)(22)(23)(24)(25)(26)(27)(28)(29), but recent advances in analytical methods, primarily the use of high-performance instrumentation such as high-performance liquid chromatography-tandem mass spectrometry(30), have resulted in limits of detection for CP as low as 0.05 picogram per square centimetre (pg/cm^2) for surface wipes(31) and 0.01 nanogram per milliliter (ng/mL) in urine samples.(30)(31)

Given the above, CP was selected as the marker drug in the current study. Therefore, for comparison purposes, only those articles that examined CP will be discussed. Note: where the

term “antineoplastic drug(s)” is used in this document, it refers to CP as one of the marker drugs, unless otherwise specified.

1.2 Pilot study conducted to ascertain nature of problem at local facilities

Despite the implementation of safe drug handling guidelines, studies have consistently found antineoplastic drug contamination on surfaces in healthcare facilities.(32)(33)(34)(35)(36) (among others) Such widespread contamination presents an opportunity for load transfer of drug residual if an individual contacts the contaminated surface.(37) This is noteworthy because dermal contact, as opposed to other routes of exposure, is considered the main route of exposure of healthcare workers to antineoplastic drugs.(11)(38)(39)(40)

Since occupational exposure assessments of healthcare workers in BC had not been performed previously, I designed a pilot study to measure drug contamination on work surfaces and ascertain the potential dermal exposure risk at select hospital pharmacies within Metro Vancouver. The pilot study found that 14 of the 23 surfaces wiped (61%) were contaminated with either CP or methotrexate, another commonly administered antineoplastic drug in BC. Furthermore, even among surfaces that were observed to have been cleaned, some had detectable levels of residual drug; in fact, some samples appeared to have post-cleaning concentrations greater than the corresponding pre-cleaning levels.(41)

The pilot study also demonstrated that 28% of hand wipe samples from pharmacy personnel had detectable levels of at least one drug product. Of note, workers who were *not* responsible for drug preparation on the day of sampling had measurable levels of antineoplastic drugs.(42) Given the findings from the pilot study, I strongly believed that this issue warranted further examination. To assist in the design of a large-scale study, a literature review was conducted to identify some of the knowledge gaps related to occupational exposure to antineoplastic drugs.

1.3 Review of existing literature

1.3.1 Only select departments have been assessed for surface contamination[a]

According to the Association paritaire pour la santé et la sécurité du travail du secteur affaires sociales (ASSTSAS)(10), which released a safe handling guide in 2008, there is a process flow of antineoplastic drugs within a facility known as the hospital medication system. Stages of the hospital medication system that are applicable to local sites include initial delivery of the drugs to the facility (delivery) and then being mixed to the correct dosage in the pharmacy (drug preparation). Subsequently, the prepared drugs, usually in intravenous (IV) form, need to be transported to patient units (transport to ward) where the drugs are administered to cancer patients (drug administration). Lastly, the drug containers, such as the manufacturer vials and IV bags, need to be disposed of in an appropriate manner (disposal). To determine antineoplastic drug contamination levels on work surfaces, wipe samples are often collected.(11) However, a review of the literature indicates that wipe sampling of surfaces has been conducted for select departments within a hospital rather than in all stages of the hospital medication system.

Surfaces situated in the drug preparation department have been studied in numerous countries. Some of the more common surfaces examined were biological safety cabinets (inside of which the drugs are prepared), countertops, waste containers, trays and the floors of the drug preparation area.(32)(34)(36)(43)(44)(45)(46)(47) CP was quantifiable on virtually all surfaces examined in the drug preparation area. Of concern is that drug residual was found despite the use of a biological safety cabinet and, in some instances, measurable levels of CP were detected outside of the biological safety cabinet.(20)(35)(48)

[a] Although closed system drug transfer devices (CSDTD) have been shown to be effective in minimizing surface contamination, they were not used at any of the local sites. Therefore, articles related to surface contamination and CSDTD usage were not cited.

Drug vials are commonly handled in the drug delivery stage and/or the drug preparation stage. Several studies have demonstrated that both the vials and the outer packaging received from drug manufacturers are contaminated.(32)(49)(50)(51)(52)(53) More locally, Touzin et al. reported contamination on the external surfaces of CP vials from the two manufacturers on the Canadian market.(54) The extent of external contamination may range from a few vials to all vials within a shipment. Connor et al. recommended that the impact of external contamination of vials on the overall contamination levels and the subsequent risk of occupational exposure should be explored further.(51) In a recent study, Hama et al. confirmed that healthcare workers who had just touched a vial were exposed to CP.(52)

A smaller number of studies have looked at surface contamination in the patient care units where antineoplastic drugs are administered.[b] Connor et al. collected wipe samples from areas where the drugs arrived at the nursing stations, carts and trays for transporting or storing drugs, areas where IV bags were hung before use, chairs, tables, and floors in patient rooms, floors in patient washrooms, waste containers, and utility rooms. CP was detected on almost all surface areas.(36) Sottani et al. sampled similar surfaces within patient administration areas in Italian healthcare facilities and reported measurable levels of CP on all surfaces sampled.(44) A Japanese study found CP contamination on 50% of the surfaces including those from the patient ward area.(43) Kromhout et al. reported contamination of patients' toilets, surfaces near the patients' beds, utility rooms (urinal washer), and corridors.(39) Cavallo et al. found the average contamination level in the patient care area was higher than in the pharmacy.(55) Hedmer et al. reported the highest surface contamination levels were on the doors in the patient washrooms and the utility rooms.(31)

[b] Surface contamination in patient units is not only due to the act of drug administration but it may also originate from patients undergoing chemotherapy who excrete the drugs via urine and other body fluids.

With documented evidence of contamination on the drug vials and in both the drug preparation and administration areas, it is possible that the contamination can spread to other areas of the hospital. Acampora et al. supported this notion by suggesting that the contamination of floors and storage shelves demonstrate the potential for these compounds to spread throughout a facility.(56) Crauste-Manciet et al. theorized that the removal of the drug vial cap could contribute to the spread of contamination.(20) In addition, the authors stated that the outside of the IV bags and workers' hands could be a major route for spreading drug residual. This is due to external contamination and potential permeation of antineoplastic drugs through gloves, respectively.(20) Another study suggested that drug contamination on floors may be spread by the footwear of workers or during cleaning of the floors and that external contamination of gloves may be transferred to other surfaces/objects.(57)

It is therefore conceivable that various surfaces at every stage of the hospital medication system may have drug contamination. However, a review of the literature could not locate studies that examined surface contamination throughout a hospital and its entire medication system.

1.3.2 Dermal contact of surfaces sampled is unknown

The previous section provides evidence that many surfaces within a hospital have measurable levels of antineoplastic drug contamination. What is not clear, however, is the actual frequency of skin contact that workers may have with these contaminated surfaces and, in turn, their exposure risk. One of the earliest studies examining surface contamination was in 1992 by Sessink et al. In this study, the authors looked at areas where cytostatic drug contamination 'may occur' during preparation due to possible spills and distribution of drugs during handling. Sampling areas chosen included the laminar airflow hood and the floor of the preparation room.(58) In a follow-up study, the authors expanded their scope and, in addition to the

pharmacy, examined the preparation and administration areas of the outpatient department and the oncology department. Additional surfaces included the working tray of the hood, floor of the preparation and administration room, floor of oncology department, front of hood, tables, and sinks.(59) Many subsequent studies have followed the sampling scheme established by Sessink et al.(47)(60) Other studies have also selected surfaces based on potential sources of contamination in the drug preparation and/or drug administration units.(31)(32)(46)(56) In some instances, no rationale was provided by the authors for selecting surfaces that were assessed for levels of drug residual.(61)(55)(48)(43)(62)

In a study by Schmaus et al., some rationale was provided for selecting the following surfaces: 1) the floor in front of the biological safety cabinet, 2) the floor in the preparation room's central area, 3) bench-top surfaces on which the drugs and materials were placed before IV mixtures were prepared, 4) surfaces on which IV containers were placed, 5) storage shelves, 6) transport boxes, and 7) waste bins. According to the authors, locations 1 – 3 were chosen because contamination can be found in areas where drug vials are unpacked and disinfected before preparing the infusions; IV bags containing cytotoxic drugs may lead to contamination if they are inappropriately handled and transported; and the surfaces of waste bins are often contaminated when cytotoxic waste is not handled properly. Lastly, the authors surmised that antineoplastic drug contamination has been found on storage shelves that hold contaminated packages of these agents.(24)

The lone study that used a sampling scheme reflective of dermal contact was by Castiglia et al. The authors employed an on-the-spot investigation to identify which surfaces may be potentially contaminated and this information was used to form the basis of their subsequent sampling strategy.(63) However, this investigation was conducted in the drug preparation room only.

As dermal contact is the main route of occupational exposure, it would appear sensible to determine the contamination levels of those surfaces that workers are likely to contact. In fact, this was suggested by Turci et al. who stated that contamination routes in working areas have to be established and exposure routes, especially skin absorption, in hospital personnel have to be identified.(11) However, the literature does not appear to reflect this notion with surfaces selected based on probability of contamination as opposed to actual contact frequency.

1.3.3 Underestimation of exposure

There is a likelihood that the literature has underestimated the number of healthcare workers that are potentially exposed to antineoplastic drugs as well as the actual exposure levels, particularly in urine samples. This section outlines these two shortcomings that currently exist in the literature.

Number of workers overall at risk

As with the surface contamination studies, occupational exposure studies have also been limited in their scope. A review of the literature indicates that studies examining occupational exposure to antineoplastic drugs have focused on select job categories.

Many have looked strictly at pharmacists that directly handle antineoplastic drugs.(48)(52)(62) Other papers have examined nursing personnel as they are tasked with drug administration and also care for patients who undergo chemotherapy.(18)(64)(65) Pharmacy technicians, often responsible for drug preparation, are another cohort that has been cited in the literature.(37) In some cases, combinations of two or more of the aforementioned job categories have been studied.(17)(36)(44). Some studies that examined multiple cohorts also included a medical doctor(43)(35), a surgeon and an anesthetist(66), as well as cleaners (31)(67)(40).

Determining the exposure levels of pharmacists, nurses and pharmacy technicians appears warranted because these cohorts handle antineoplastic drugs on a fairly regular basis and often at high concentration/doses. Nevertheless, since it is hypothesized that surface contamination is likely throughout the entire hospital medication system, this does not preclude other job categories from being exposed. Sorsa et al. produced a list of potentially exposed healthcare workers which includes pharmacy personnel preparing the drugs, hospital staff involved with drug administration, physicians and nurses in patient care areas, cleaning and laundry personnel, scientists and laboratory personnel, and drug transport personnel.(68) However, exposure studies of healthcare personnel besides pharmacists, nurses and pharmacy technicians are limited. Fransman et al. demonstrated that cleaning personnel have dermal contamination.(67) Similarly, Kusnetz and Condon concluded that auxillary healthcare personnel, such as care aides, are at risk of exposure to antineoplastic drugs.(69)

One way to identify the exposure risks of various healthcare workers is to look at exposures of personnel in different departments. Believed to be one of the first papers looking at several departments, Sessink et al. studied exposure in four departments. The departments were the clinical pharmacy department (preparation), outpatient department (preparation), outpatient department (administration) and oncology department (administration). Unfortunately, the authors examined the exposures of pharmacy technicians and nurses only.(59)

Another means to examine exposure risks of various healthcare workers is to identify the risks associated with tasks involved with handling antineoplastic drugs. Fransman et al. measured dermal exposure to CP during the performance of five tasks: 1) preparation of antineoplastic drugs in the hospital pharmacy; 2) decanting patient urine; 3) washing the patient; 4) removing the sheets from the patient's bed; and 5) cleaning the patients' toilet on the oncology ward of the

hospital. However, the authors' evaluation was limited to pharmacy technicians, oncology nurses and cleaners.(67)

Since surface contamination is conceivable throughout the hospital medication system and not strictly isolated to the drug preparation and drug administration units, the total number of healthcare workers exposed to antineoplastic drugs may be much higher than previously thought.(70) However, a literature review was unable to find studies that simultaneously ascertained the exposure levels of healthcare personnel that work throughout the hospital medication system.

Urinary contamination levels

The quantification of antineoplastic drugs in urine samples is used to determine occupational exposure across all exposure routes, including dermal, inhalation or ingestion.(36) In particular, measuring CP in urine has proven to be an appropriate biomarker to estimate doses that have been taken up in the body.(71) Many studies have found measurable levels of CP in the urine samples of exposed workers indicating that absorption does indeed take place.(12) However, pharmacokinetic studies suggest that less than 20% of absorbed CP is excreted unchanged in the urine and the rest is metabolized and/or eliminated through other means e.g. feces, expired breath.(72) Metabolism of CP is influenced by factors related to the drug itself (e.g., dosage, route of administration, and drug combination) as well as the person (e.g., age, gender, and hepatic function).(72) This results in both inter- and intra-individual variations in the pharmacokinetics of CP.(71) Given this, if CP alone is measured, the urine levels reported likely underestimate the actual amount absorbed by a worker.

To address this shortcoming, both Sottani et al.(44) and Turci et al.(66) suggested that quantifying the amount of parent product, CP, and one or more of its urinary metabolites would

be a more accurate reflection of exposure (Figure 1-2). However, a review of the literature did not reveal any studies with more than 20 participants that measured CP and its metabolites.

1.3.4 Dearth of data related to the determinants of contamination or exposure

Numerous studies have examined surface contamination levels while others have evaluated occupational exposure levels of antineoplastic drugs through hand wipes or urine samples. Few studies have examined the factors that may be associated with such contamination or exposure. By identifying factors that are associated with elevated or reduced contamination/exposure levels, control measures that specifically target these determinants can be implemented to minimize the risk potential.

Surface contamination

Only two studies have addressed determinants of surface contamination. One found no association between the number of drug handling events and the proportion of surface wipe samples with measurable drug residual.(36) The other study concluded no apparent correlation between the surface contamination levels and the amount of CP prepared annually, the age of cytotoxic suite or the biological safety cabinet, decontamination and cleaning procedures, or the staff preparing chemotherapy.(34) These studies examined only the drug preparation and drug administration areas. Determinants of contamination for surfaces throughout the hospital medication system have yet to be evaluated.

Occupational exposure

With respect to occupational exposure in general, a number of studies have indicated various determinants that lead to an elevated risk of exposure or factors that have no association with exposure. Testa et al. concluded that age, gender and the experience of a worker are *not* likely

determinants of exposure risk.(73) In their review, Ritchie et al. found that lack of compliance with safe work practices was associated with an elevated risk of exposure.(6)

Factors related specifically to dermal exposure have also been examined. Dermal contamination levels have been found to be higher if a worker handles drug vials.(7)(40) Friese et al. found that organizational factors, such as adequate staffing and a check-and-balance system for drug administration, reduced potential skin exposure.(74)

Reported determinants of urinary exposure differ from those for dermal exposure. Schreiber et al. found the following factors influenced uptake of antineoplastic drugs: the amount processed (for workers responsible for drug preparation); the number of preparations handled (for workers responsible for drug preparation and those who assisted in the drug preparation); and hazardous waste that is stored in garbage bins with a lid that can be opened.(75) The importance of the amount handled was supported in a recent study(51) but was also contradicted by Favier et al. who found no correlation between the amount handled and urinary excretion.(76) Rekhadevi et al. found that age, years of exposure and duration of handling antineoplastic drugs per day were positively associated with urinary CP concentrations, though age was the lone variable that was statistically significant.(64)

These determinants studies included the following select hospital departments and/or healthcare personnel: pharmacy department(40)(51)(75), patient administration units(40)(64), pharmacists(40)(75), pharmacy technicians(40)(75), nurses(40)(64)(74) and cleaners.(40) Determinants of occupational exposure for all at-risk job categories throughout the hospital medication system have yet to be evaluated.

1.3.5 Occupational exposure likely to continue and possibly trend upwards

According to the Canadian Cancer Society, the number of cancer cases is expected to steadily rise as the Canadian population increases and ages.(77) With more cancer cases, there will be an increase in the number of patients seeking treatment with antineoplastic drugs. Therefore, healthcare workers' exposure to these hazardous agents will persist with a strong possibility that it will increase in the near future.

In addition, antineoplastic drugs are increasingly being utilized for the treatment of other diseases besides cancer including non-malignant diseases such as aplastic anemia (requiring bone marrow transplants) and arthritis. In turn, the potential for exposure of healthcare providers to these drugs will increase.(7) Furthermore, since the use of antineoplastic drugs has expanded into other specialties, the number of hospital workers who are not properly trained in their safe handling has also increased.(9)

1.3.6 Lack of consistent and/or effective policies to reduce occupational exposure

In addition to addressing gaps in the literature, examining the issue of healthcare workers' exposure to antineoplastic drugs is also likely to have policy implications. Currently, there is no recognized occupational exposure limit for antineoplastic drugs whereby an exposure concentration is deemed to be safe and unlikely to result in toxic effects. In instances where exposure limits are not available for carcinogens like CP, occupational hygienists have adopted the principle of maintaining exposures as low as reasonably achievable (ALARA). However, the challenge lies in defining the ALARA level as this cannot be achieved until an exposure assessment is completed to ascertain current exposure levels.

Despite the implementation of control measures indicated in safe handling guidelines, both surface contamination and worker exposure continue to occur. Through the identification of determinants of contamination/exposure, it may be possible to strengthen these existing guidelines in order to reduce the risk.

1.4 Rationale for current study and research questions

Based on the results from the pilot study as well as knowledge gaps identified in the literature, a full-scale study to examine healthcare workers' exposure to antineoplastic drugs was developed and submitted for funding in February 2008.

The following were the key research questions that the study was designed to answer:

- Is antineoplastic drug contamination found on surfaces located throughout the hospital medication system?
- Are healthcare workers throughout the hospital medication system occupationally exposed to antineoplastic drugs?
- What are the factors that are associated with surface contamination and occupational exposure (dermal and urinary contamination) throughout the hospital medication system?

To answer these questions, this study had the following specific research objectives:

Objective 1: Identify surfaces most likely contaminated and the job categories potentially at risk of exposure to antineoplastic drugs throughout the hospital medication system (**Chapter 2**);

Objective 2: Quantify the surface contamination levels throughout the hospital medication system and identify determinants associated with surface contamination (**Chapter 3**);

Objective 3: Assess the dermal CP contamination levels of at-risk healthcare job categories and identify determinants associated with dermal exposure (**Chapter 4**); and

Objective 4: Determine the urinary concentrations of CP and three of its metabolites in at-risk healthcare job categories and identify determinants associated with urinary contamination (**Chapter 5**).

1.5 Dissertation structure

This dissertation consists of six chapters: this introductory chapter, four research chapters and a concluding chapter. The research chapters were written with the intention of submission to peer-reviewed journals. The four research chapters and the concluding chapter are outlined below:

Chapter 2 Identification of surfaces contaminated and job categories exposed throughout the hospital medication system

The purpose of this phase of the research was to conduct site observations in order to determine the hospital medication system at each participating site and ascertain which surfaces are potentially contaminated with antineoplastic drugs. It also identified the various healthcare job categories that are likely to contact the contaminated surfaces. The overall goal of this phase was to assist in planning an appropriate sampling strategy for the subsequent research chapters.

Chapter 3 Evaluation of surface contamination throughout the hospital medication system and identification of determinants of such contamination

Wipe samples were collected from those surfaces identified in Chapter 2 as being potentially contaminated and subsequently analyzed to quantify the amount of CP. The goal of this research was to test the theory that surface contamination exists throughout the hospital medication

system. Another outcome of this chapter was the identification of hospital-related factors that are associated with surface contamination.

Chapter 4 Evaluation of healthcare workers' dermal exposure throughout the hospital medication system and identification of determinants of such exposure

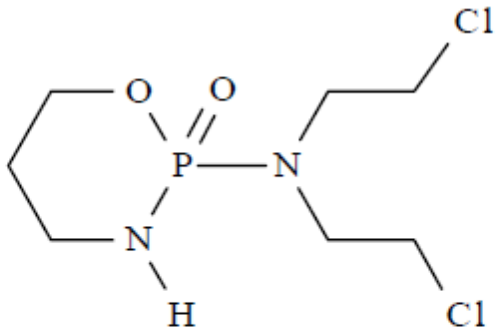
Workers from those job categories identified in Chapter 2 as being potentially exposed were recruited to participate in the study. Utilizing a similar sampling method as employed in Chapter 3, participants' hands were wiped and subsequently analyzed to measure the amount of CP. This research aimed to determine the dermal contamination levels of healthcare workers at risk of exposure to antineoplastic drugs due to their role in the hospital medication system. Participants were also provided with a self-administered questionnaire regarding knowledge and training and were surveyed at the time of sample collection about known contact with CP. Variables from the survey instruments were used to identify determinants of dermal exposure.

Chapter 5 Evaluation of healthcare workers' urinary contamination level throughout the hospital medication system and identification of determinants of such contamination

Dermal samples only provide the level of external contamination whereas urine samples serve to confirm that the drug has been absorbed and, therefore, have the potential to result in chronic adverse health effects. The same workers who provided hand wipe samples were also asked to submit urine samples. Urine samples were analyzed for CP and three of its metabolites. As in the previous chapters, determinants associated with urinary contamination were identified and discussed.

Concluding chapter

The final chapter provides an overview of the key findings, lists a number of recommendations resulting from the study that may minimize the risk potential, discusses the strengths and limitation of the study and, lastly, summarizes some possible future research arising from the current study.



$C_7H_{15}Cl_2N_2O_2P$

Relative molecular mass: 261.1

Figure 1-1 Structural and molecular formula and relative molecular mass of cyclophosphamide(15)

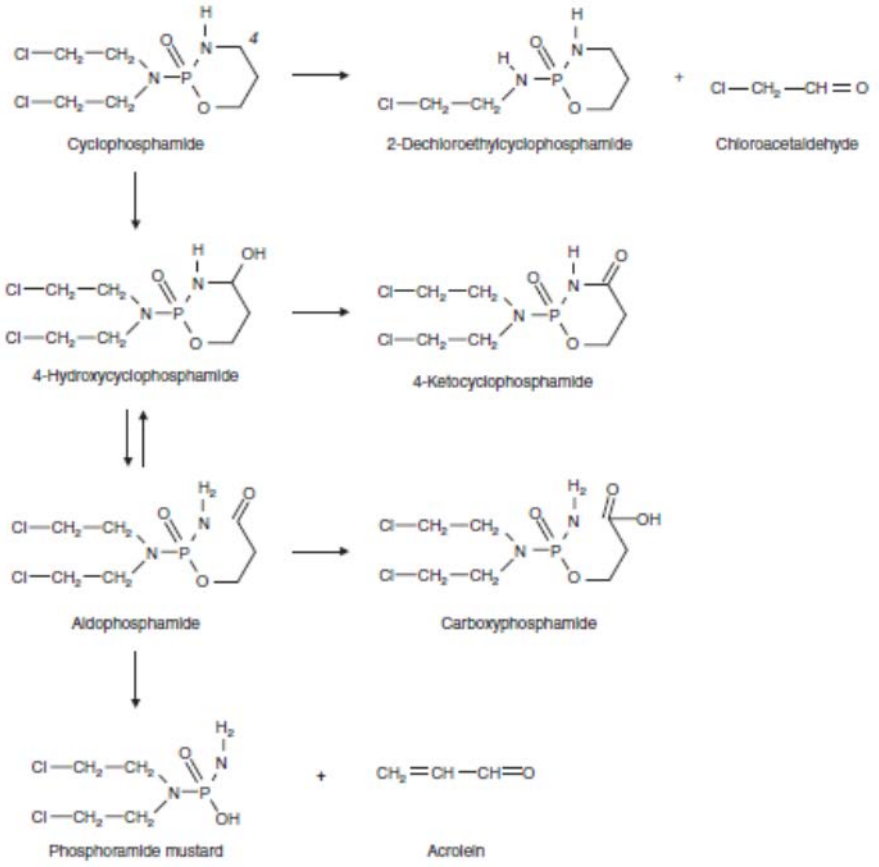


Figure 1-2 Metabolism of cyclophosphamide. The inactivation pathways are depicted horizontally, while cyclophosphamide activation is shown vertically.(13)

2 IDENTIFICATION OF SURFACES CONTAMINATED AND JOB CATEGORIES EXPOSED THROUGHOUT THE HOSPITAL MEDICATION SYSTEM

2.1 Synopsis

Antineoplastic drugs are known to circulate within a healthcare facility referred to as the hospital medication system (process flow of drugs from cradle-to-grave) which consists of several different departments involving various healthcare job cohorts. However, virtually all environmental contamination and occupational exposure studies have restricted their assessment to select areas only, namely the drug preparation and the drug administration units. A number of studies have suggested that drug contamination may spread to other areas resulting in exposure to a broader range of healthcare workers. The purpose of this chapter was to identify which surfaces throughout the hospital medication system may be contaminated with antineoplastic drugs and, in addition, ascertain which healthcare job categories are likely to contact these surfaces. Repeated passive observations were conducted at each of the participating sites. During each observation, potentially contaminated surfaces were documented and both the job title and frequency of contact with the surface were recorded. The hospital medication system at each of the sites consisted of five stages: delivery, drug preparation, transport (of drugs) to ward, drug administration and disposal. Various surfaces at every stage were believed to have drug residual because a drug container was placed on it or a worker with contaminated gloves/hands touched the surface. Pharmacy receivers, pharmacy technicians, pharmacists, and nurses were consistently found to be in contact with contaminated surfaces at all participating sites. Up to 11 job categories per site may be at risk of exposure to antineoplastic drugs.

2.2 Introduction

Antineoplastic (cytotoxic) drugs are widely used agents for the treatment of cancer. Some of these drugs act by interfering directly with the deoxyribonucleic acid (or its synthesis) of tumour cells and thereby interrupt their growth. Unfortunately, antineoplastic drugs are generally non-selective and therefore normal (non-tumour) cells may also be damaged which, in turn, results in toxic effects.(2) Given this, there is a risk to healthcare workers who handle, prepare, and/or administer antineoplastic drugs.

Numerous studies have examined antineoplastic drug contamination in healthcare facilities. Studies from several countries have demonstrated surface contamination of biological safety cabinets, countertops, cabinets and floors within the drug preparation area.(59)(60)(61)(24)(19) Detectable levels of environmental drug contamination have also been found in patient care areas where antineoplastic drugs are administered.(55) A recently published summary of surface contamination levels found in the literature reported that cyclophosphamide (CP) ranged in concentration from not detected to 3,834 nanograms per square centimeter (ng/cm^2), which suggests that existing control measures are not effective in reducing contamination levels.(33) In the absence of any current occupational exposure limits for CP (and most other antineoplastic drugs), it is therefore important to minimize contamination.

A literature review revealed that these surface contamination studies have primarily focused on two departments within a healthcare facility – the pharmacy, where the drugs are prepared, and the administration units where the prepared drugs are given to patients. The emphasis on these two departments is warranted since direct handling of the drugs is expected during both preparation and administration. However, given the fact that the drugs need to be initially delivered to the pharmacy, then transported to the wards and eventually disposed as part of the

hospital medication system (process flow of drugs throughout a healthcare facility from cradle-to-grave), it is conceivable that other areas of a facility may have drug residual and, therefore, the number of healthcare workers at risk of exposure is underestimated.

The potential for other healthcare workers to be occupationally exposed to antineoplastic drugs is supported in the literature whereby mechanisms of drug contamination spread have been proposed. Surface contamination may arise as early as the facility receiving stage in the hospital medication system as it has been documented that drug vials are often contaminated on the outside.(49)(50)(32) It is also possible that drug residue is spread by the footwear of workers or during cleaning of floors and that external drug contamination on gloves may be transferred to other objects or surfaces.(57) Overall, this suggests a need to examine the healthcare facility as a whole, not just the pharmacy and drug administration units, to determine the extent of antineoplastic drug contamination from the point at which the agents are received at the facility through to disposal or excretion. To our knowledge, no existing literature has investigated this issue.

The current study aims to identify surfaces throughout the hospital medication system whereby antineoplastic drug contamination may be possible and to ascertain the various healthcare job categories that may be at risk of dermal exposure to antineoplastic drugs via contact with the contaminated surfaces - not just drug administration nurses and pharmacy personnel.

2.3 Methods

2.3.1 Selection of participating sites

Participating sites were selected from healthcare facilities situated within the Metro Vancouver area of British Columbia, Canada that prepare and administer CP, the marker drug in this study.

The sites finalized for inclusion were determined by asking a pharmacy member from each participating health administration authority which of their facilities are the largest users of CP on an annual basis (based on overall frequency of compounding). In total, five major acute care hospitals and one cancer treatment centre participated in the study.

2.3.2 Informant interviews

Interviews with key informants were conducted in order to understand the site-specific hospital medication system and to predict how and where a worker may be exposed to antineoplastic drugs. Key informants included supervisors/managers, clinical nurse leaders, and team leaders such as the senior pharmacy technician. At all sites, the initial interview was conducted in the pharmacy department as their personnel would be familiar with how the drugs arrive at their department and where the prepared drugs are transported for eventual administration. Subsequently, additional interviews were scheduled with those departments identified by the pharmacy informant as being part of the hospital medication system. All departments at each site involved in the hospital medication system were interviewed with the exception of housekeeping which is operated by the same external contractor at each site; the company declined to participate in the study.

The duration of each interview was at least twenty minutes. All interviewees were asked questions related to the shift when antineoplastic drugs are primarily handled, prepared or administered; circumstances under which workers may be exposed to antineoplastic drugs; and the likely job categories which may be at risk of exposure. In addition, pharmacy personnel were questioned about their understanding of the hospital medication system at their site.

2.3.3 Site observations

Passive (non-intrusive) site observations at each site were conducted by members of the research team to visually establish the hospital medication system and to identify which surfaces/objects may be contaminated with antineoplastic drugs as well as those job categories potentially at risk of dermal exposure via contact with the contaminated surfaces.(78) An employee was considered "at-risk" if they physically handled the drugs, contacted a potentially drug-contaminated surface/object, or used an object previously touched by another worker suspected of having drug-contaminated hands/gloves. A standard observation checklist was developed and used to record: a) the surfaces/objects which came into contact with the drug products, b) the job category of the worker that contacted the drugs and/or the contaminated surfaces and c) the associated frequency of contact of surfaces/objects for each worker (see Appendix A).

At all sites, the observations began in the Pharmacy department where antineoplastic drug preparation was observed. We then followed the drugs as they were transported to the unit where they would be administered. Where prepared drugs were delivered to more than one unit, we randomly selected one unit to follow the drug. We conducted observations of the other unit(s) on separate occasions. There was considerable variation with respect to delivery times of the antineoplastic drugs to the healthcare facility. To accommodate this, we scheduled site visits to specifically observe the receiving process but not necessarily review other areas of the hospital medication system.

Overall, in order to understand the entire hospital medication system, each site was observed on at least five separate occasions over a course of twelve months starting in June 2009. For each site visit, at least one task cycle was observed in each department. Examples of "one task cycle" include observing a porter picking up a drug order and delivering to the drug administration unit

for the drug transport stage; and observing the pharmacy technician compound the chemotherapy drug dose for one patient during drug preparation. By performing repeated observations the sequence of each site's hospital medication system was determined and the job categories with potential risk of exposure to antineoplastic drugs were identified.

2.3.4 Data analysis

The contact frequency of a surface/object was averaged over the number of observation periods at each site and then ranked by order of frequency for each stage of the hospital medication system. For the drug delivery as well as the transport to ward stages, the top three most frequently contacted surfaces were presented in the frequency bar graphs. With respect to the drug preparation and drug administration steps, the top five most frequently contacted surfaces are presented. The rationale for reporting a varying number of surfaces is that drug delivery and transport to the ward are more standard processes with less variability. In addition, both tasks are less likely to be influenced by individual and/or patient factors than either drug preparation or drug administration and therefore fewer surfaces/objects are contacted overall.

2.4 Results

2.4.1 General hospital medication system

As shown in Figure 2-1, the general sequence of the hospital medication system for each of the participating facilities has a minimum of the following six stages: 1) delivery of the antineoplastic drugs to the facility, 2) drug preparation, 3) transport to ward, 4) drug administration, 5) disposal and, 6) waste retrieval. As disposal of the waste containers and waste retrieval is performed by private companies that declined to participate in the study, more specific details for these two steps are unavailable.

2.4.2 Description of participating facilities

Table 2-1 provides a descriptive summary of each of the participating facilities. All six sites were situated in an urban centre and, at every facility, CP is one of the top five most frequently compounded antineoplastic drugs (For example, Site E alone purchased 1,715 grams of CP in 2011). All facilities were acute care hospitals except Site F which is a cancer centre. Sites B, E and F have the drugs initially delivered to the shipping/receiving department whereas the remaining sites have the drugs delivered directly to the pharmacy department. With the exception of Site D, antineoplastic drugs are prepared in dedicated isolation rooms situated in the pharmacy department. At Site D, antineoplastic drugs are prepared adjacent to an area for drugs that are not used for chemotherapy.

The prepared drugs are delivered by various job categories to the administration wards, with one site (Site F) having up to three different job categories performing this task. Drugs are either administered in an out-patient clinic or within in-patient wards. The antineoplastic drugs are administered in three wards at sites D and E. In all instances, the antineoplastic drugs are disposed of within the pharmacy (the manufacturers' vials) as well as in the drug administration wards (the intravenous bags). In the "notes" section of Table 2-1, it can be seen that each facility is designed slightly differently from the others. In most instances, the pharmacy, where drug preparation takes place, is situated on a different floor from where the drug administration takes place.

2.4.3 Contact frequency of work surfaces/objects

Figures 2-2 to 2-5 display the frequency of surfaces that came into contact with antineoplastic drugs and/or potentially drug-contaminated surfaces contacted by healthcare workers for each stage of the hospital medication system. According to Figure 2-2, the box cutter is the most

frequently contacted object during drug delivery as it is used to open packages of drug shipments. The cart is the second most frequently contacted surface during this stage as it is used to deliver drug shipments from shipping/receiving to pharmacy as well as from pharmacy receiving to the main pharmacy (where the drugs are stored).

With respect to drug preparation, Figure 2-3, the biological safety cabinet is the most frequently contacted surface as antineoplastic drugs are prepared in these cabinets at all sites. The next most frequently contacted object during drug preparation is a writing instrument found inside the biological safety cabinet. The writing instrument is used by the pharmacy technician to label the prepared drugs and/or verify drug dosages. Following these two surfaces/objects, there is a great deal of variability with respect to what is contacted and how frequently they are contacted.

In the third stage of the hospital medication system, drug transport within the facility, Figure 2-4 shows that the bin/drawer where drugs are held for pick up is the most frequently contacted surface during the drug transport stage. It should be noted that Site B is not represented in this figure because drug transport is not required at this site since the pharmacy is immediately adjacent to the out-patient clinic.

During drug administration (Figure 2-5), the intravenous hook/pump is the object that is overwhelmingly contacted by workers because virtually all of the drugs observed were in solution form and had to be administered intravenously using the mechanical pump. Similar to the drug preparation stage, there is a subsequent assortment of surfaces which are contacted across the sites during drug administration.

Note that there is no corresponding bar graph for the disposal stage as only a total of three surfaces were found to be contacted by hospital employees (recall that all sites have contracted their housekeeping services to a company that declined to participate in the study). These three

surfaces, all from Site E, were an elevator button (to waste holding floor), a door handle (to waste holding room) and a biohazard cart.

2.4.4 Job categories at risk of exposure

Table 2-2 summarizes the stages of the hospital medication system with the corresponding job categories that may be at risk of exposure at each of the participating sites. The pharmacy receiver, pharmacy technician, pharmacist, and nurse are potentially exposed to antineoplastic drugs at all sites. During transport of the prepared drugs to the ward, various job categories are at risk of exposure via handling of the antineoplastic drugs. Among the stages of the hospital medication system, drug administration has the most job categories (six) at potential risk of exposure.

With respect to disposal of the drug products, Site E had a unique job category known as "biopackers" who are responsible for transferring the sealed waste containers from a holding area to a waste disposal room, where the containers would subsequently be picked-up by a waste disposal company.

Based on the information provided by the key personnel during the interviews, it is estimated that over 500 workers at the six participating sites may be occupationally exposed. The distribution of the various job categories at each site that are potentially exposed is shown in Table 2-3.

2.5 Discussion

Our study suggests that surface contamination may occur at every stage of the hospital medication system within a healthcare facility. As a result, the potential for occupational exposure to antineoplastic drugs also occurs at every stage. Those job categories most likely

exposed are pharmacy receiver, pharmacy technician, pharmacist, and nurse as these cohorts were consistently observed to be in contact with antineoplastic drugs at each of the six participating sites. Up to 11 job categories (not including housekeeping) per site are potentially at risk of exposure. The characteristics of a site that results in the most number of job categories exposed include: a) having the drugs initially delivered to the shipping/receiving department (as opposed to directly to the pharmacy), b) having multiple job categories responsible for transport of prepared drugs to the ward(s) and, c) having more than one drug administration unit.

Our study builds on the list of healthcare workers exposed to antineoplastic drugs due to handling activities developed by the National Institute for Occupational Safety and Health (NIOSH).(9) In addition to the cohorts specified by NIOSH, our results suggest that it is reasonable to add the following personnel to the existing list: unit clerk, porter, volunteer, ward aide, dietician, and biopacker.

Although our study primarily focused on occupational exposure, it is conceivable that patients, their family members, and their friends are also at risk of exposure as suggested by Sorsa et al.(68) This is because communal objects such as elevator buttons, door handles and patient chair side tables, which may be contacted by non-hospital personnel, were observed to be frequently contacted in our study.

As discussed previously, almost all studies related to antineoplastic drug contamination on surfaces have examined either the drug preparation area and/or the drug administration area. Based on a review of the literature, we were only able to find one study which examined surface contamination of multiple departments within a healthcare facility. The authors examined four departments within a facility, the clinical pharmacy, outpatient department (preparation), outpatient department (administration) and oncology department, and found detectable levels of

antineoplastic drugs in every department.(59) As our study consisted of multiple sites with repeated observations at each site, we believe that there is likely to be surface contamination in other departments in addition to the drug preparation and drug administration areas.

With respect to the risk of exposure, Connor and McDiarmid proposed general handling guidelines to prevent occupational exposure to antineoplastic drugs at each stage of the hospital medication system that was indicated in the current study (except waste retrieval).(7) This implies that an exposure potential is probable throughout the entire medication system.

2.5.1 Limitations

Among the study limitations, we were unable to ascertain the frequency of contact associated with housekeeping personnel as they are employees of a company that declined to participate in our study. We can surmise that housekeepers would contact the cytotoxic waste containers but cannot estimate the contact risk for other surfaces. As waste containers, which have been shown to be contaminated in other studies(36)(44), were frequently contacted during drug administration by nursing staff, we can infer that housekeepers do indeed face an exposure potential. Another limitation is the possible absence of certain job categories and/or surfaces despite repeated site observations. Nevertheless, since we performed the site observations on multiple days and observed different individuals, we are confident that we have captured a reasonably representative understanding of the hospital medication system, the job categories commonly at risk of exposure and the potentially contaminated work surfaces at each site.

2.5.2 Summary

To our knowledge, this is the first study of its kind to examine the occupational exposure potential to antineoplastic drugs throughout the entire hospital medication system of a healthcare

facility. Based on the results of this study, we are now able to develop an appropriate sampling strategy for all job categories considered at risk of exposure. In addition, we have also gained an understanding of which surfaces may be contaminated with antineoplastic drugs and, in turn, allow us to conduct a detailed assessment of environmental drug contamination throughout the entire healthcare facility. This is important in order to validate that existing control measures are not only appropriate in reducing occupational exposure to antineoplastic drugs but that they are comprehensive in scope to protect all at-risk job categories.

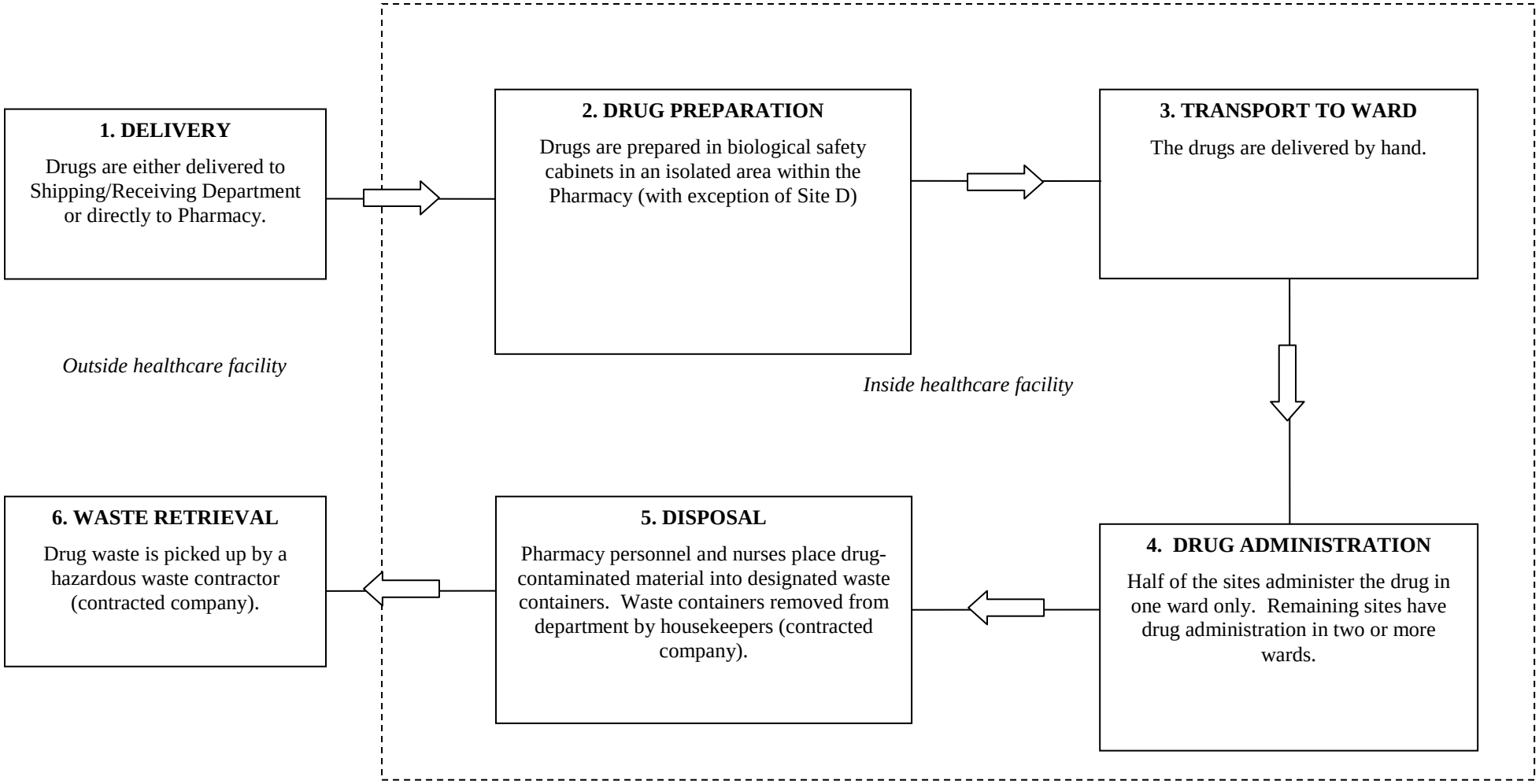


Figure 2-1 Overview of hospital medication system within participating facilities

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Table 2-1 Description of participating facilities

Site	A	B	C	D	E	F
Type	Hospital	Hospital	Hospital	Hospital	Hospital	Cancer Centre
1. Drug Delivery *(how vials are delivered from manufacturer)*	Direct to pharmacy	Via shipping/ receiving to pharmacy	Direct to pharmacy	Direct to pharmacy	Via shipping/ receiving to pharmacy	Via shipping/ receiving to pharmacy
2. Drug Preparation* *(where drugs are prepared)*	In isolated room	In isolated room	In isolated room	In non-isolated room	In isolation room	In isolation room
3. Transport to Ward *(job category tasked with transport)*	By porter	By pharmacist	By ward aide	By porter or ward aide	By porter or nurse	By nurse or unit clerk or pharmacy personnel
4. Drug Administration *(type of patient ward)*	1 out-patient clinic	1 out-patient clinic	1 out-patient clinic	2 in-patient wards; 1 out-patient clinic	1 in-patient wards; 2 out-patient clinics	1 in-patient ward; 1 out-patient clinic
5. Drug Disposal *(department where disposal occurs)*	Pharmacy and out-patient clinic	Pharmacy and out-patient clinic	Pharmacy and out-patient clinic	Pharmacy and drug administration wards	Pharmacy and drug administration wards	Pharmacy and drug administration wards
Notes *(unique features of each site)*	Pharmacy and out-patient clinic are on different floors	Pharmacy is adjacent to the out-patient clinic	Pharmacy and out-patient clinic are on different floors	Drug administration wards are in a separate building from pharmacy on three different floors	In-patient ward is on same floor as pharmacy; out-patient clinics are in a separate building from pharmacy	Out-patient clinic on same floor as pharmacy; in-patient ward is one floor below the pharmacy

** isolated = room is designated strictly for antineoplastic drug preparation; non-isolated = room is open-concept with biological safety cabinets for preparing antineoplastic drugs and other hoods for preparing non-cytotoxic drugs*

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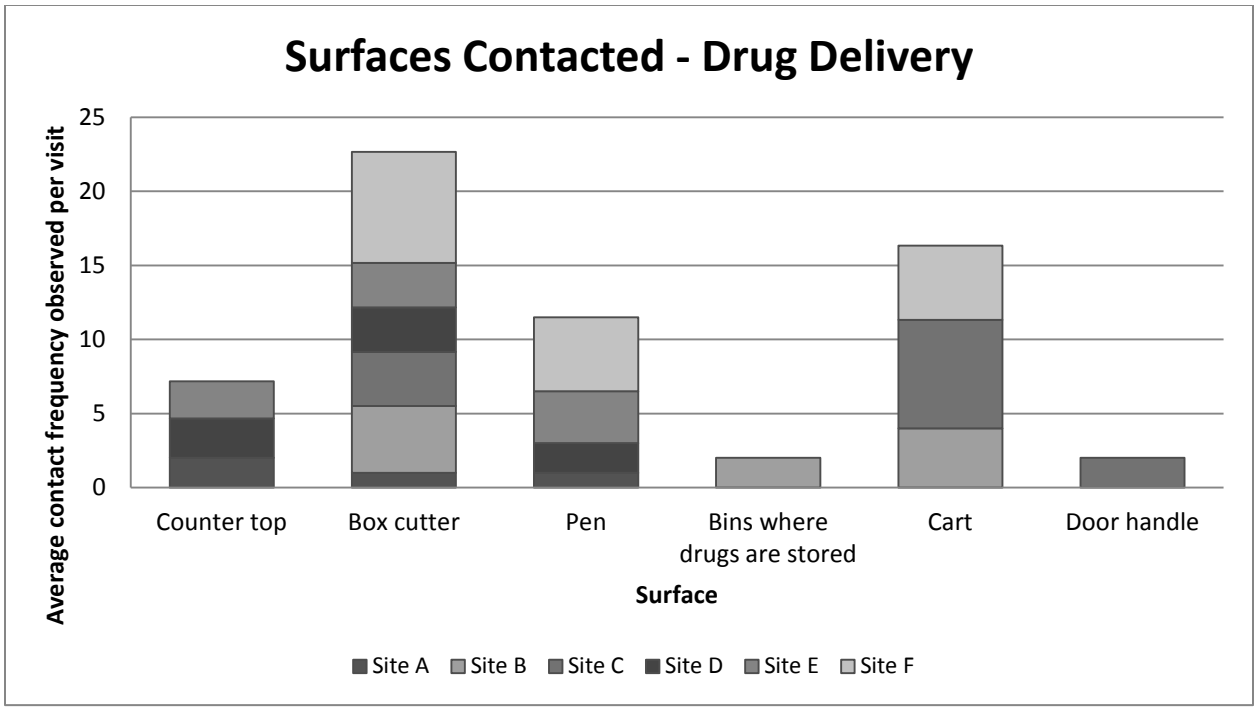

Figure 2-2 Average contact frequency of potentially contaminated surfaces observed per task cycle during drug delivery

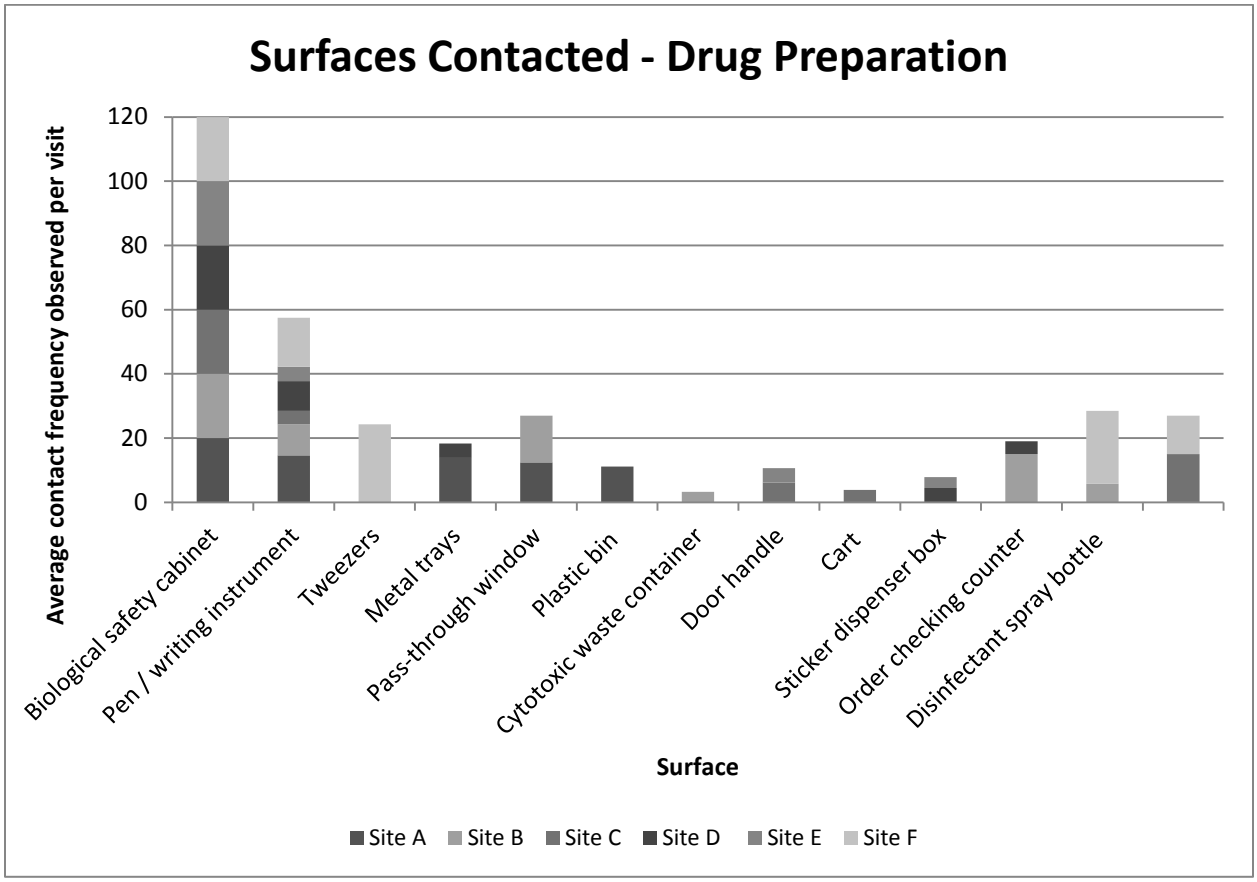

Figure 2-3 Average contact frequency of potentially contaminated surfaces observed per task cycle during drug preparation

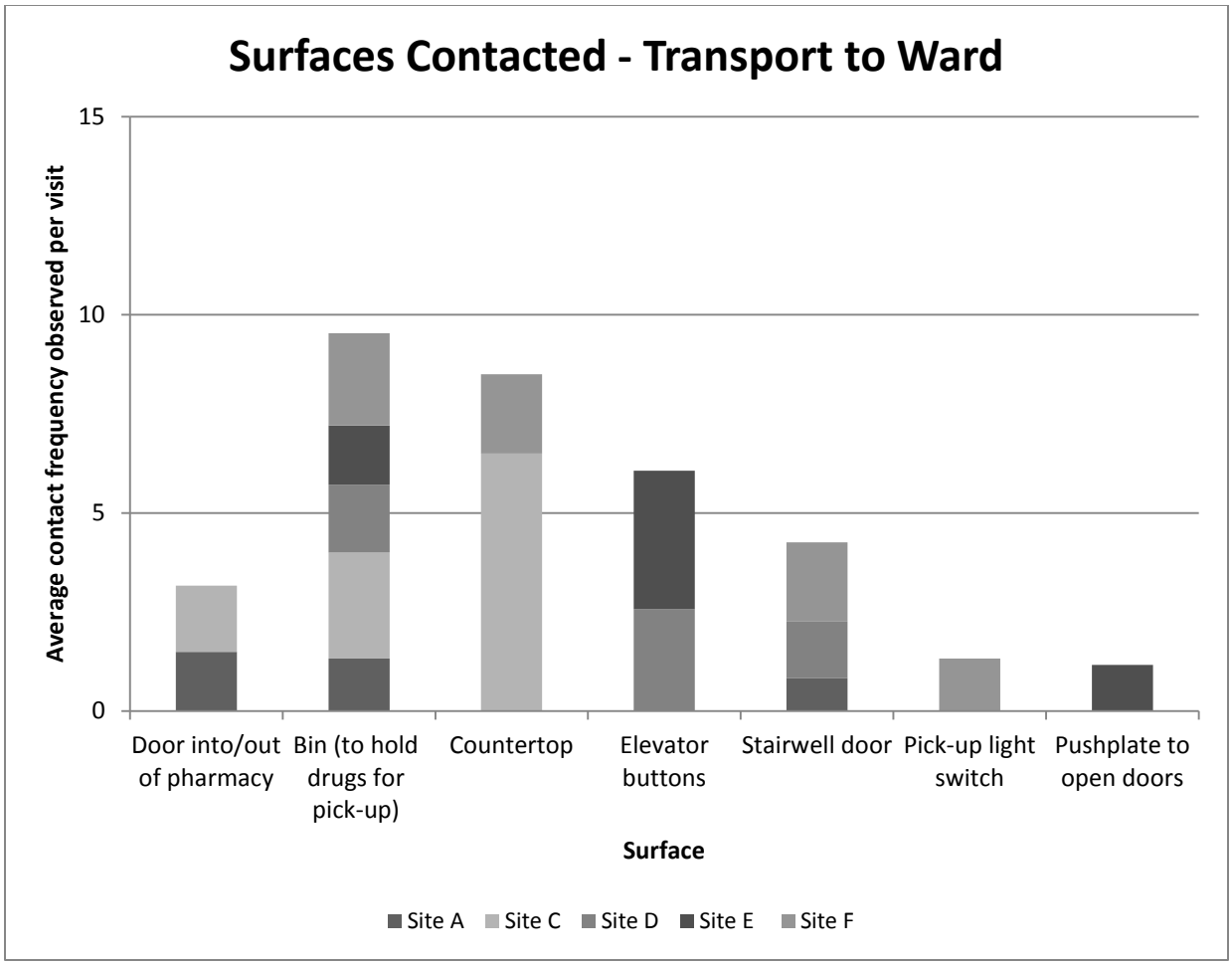

Figure 2-4 Average contact frequency of potentially contaminated surfaces observed per task cycle during drug transport

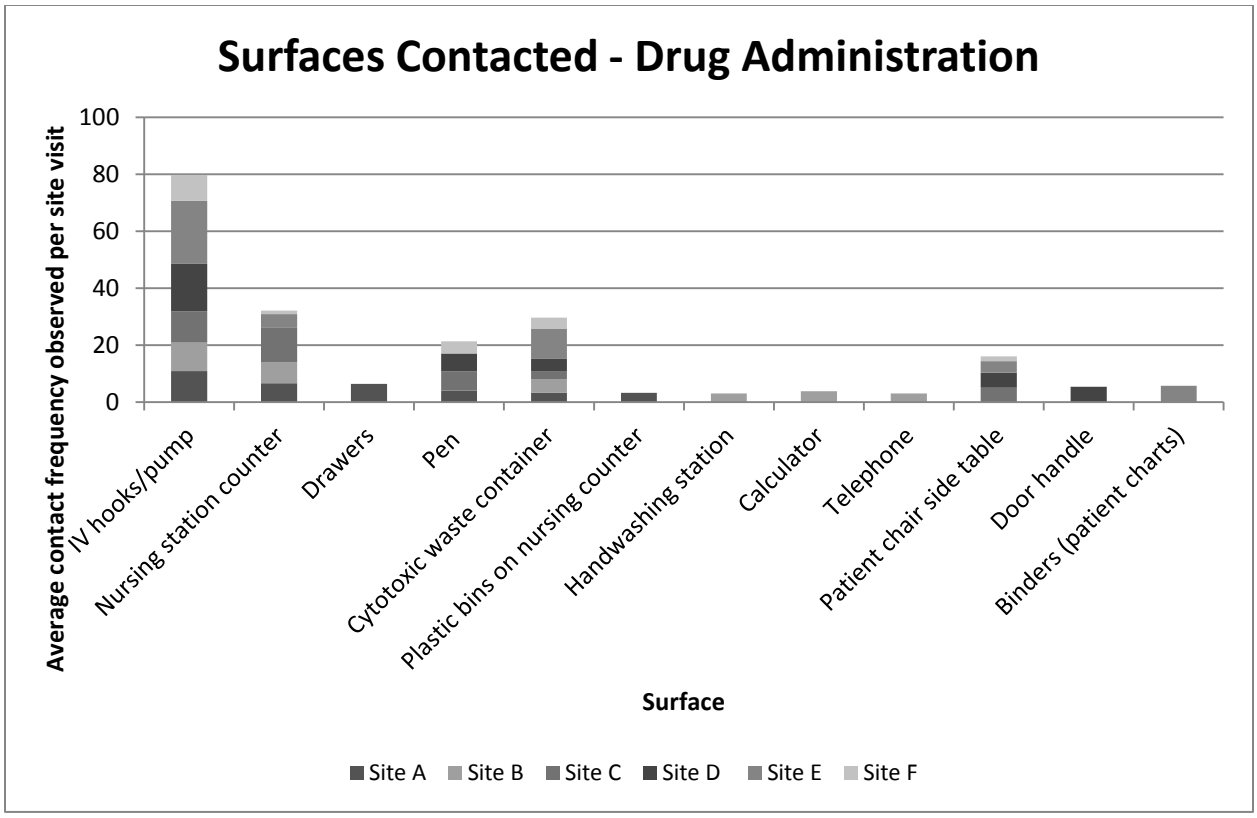

Figure 2-5 Average contact frequency of potentially contaminated surfaces observed per task cycle during drug administration

Table 2-2 Number of observed job categories and associated tasks with potential for dermal exposure at each healthcare facility

Potentially at-risk job categories at each stage of the hospital medication system	Participating sites where listed exposure pathway is found			
	Handles drugs*	**Prepares drugs**	**Administers drugs**	**Contacts drug-contaminated surfaces**
1. Delivery				
Shipper/receiver	3 sites (B, E, F)	0 sites	0 sites	0 sites
Pharmacy Receiver	All 6 sites	0 sites	0 sites	All 6 sites
2. Drug Preparation				
Pharmacy Technician	All 6 sites	All 6 sites	0 sites	All 6 sites
Pharmacist	All 6 sites	0 sites	0 sites	All 6 sites
3. Transport to Ward				
Porter	3 sites (A, D, E)	0 sites	0 sites	3 sites (A, D, E)
Nurse	2 sites (E, F)	0 sites	0 sites	2 sites (E, F)
Pharmacist	2 sites (B, F)	0 sites	0 sites	2 sites (B, F)
Unit Clerk	One site (F)	0 sites	0 sites	One site (F)
Ward Aide	2 sites (C, D)	0 sites	0 sites	2 sites (C, D)
4. Drug Administration				
Nurse	All 6 sites	0 sites	All 6 sites	All 6 sites
Volunteer	0 sites	0 sites	0 sites	2 sites (A,B)
Unit Clerk	3 sites (D, E, F)	0 sites	0 sites	All 6 sites
Clinic Pharmacist	1 site (A)	0 sites	0 sites	2 sites (A, C)
Dietician	0 sites	0 sites	0 sites	2 sites (A,B)
Oncologist	0 sites	0 sites	0 sites	1 site (A)
5. Disposal				
Nurses	All 6 sites	0 sites	0 sites	All 6 sites
Pharmacist	5 sites (A, B, D, E, F)	0 sites	0 sites	5 sites (A, B, D, E, F)
Pharmacy Technician	1 site (C)	0 sites	0 sites	0 sites
Biopacker	1 site (E)	0 sites	0 sites	1 site (E)

** includes shipments, drug vials, intravenous bags and waste containers*

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Table 2-3 Number of workers per at-risk job category at participating facilities

Department	Job Category	Site A	Site B	Site C	Site D	Site E	Site F	Subtotals
Pharmacy	Pharmacy Technician	6 FT; 6.0 FTE	0 FT; 2 PT 1.8 FTE	13 FT; 3 PT 15.1 FTE	7 FT; 2 PT 7.85 FTE	27 FT; 4 PT 30.2 FTE	7 FT; 4 PT 9.0 FTE	60 FT; 15 PT 69.95 FTE
	Pharmacy Receiver	3 FT 3.0 FTE	0 FT; 10 PT 0.25 FTE	2 FT; 2 FTE	4 FT 4 FTE	3 FT 3 FTE	1 FT 1 FTE	13 FT; 10 PT 13.25 FTE
	Pharmacist	4 FT; 2 PT 4.8 FTE	1 FT 1 FTE	11 FT; 9 PT 16.89 FTE	6 FT; 1 PT 6.5 FTE	31 FT; 7 PT 35.7 FTE	7 FT; 5 PT 9.5 FTE	66 FT; 25 PT 74.39 FTE
Drug Administration Unit	Nurse	4 PT 2.60 FTE	1 FT; 6 PT 4.0 FTE	6 FT; 1 PT 6.0 FTE	60 FT; 11 PT 67.2 FTE	54 FT; 26 PT 73.77 FTE	26 FT; 16 PT 35.10 FTE	147 FT; 64 PT 188.67 FTE
	Pharmacy technician (oncology unit)	1 PT 1 FTE	N/A	N/A	N/A	N/A	N/A	1 PT 1 FTE
	Clinical Pharmacist (oncology unit)	1 FT 1 FTE	N/A	1 FT 1.0 FTE	N/A	N/A	N/A	2 FT 2 FTE
	Volunteer	7 PT 0.8 FTE	10 PT 5.0 FTE	N/A	N/A	N/A	N/A	17 PT 5.8 FTE
	Unit Clerk	2FT; 1 PT 2.40 FTE	3 FT; 1 PT 3.0 FTE	Could not obtain	5 FT; 4 PT 7. 83 FTE	1FT; 1PT 1.20 FTE	6 FT; 7 PT 8.0 FTE	17 FT; 14 PT 22.43 FTE
	Oncologist	1 FT; 2 PT 1.8 FTE	N/A	N/A	N/A	N/A	N/A	1 FT; 2 PT 1.8 FTE
	Ward Aide	N/A	N/A	1 FT 1.0 FTE	2 FT 2 FTE	N/A	1 FT 1 FTE	4 FT 4.0 FTE
	Dietitian	2 PT 0.5 FTE	1 PT 0.4 FTE	N/A	N/A	N/A		3 PT 0.9 FTE
Patient Transport	Porter	8 FT; 3 PT 9.3 FTE	N/A	N/A	2 FT; 1 PT 2.8 FTE	44 FT; 10 PT 51.0 FTE		54 FT; 14 PT 33.1 FTE
Shipping/Receiving	Shipper/Receiver	N/A	Could not obtain	N/A	Could not obtain	3 FT 3 FTE	4 FT 4.0 FTE	7 FT 7 FTE
							TOTALS	**357 FT; 162 PT** **424.29 FTE**

FT= full time; PT = part-time; FTE= full-time equivalent; N/A = not applicable to the site

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3 EVALUATION OF SURFACE CONTAMINATION THROUGHOUT THE HOSPITAL MEDICATION SYSTEM AND IDENTIFICATION OF DETERMINANTS OF SUCH CONTAMINATION

3.1 Synopsis

The site observations reported in Chapter 2 indicated that surfaces situated throughout the hospital medication system might be contaminated with antineoplastic drugs. This chapter aimed to quantify the cyclophosphamide (CP) levels on these surfaces. In addition, determinants of surface contamination were identified. A weighted sampling approach was taken whereby more samples were collected from surfaces within the drug preparation and the drug administration stages than other stages. Moistened wipes were used to sample surfaces, which were subsequently analyzed to determine the concentration of CP using high-performance liquid chromatography-tandem mass spectrometry. Both descriptive and inferential statistics were performed. A manual backwards stepwise multiple regression was conducted to identify the determinants. Overall, 229 surfaces were sampled, with duplicates for most, resulting in 438 surface wipes. The mean CP concentration was 0.201 ng/cm^2, the geometric mean 0.019 ng/cm^2 and the geometric standard deviation 2.54, with a range of less than the limit of detection (LOD) (0.356 ng/wipe; LOD in ng/cm^2 varied with surface area) to 26.1 ng/cm^2 (64% of samples had concentrations less than the limit of detection). The drug preparation stage had the highest average contamination. Hospitals with more drug transport job categories had higher levels of surface contamination. Reported handling of CP and cleaning of surfaces did not appear to be associated with contamination. The drug preparation and drug administration stages of the hospital medication system and a higher number of job categories responsible for drug transport were factors associated with surface contamination.

3.2 Introduction

Safe handling guidelines, which often include cleaning and decontamination procedures, have been developed for workplaces where antineoplastic drugs are present. Despite the implementation of these guidelines in healthcare facilities, many studies have demonstrated that antineoplastic drug contamination of various work surfaces still occurs.(56)(36)(31)(34) Such surface contamination means healthcare workers are potentially at risk of dermal contact – which is believed to be the primary route of occupational exposure to these hazardous agents.(11)(67) The literature provides evidence that occupational exposure to antineoplastic drugs may result in genetic damage, adverse reproductive effects, as well as an increased cancer risk.(5)(6)(7)

Almost all prior studies have focused on examining surface contamination levels in the pharmacy department where the drugs are prepared and/or in the patient units where the drugs are administered. However, given that the drugs must initially be delivered to the facility, transferred to the pharmacy to be mixed, transported to a patient unit, administered and then disposed, surfaces in other areas of the hospital may also have drug residual.(79) To our knowledge, no single study has examined surface contamination throughout the hospital medication system (process flow of drugs within a facility from cradle-to-grave) and, subsequently, identified determinants of such contamination.

In Chapter 2, we identified the hospital medication system at several facilities and conducted observations to identify potentially contaminated surfaces that are frequently touched by healthcare workers.(80) In this chapter, the surface contamination levels are quantified and factors that may be associated with surface contamination in the hospitals are examined. As cyclophosphamide (CP) is frequently administered at the participating sites and has been

extensively examined in other occupational exposure studies, it was used as the marker drug in this study.

3.3 Methods

3.3.1 Selection of surfaces to be sampled

Five participating sites were acute care hospitals and one was a dedicated cancer treatment hospital. At all sites, antineoplastic drugs were prepared in Class II biological safety cabinets but none of the participating facilities used closed system drug transfer devices, e.g. PhaSeal®, for preparation. Passive (non-intrusive) site observations were performed to identify the hospital medication system for each facility and to identify those surfaces that were most frequently contacted by hands of healthcare workers throughout the hospital medication system; these methods and results are reported in detail elsewhere.(80)

The medication system was sub-divided into five separate stages: 1) delivery, 2) drug preparation, 3) transport to ward, 4) drug administration and 5) waste disposal.(80) At each hospital, the five most frequently contacted surfaces from stages 1, 3 and 5 and the eight most frequently contacted surfaces from stage 2 and 4 were selected for sampling. The rationale for sampling a different number of surfaces is that drug preparation and drug administration included more complex tasks with greater variability, such as individual and patient factors, than the other stages and therefore more surfaces/objects were contacted overall.

The contracted company that handled waste at all participating hospitals declined to participate in the study. This resulted in relatively fewer samples collected during the waste disposal stage. However, where certain elements of waste disposal were performed by hospital employees, e.g. transfer of cytotoxic drug waste to a holding station, we were able to collect wipe samples.

3.3.2 Wipe sample collection

Sample collection took place between March 2010 and January 2011. Sampling days were based on availability of research team members as well as consent from all affected departments at each hospital. Duplicate samples of most surfaces were collected with at least a four-month lag between the two collection times (mean 174 days; range 123 to 288 days).

A previously described protocol for surface sampling was employed(41) with some minor modifications. Briefly, we used a 10 cm x 10 cm plastic sampling template for flat surfaces having a surface area greater than 100 cm^2. For other objects such as door handles and writing instruments, where the overall surface area was less than 100 cm^2 and/or was not flat, the entire object was wiped and the surface area estimated by measuring the object's dimensions. For non-flat objects with an overall surface area greater than 100 cm^2, the area most likely to be contacted by an individual's hands was demarcated for sampling. For instance, the handle of a cart was wiped rather than the entire cart.

The research assistant wore a new pair of disposable gloves for each sample collected. A Kimwipe® (Kimberly-Clark Inc., Mississauga, ON) pre-moistened with 0.1 M ammonium acetate (Sigma Aldrich, Oakville, ON) was used to wipe each surface. All collected wipes were placed into separate vials and shipped on ice within 24 hours of sample collection to the analytical lab where they were stored at -20^oC until analysis. Both travel and field blanks were collected for quality control purposes.

3.3.3 Wipe sample preparation

After thawing the samples, 5.5 mL of 0.1 M ammonium acetate (Sigma Aldrich, Oakville, ON) solution was added to each vial. The wipes were sonicated for 20 minutes to extract the drug

residue and then placed into a disposable 10-mL syringe where the solution was squeezed out of the wipe into a 20-mL vial. One mL of the solution was removed and placed into a liquid-chromatography vial with 50 µL of internal standard, D4-cyclophosphamide (Bielefeld University, Bielefeld, Germany).

3.3.4 Wipe sample analysis

Wipes were analyzed for CP by high-performance liquid chromatography-tandem mass spectrometry using an Agilent Technologies 6410 with a Zorbax XDB-C18 column (Agilent Technologies, Santa Clara, CA) and the electrospray ionization in the positive ion mode. The mobile phase was a gradient of 5 mM Ammonium Acetate:100% Methanol (A:B) and samples were run at a flow rate of 0.5 mL/min. A 5-point calibration curve was used and, for quality control purposes, a calibration standard was run for every 10 samples. For additional quality control, method blanks were included in the analysis and duplicate analysis took place for every tenth sample. The limit of detection (LOD), established using the 3:1 signal-to-noise ratio, was 0.356 nanogram per wipe (ng/wipe). The method recovery rate was 97% and each resulting sample concentration was adjusted to reflect this. The surface area of each wiped object was calculated and drug contamination levels were reported in nanograms per square centimetre (ng/cm^2) as in similar studies.(11)

3.3.5 Supplemental data collection

For each surface wipe sample, members of the research team conducted a brief survey of the healthcare worker who was in closest proximity to the surface sampled (see “Drug Handling and Cleaning Questions” in Appendix B). The following questions were asked:

- To your knowledge, was cyclophosphamide handled, prepared and/or administered prior to collection of the wipe sample (on this work shift)?
- To your knowledge, was there a spill/leak of cyclophosphamide earlier in the day on this surface?
- To your knowledge, was the surface/object cleaned prior to collection of wipe sample (end of previous shift until present time)?

Response options for all three questions were “yes”, “no”, or “don’t know”. In those instances where a healthcare worker was not readily available, i.e. generally public areas such as elevators and stairwell doors, the response was classified as “unknown” for all three questions.

Other data recorded were the characteristics of the hospital and attributes of the collected wipe sample. Hospital characteristics included the hospital type (acute care or cancer treatment), whether the hospital had an isolated drug preparation area (yes or no), the number of job categories responsible for drug transport, the number of drug administration units, the number of job categories working in the drug administration unit, and where drugs were initially delivered to the facility (shipping/receiving department or direct to the pharmacy).(80) Details of each wipe sample included the stage of the hospital medication system where the surface was sampled, the type of surface/object collected, and the relative date of sampling (with the first sampling day designated as day 1). Each one of the aforementioned served as an independent variable in the data analysis.

3.3.6 Data analysis

The distribution of surface contamination levels was examined with the data untransformed and ln-transformed. Summary statistics were generated (arithmetic mean (AM), geometric mean (GM), geometric standard deviation (GSD), minimum and maximum, and the proportion less

than detection limit) for all wipe samples and stratified by each of the independent variables indicated previously. The response categories "don't know" and "unknown" were combined for data analysis purposes. Bivariate analyses were performed to examine the relationship between CP contamination level (ln-transformed) and each of the aforementioned independent variables separately, using one-way ANOVA (categorical variables) or simple linear regression (continuous variables). Tukey's post-hoc test was used to determine which differences in geometric means were significant in ANOVA. A paired t-test was performed to determine if there was a difference in means between the two sampling periods.

All independent variables with $p < 0.15$ in the bivariate analyses were then offered in multiple linear regression, with a random effect for the surface identification number to account for potential correlation within repeated samples of the same surface. A manual backwards stepwise regression was employed to identify those independent variables that were associated with surface contamination levels. Independent variables with $p < 0.05$ were retained in the final model. A residual plot was generated to determine the appropriateness of the final model. Statistical analyses were performed using SPlus v. 8.0 for Windows (Insightful Corp., Seattle, WA).

3.3.7 Reporting of results

A large proportion of surface wipes had contamination levels less than the instrument's limit of detection (LOD). To alert the reader, in Tables 3-1 and 3-3, we report the proportion of values less than the LOD. To investigate which factors were related to surface contamination, 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.(81) Laboratory-calculated concentrations below the method limit of detection were available to us. Although this data has

a lower signal-to-noise ratio than the data above the detection limit, it is based on the actual measurements and should reflect actual contamination more accurately than a single substitute value for all data below the detection limit, a technique often used for data below detection limits.(82) We therefore used actual analytical data instead of substitute values for observations below the detection limit for all descriptive statistics and inferential analyses. When ln-transformed, the data more closely exhibited a normal distribution; therefore, all statistical analyses utilized the ln-transformed values and the GMs were compared in ANOVA.

3.4 Results

3.4.1 Overall summary of surface contamination levels

A total of 229 surfaces were sampled at the participating hospitals, with 209 duplicates, for a total of 438 samples. Overall, 279 of the 438 samples (64%) had concentrations below the limit of detection (0.356 ng/wipe). The AM concentration was 0.201 ng/cm^2, the GM 0.019 ng/cm^2 and the GSD 2.54, with a range of less than LOD (0.356 ng/wipe; LOD in ng/cm^2 varied with surface area) to 26.1 ng/cm^2. The number of samples collected per hospital ranged from 47 to 102 samples. The results of the paired t-test did not find any statistically significant difference in average drug contamination levels between the duplicate samples.

3.4.2 Surface contamination levels by medication system stage

Figure 3-1 provides an overview of the contamination levels found on the 55 different catgeories of surfaces sampled, stratified by the stage of the hospital medication system. The most contaminated surface at each stage was as follows: 1) delivery – elevator button (0.050 ng/cm^2); 2) drug preparation – pen (26.2 ng/cm^2); 3) transport to ward – bin for drug pick up (0.106

ng/cm^2); 4) drug administration – IV pump (0.454 ng/cm^2); and 5) waste disposal – elevator button (0.006 ng/cm^2).

Figure 3-2 indicates that the stage with the highest average contamination levels was drug preparation (AM=0.592 ng/cm^2, GM=0.067 ng/cm^2). In Tukey post-hoc testing for stage of hospital medication system, drug preparation had a statistically significant higher mean contamination level than both the drug delivery and drug administration stages. Of note, there was a gradual decrease in the proportion of detectable samples in the three hospital medication system stages that followed drug preparation. It should also be noted that the GM at the transport stage was slightly higher than the GM at the drug preparation stage and the stage with the greatest variability in surface contamination levels was drug delivery (GSD=6.68).

3.4.3 Surface contamination levels based on hospital characteristics

Categorical variables

Table 3-1 summarizes the surface contamination levels by categorical hospital characteristics. Although not statistically significant, the geometric mean concentration at the participating cancer centre was higher than at the acute care hospitals (F(1,436)=2.97, p=0.086; 3.2 times difference in GMs). At hospitals where drugs shipments were received at the shipping/receiving department, the geometric mean surface contamination levels were higher though not statistically significant (F(1,436)=0.217, p=0.64; 1.4 times difference in GMs) than at sites where the drugs were sent directly to the pharmacy department. Lastly, there was no statistically significant difference whether the drugs were prepared in an isolated preparation room or not (F(1,436)=0.039, p=0.84; 0.003 ng/cm^2 difference in GMs).

Continuous variables

Table 3-2 summarizes the surface contamination levels by continuous hospital characteristics. Only one variable was statistically significant: with more drug transport job categories, there was higher surface contamination. Neither the number of drug administration units nor the number of job categories in the drug administration unit observed to contact drug-contaminated surfaces were associated with contamination levels.

3.4.4 Surface contamination levels based on reported CP handling, spills and surface cleaning

Table 3-3 is an overview of the surface contamination levels based on reported CP usage and surface cleaning. There were no reported spills or leaks on any of the surfaces. The highest AM and GM contamination levels occurred when CP was reportedly used prior to sampling. However, the highest individual recorded contamination level occurred when CP was reportedly *not* handled, prepared and/or administered prior to sampling. The difference in contamination levels between the three reported CP usage categories was statistically significant. In the Tukey post-hoc test, reported handling, preparation, or administration of CP had statistically significant higher levels than ‘don’t know’ or ‘unknown’ CP usage.

With respect to surface cleaning, the highest GM was when the surface was cleaned, whereas the highest AM and the highest individual contamination level occurred when the surface was reportedly *not* cleaned. The difference in contamination levels between the three reported surface cleaning categories was not statistically significant ($F(2,435)=1.27$, $p=0.28$; 3.8 times difference between minimum and maximum GM).

Table 3-4 presents a cross tabulation of surface contamination levels by reported CP handling and surface cleaning. Despite the fact that CP was not reportedly handled, prepared, or administered on the work shift for 245 of all samples collected (56%), detectable levels were still found. The maximum individual contamination measurement was found when no CP was reportedly used and the surface was reported as not cleaned (a pen inside the biological safety cabinet at Site E). The highest arithmetic mean contamination (0.730 ng/cm^2) and geometric mean (0.098 ng/cm^2) was found when CP was reported as used *and* the surface reported to have been cleaned.

3.4.5 Surface contamination levels based on attributes of the wipe sample

In total, 55 different categories of surfaces/objects were sampled. Differences in the contamination levels between the type of surface/objects were nearly statistically significant in ANOVA ($F(54,383)=1.35$, $p=0.06$). In Tukey post-hoc testing, tweezers used during drug preparation had higher contamination levels than 19 other surface categories (biological safety cabinet, IV hook, IV pump, pass through window, bin, box cutter, calculator, cart, countertop, door handle, drawer, elevator button, keyboard, pen, patient bedside table, patient chair side table, refrigerator, sink handles, sticker dispenser and re-sealable plastic bags), and elevator button had significantly lower contamination levels than three other surface categories (marker, pen, and vial).

There were no apparent temporal trends in surface contamination as we found no statistically significant difference with respect to the relative sequence by which samples were collected ($p=0.12$).

3.4.6 Multiple linear regression model

Six of the twelve independent variables were found to have $p < 0.15$ following bivariate analyses: 1) the type of hospital, 2) the number of job categories responsible for drug transport, 3) the stage of the hospital medication system, 4) the type of surface/object sampled, 5) whether CP was reportedly handled/prepared/administered on the sampling shift and 6) the relative sampling sequence. All other independent variables had $p > 0.20$.

These six independent variables were offered into a multiple linear regression to predict drug contamination on surfaces with the surface identification number inputted as a random effect. Using backwards stepwise regression as described in the Methods, two independent variables remained in the final model: the number of job categories responsible for drug transport and the stage of the hospital medication system. According to Table 3-5, having more drug transport job categories was positively associated with higher surface contamination levels and the drug preparation and drug administration stages had the highest contamination.

A review of the residual plot found that there were larger residuals at higher surface contamination levels resulting in a 'funnel-like' distribution. This may be due to the large proportion of samples that were found to be less than the detection limit.

3.5 Discussion

Until now, no single study has measured the drug residual levels on surfaces throughout the hospital medication system and, subsequently, identified the determinants of such contamination. Our findings indicate that, although a large proportion of samples did not have detectable contamination, various surfaces at *every* stage of the hospital medication system had drug residual at the participating facilities. Thus, our study is in agreement with others that there is

surface contamination despite the implementation of controls;(36)(34)(62)(45)(40)(83)(46) but extends these findings beyond the drug preparation and patient administration areas. The current study also provides evidence of contamination of surfaces that healthcare workers are likely to contact with their hands through the course of their duties such as door handles, carts and writing instruments (based on site observations in Chapter 2). Other studies have detected contamination on some surfaces that may or may not be contacted by healthcare workers, such as the floor in the drug preparation area.(60)(24)(31)

Our review of the literature found only two studies that have identified determinants of surface contamination. Connor et al. found no correlation between the number of handling events and the percentage of surface wipe samples that had measurable levels of antineoplastic drug.(36) Siderov et al. did not detect correlation between surface contamination levels and any of the following variables: 1) amount of CP prepared annually, 2) age of cytotoxic suite and the biological safety cabinet, 3) decontamination and cleaning procedures, and 4) the staff member preparing chemotherapy.(34) These papers examined the drug preparation and patient administration areas only.

In our examination of factors which may influence drug contamination of surfaces throughout the hospital medication system, we identified two variables that were statistically significant in the multiple linear regression model: 1) the stage of the hospital medication system and 2) the number of job categories responsible for drug transport. Employee-reported use of CP was not associated with surface contamination levels in the current study. This finding concurs with Hedmer et al.(31) who found measurable levels on surfaces even though drugs were not handled on the sampling dates.

It is not surprising that the stage of the hospital medication system is associated with the highest surface contamination levels. One would expect the drug preparation stage to be the most critical because the concentrated drugs are routinely handled and mixed there. Our finding is consistent with the conclusion of others.(36) We and others detected drug contamination on the outside of the manufacturer vials.(51)(53)(32) According to Sessink and Bos, contamination already present on vials before the initiation of preparation will result in further distribution of the drug,(2) which was confirmed in the present study with measurable levels of drug residual in subsequent stages of the hospital medication system. The presence of contamination in stages following drug preparation may be due to worker contact with communal objects such as door handles, trays, and writing instruments.(41) It has been suggested that surfaces in the last three stages of the hospital medication system are generally more porous than those in the drug preparation area and therefore drug residual can diffuse into the pores and may accumulate over time because they are environmentally stable.(31) The potential that the drug preparation stage contributes to contamination in the remaining stages of the hospital medication system is suggested by the decrease in the proportion of detectable samples as one progressed from drug preparation to subsequent stages (see Figure 3-2).

With respect to the second determinant, our regression model found that the more job categories involved with drug transport (from the drug preparation area to the drug administration units), the higher the surface contamination levels. We speculate that this may be attributed to more handling events of the prepared drugs by a variety of individuals – a large proportion of whom are not formally trained regarding the hazards of these agents or the safe handling requirements (training history of participants is discussed in Chapters 4 and 5). Interestingly, one study suggested that contamination should not occur during transport because the prepared drugs are

protected by a secondary container e.g. paper bag.(20) Given this and the fact that we are the first to identify this determinant, it is important to see if future studies can replicate our result.

Although we identified two potential determinants of surface contamination, we were unable to explain the exact mechanism of spread of antineoplastic drugs. The utilization of a tracer may be a way to address this question(84)(85) but it needs to be traceable at the start of the hospital medication system (i.e. at the drug delivery stage not drug preparation) in order to provide a comprehensive account of how these hazardous agents are spread.

Table 3-6 compares the CP contamination levels that we found for specific objects at each stage and those reported by others (note that only recent studies that reported contamination levels in ng/cm^2 are presented). Overall, the mean contamination levels from the current study were lower than those reported elsewhere. We agree with others who performed multi-site studies that surface contamination levels vary from site-to-site.(36)(34)(44) According to Touzin et al. variability in surface contamination may be related to the layout of the workplace which can impact work techniques (i.e. proximity of drug storage relative to drug preparation) as well as the size of working area where drugs are handled.(33)

A review of Table 3-6 shows that our findings were most comparable to those reported by Touzin et al.(33) and Connor et al (2010).(36) Both studies were conducted in facilities that are known to follow the National Institute for Occupational Safety and Health guidelines for the safe handling of hazardous drugs and most of our facilities had similar controls in place, i.e. clean room design, and anterooms between the preparation area and the adjacent areas with pass-through windows for the compounded drug to leave the preparation area. Regardless of these control measures, all three studies had measurable levels of drug residual indicating persistent contamination and worker exposure potential.

Of note, the reported cleaning of the surface prior to wipe sampling was not associated with contamination levels. The lack of association may be attributed in part to errors in reporting by the healthcare workers responding to the survey. The majority of the responses to our question "To your knowledge, was the surface/object cleaned prior to collection of wipe sample" was "don't known/unknown" (238 of 438 samples or 54%). This suggests that cleaning was not frequent or that workers were not aware of cleaning activities, or both. Regardless, others have questioned the cleaning efficacy of surfaces. Sessink et al.(59) suggested drug residual could be spread due to the lack of cleaning effectiveness. Turci et al.(66) noted that contamination was found even before drug preparation activities, implying that decontamination protocols between preparations were incomplete. The apparent lack of temporal variability in surface contamination is consistent with Hedmer et al.'s findings(31) and raises questions of cleaning effectiveness as well. A recent study showed that existing cleaning protocols are not 100% effective in reducing contamination levels and may lead to possible accumulation of drug residual.(86) We therefore agree with Sugiura et al.'s suggestion that effective environmental cleaning needs to be performed to remove drug residual to prevent the introduction of new contamination.(35) Cleaning agents which specifically target the drug products may be more effective than detergents or disinfectants.(87)

Although there is no established occupational exposure limit, the United States Pharmacopeia (USP) recently indicated a maximum surface contamination level of 1 ng/cm^2 of CP to limit the risks of absorption (uptake) in humans.(33) In our study, eight of the 438 (2%) surfaces sampled exceeded this level. In four (50%) of these samples, there was either no use of CP or use was unknown prior to sampling. Cleaning was not performed or was uncertain for five of the eight surfaces. The surface contamination levels represent a point in time only and are not reflective

of the potential for repeated contact by healthcare workers which could conceivably exceed 1 ng/cm^2 over the course of a work shift. Given this and the fact that local regulatory bodies have not prescribed the USP threshold, the principle adopted by occupational hygienists in those instances where no limit has been established is to keep exposure levels as low as reasonably achievable.

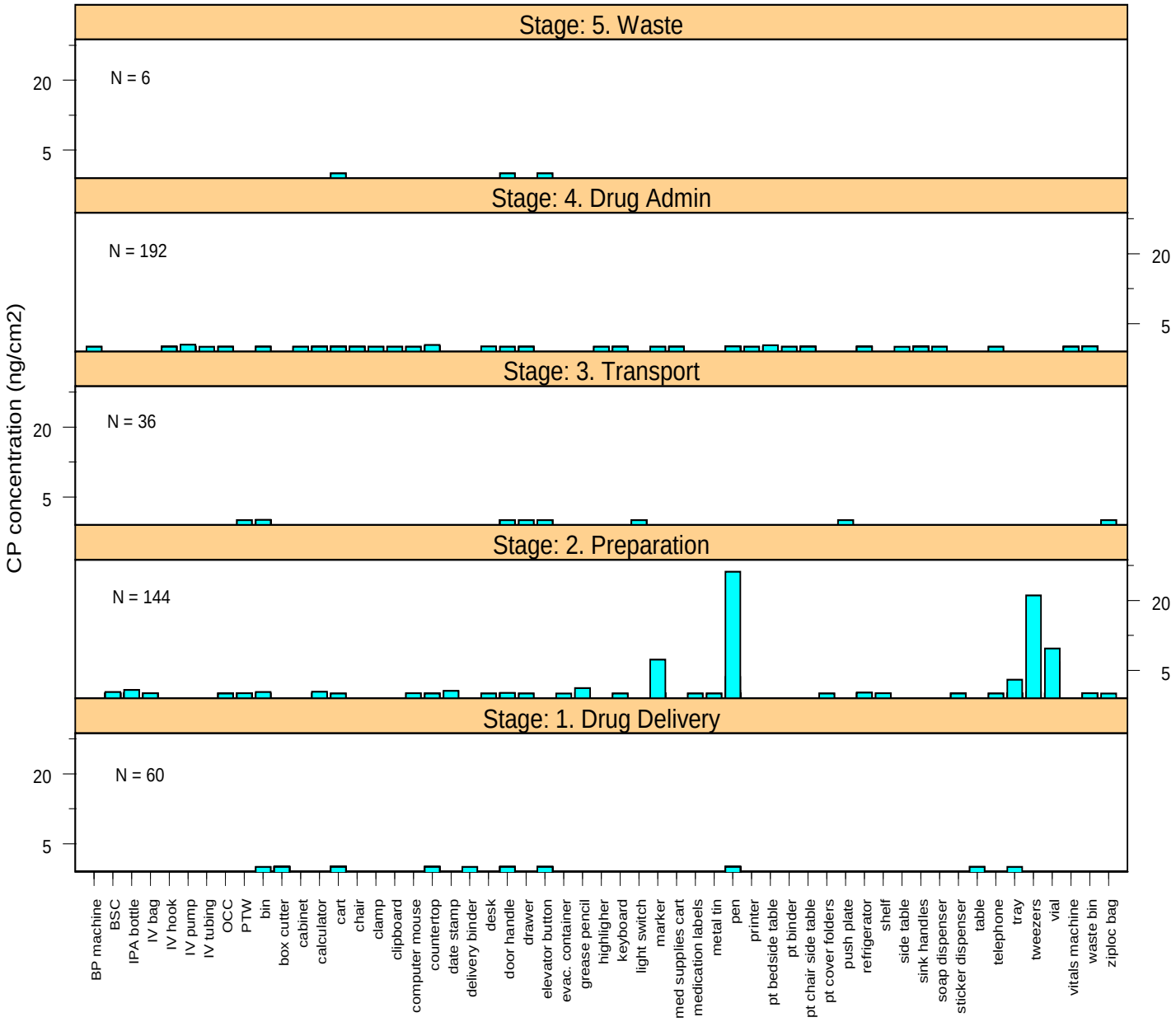
3.5.1 Limitations

It should be noted that we did not take into consideration the wipe efficiencies from each surface sampled; therefore, the concentrations reported in this study may underrepresent the actual amount of CP on the surfaces sampled. [Note that others have also assumed 100% wipe recovery(34)(35)] Additionally, we only analyzed for CP and did not consider potential surface contamination by other antineoplastic drugs. This can also underestimate the surface contamination levels and the resulting exposure risk. Another limitation of the study is that we were unable to confirm whether CP was handled prior to sample collection. Utilization of a diary by healthcare workers may help to overcome this limitation(36) but could be challenging to implement in those areas where multiple people are involved i.e. sites have several porters perform various tasks and no individual porter is dedicated strictly for drug transport. Body fluids from patients undergoing chemotherapy are known to contain antineoplastic drugs.(71) Thus, bed sheets and the patient washrooms may be contaminated. However, we did not sample these surfaces because a) we are uncertain of the effectiveness of our sampling method in recovering drug residual on highly porous material such as linens and b) sampling of patient areas is difficult without compromising patients' privacy. As such, the number of surfaces contaminated throughout the hospital medication system is likely an underestimate. Lastly, we

did not record the cleaning agents employed at each facility; this would be a useful addition in future studies.

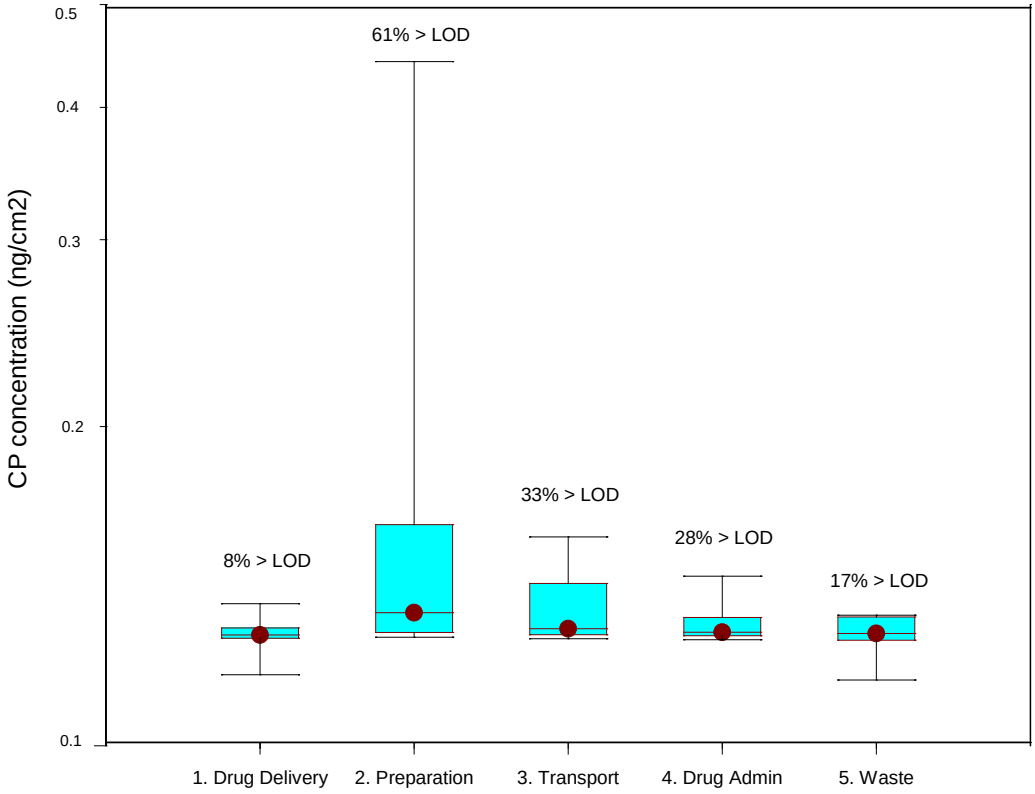
3.5.2 Summary

In summary, measurable levels of drug residual were found on a variety of surfaces situated throughout *all* stages of the hospital medication system. Given these findings, we suspect that healthcare job categories involved in some capacity with the hospital medication system are at potential risk for dermal contact with these surfaces. For instance, external contamination on the vials presents an opportunity for exposure as soon as the drug shipment arrives at the healthcare facility.(52) With respect to determinants, we identified the drug preparation and drug administration stages of the hospital medication system and a larger number of transport job categories as being associated with surface contamination in the hospitals studied. This finding provides a basis for targeting interventions to reduce contamination. To our knowledge, this is the first study of its kind to identify determinants of surface contamination throughout the hospital medication system; therefore, further research is recommended to determine the generalizability of the findings.



Note: where no bar is present, that surface was not sampled in that stage

Figure 3-1 Average cyclophosphamide (CP) contamination levels (in ng/cm^2) on the 55 different categories of surfaces sampled stratified by the stage of the hospital medication system



	Drug Delivery	Preparation	Transport	Drug Admin	Waste
N	60	144	36	192	6
Arithmetic Mean	< 0.356 ng/wipe*	0.592	0.010	0.013	< 0.356 ng/wipe*
Std Dev	0.0215	3.00	0.021	0.053	0.010
Geometric Mean	< 0.356 ng/wipe*	0.067	0.009	0.008	< 0.356 ng/wipe*
Geometric Std Dev	6.68	2.65	1.14	1.23	1.09

ANOVA < 0.005; whiskers represent 10th and 90th percentiles
** LOD of 0.356 ng/wipe; LOD in ng/cm^2 varied with surface area of sampled object*

Figure 3-2 Box plot and summary statistics of cyclophosphamide (CP) surface contamination levels (in ng/cm^2) by stage of hospital medication system

Table 3-1 Surface contamination levels based on categorical variables of hospital characteristics

Variable	N	AM (ng/cm^2)	SD (ng/cm^2)	GM (ng/cm^2)	GSD	ANOVA (p-value)*	% < LOD
Hospital Type							
Cancer Centre	99	0.416	2.42	0.041	2.28	0.086	59.6
Acute Care Hospital	339	0.138	1.49	0.013	2.61		65.2
Isolated preparation room							
No	87	0.053	0.325	0.016	1.54	0.840	74.7
Yes	351	0.238	1.94	0.019	2.77		61.3
Where drugs are initially delivered							
Pharmacy	183	0.068	0.544	0.015	1.54	0.642	65.6
Shipping/Receiving	255	0.296	2.23	0.021	3.20		62.7

** where the dependent variable was the ln-transformed surface contamination level*

Table 3-2 Bivariate results of surface contamination levels according to hospital characteristic variables that are continuous in nature

Variable	Intercept	Coefficient	SE	p-value*
No. of transport job categories	-2.17	0.130	0.060	0.029
No. of drug administration units	-2.06	0.063	0.051	0.214
No. of drug admin job categories	-1.80	-0.037	0.039	0.337

** where the dependent variable was the ln-transformed surface contamination level*

Table 3-3 Bivariate results of surface contamination levels based on reported cyclophosphamide (CP) handling and surface cleaning

Variable	N	AM (ng/cm^2)	SD (ng/cm^2)	GM (ng/cm^2)	GSD	ANOVA (p-value)*	% < LOD
Reported CP usage							
Don't know/Unknown	123	0.254	2.00	0.007	4.45	0.047	70.7
No	245	0.135	1.68	0.015	1.58		67.8
Yes	70	0.339	1.45	0.060	2.37		38.6
Reported surface cleaning							
Don't know/Unknown	238	0.166	1.51	0.010	3.03	0.281	68.5
No	132	0.250	2.29	0.025	1.86		61.4
Yes	68	0.227	1.25	0.039	2.05		52.9

** where the dependent variable was the ln-transformed surface contamination level*

Table 3-4 Summary statistics for cyclophosphamide (CP) surface contamination levels based on employee-reported CP usage and surface cleaning during the work shift

		Was cyclophosphamide handled/prepared/administered prior to sampling?		
		Don't know/ Unknown	**No**	**Yes**
Was the surface cleaned prior to sampling?	**Don't know /Unknown**	N=107 Mean = 0.284 GM = 0.003 Max = 21.1	N = 110 Mean = 0.010 GM = 0.007 Max = 0.41	N = 21 Mean = 0.377 GM = 0.075 Max = 6.72
	No	N = 7 Mean = 0.025 GM = 0.020 Max = 0.12	N = 95 Mean = 0.325 GM = 0.024 Max = 26.1	N = 30 Mean = 0.065 GM = 0.030 Max = 1.15
	Yes	N = 9 Mean = 0.077 GM = 0.056 Max = 0.30	N = 40 Mean = 0.022 GM = 0.013 Max = 0.48	N = 19 Mean = 0.730 GM = 0.098 Max = 9.71

Mean, GM and Max values reported in ng/cm^2

Table 3-5 Coefficients, standard errors and p-values for multiple linear regression model showing factors related to surface wipe contamination levels (ln-transformed)

Variable	**Coefficients**	**Standard Error**	**p-value**
Intercept	-3.015	0.241	<0.0001
No. of transport job categories	0.213	0.088	0.017
Stage 1 Drug Delivery	Reference		
Stage 2 Preparation	0.869	0.205	<0.0001
Stage 3 Transport	0.397	0.287	0.169
Stage 4 Drug Admin	0.488	0.197	0.014
Stage 5 Waste	0.382	0.582	0.512

Table 3-6 Reported cyclophosphamide contamination levels in ng/cm^2 found in healthcare facilities

Stage	Object	Mean concentration (range)	Author and Country
Drug Delivery	Unable to find comparable results in the literature		
Drug Preparation	Biological safety cabinet (hood work surface)	0.056 (0.007-0.130)	Touzin et al., Canada (2009)(33)
		0.101 (ND – 0.38)	Siderov et al., Australia (2009)(34)
		18.1	Connor et al., USA (2010)(36)
		0.009 (0.003 – 0.2)	Hedmer et al., Sweden (2005)(32)
		0.01	Sugiura et al., Japan (2010)(35)
		47.1	Sottani et al., Italy (2011)(44)
		0.01	Tanimura et al., Japan (2009)(48)
		0.01	Sugiura et al., Japan (2010)(43)
		0.052 (ND – 0.0321)	*Current study*
	Drug vial	9 (ND – 912)	Schierl et al., Germany (2010)(53)
		0.127 (ND – 0.53)	Hama et al., Japan (2011)(52)
		0.1	Favier et al., France (2003)(49)
		1.28 (ND – 9.71)	*Current study*
	Pass through	0.200	Connor et al., USA (2010)(36)
		0.257	Sottani et al., Italy (2011)(44)
		0.019 (ND – 0.063)	*Current study*
	Pharmacy checking counter	0.013 (0.005-0.029)	Touzin et al., Canada (2009)(33)
		0.133 (ND – 0.67)	Siderov et al., Australia (2009)(34)
		0.039*	Schmaus et al., Germany (2002)(24)
		1.7	Connor et al., USA (2010)(36)
		4.63	Sottani et al., Italy (2011)(44)
		0.008 (ND – 0.041)	*Current study*
Transport	Cart	0.534 (0.01 – 1.94)	Connor et al., USA (1999)(60)
		ND	Connor et al., USA (2010)(36)
		0.002 (ND – 0.038)	*Current study*
Drug Administration	Bed side table	2.65	Sugiura et al., Japan (2010)(43)
		0.052 (ND - 0.328)	*Current study*
	Handle of fridge	ND	Ziegler et al., United Kingdom (2002)(88)
		GM 0.0002	Hedmer et al., Sweden (2008)(31)
		0.039 (ND - 0.191)	*Current study*
	Nursing station countertop	27	McDevitt et al., USA (1993)(19)
		0.03	Connor et al., USA (2010)(36)
		0.014 (ND - 0.406)	*Current study*
	Sink	8.5	McDevitt et al., USA (1993)(19)
		0.0006 (ND - 0.0170)	*Current study*
	IV bags	N/A (0.1 – 533)	Martins et al., Brazil (2009)(46)
		0.91(Centre 1); 0.07 (Centre 2)	Crauste-Manicet et al., France (2005)(20)
		0.206	Sottani et al., Italy (2011)(44)
		0.022 (ND - 0.104)	*Current study*
Waste	Waste container	0.08	Connor et al., USA (2010)(36)
		0.042*	Schmaus et al., Germany (2002)(24)
		0.010 (ND – 0.110)	*Current study*

** median levels presented; ND = not detected*

4 EVALUATION OF HEALTHCARE WORKERS' DERMAL EXPOSURE THROUGHOUT THE HOSPITAL MEDICATION SYSTEM AND IDENTIFICATION OF DETERMINANTS OF SUCH CONTAMINATION

4.1 Synopsis

Chapter 3 demonstrated that antineoplastic drug contamination is found on surfaces located throughout the hospital medication system. This is of concern as dermal contact is known to be the primary route of occupational exposure for healthcare workers. The aim of this chapter was to ascertain the dermal contamination levels of those healthcare job categories observed in Chapter 2 that have a high probability of contacting the surfaces that have drug residual. In addition, determinants associated with dermal contamination were identified. Using similar methods employed in Chapter 3, wipe samples were collected from healthcare workers' hands and subsequently quantified for CP using high-performance liquid chromatography-tandem mass spectrometry. Participants were also asked to answer a questionnaire regarding knowledge and behaviours with respect to antineoplastic drugs as well as complete a brief survey regarding contact with CP on the work shift. Up to three representatives from each job category at each site were invited to participate. In total, 225 wipe samples were collected (115 participants with 110 providing a duplicate). Overall, the dermal concentration AM was 0.360 ng/wipe, the GM < LOD, the GSD 1.98, and the range less than 0.356 to 22.8 ng/wipe (80% of samples were less than the detection limit). When stratified by job title, every maximum concentration exceeded the detection limit with the job group "other workers in the drug administration unit" (volunteers, oncologists, ward aide and dieticians) having the highest mean contamination level. Participants' hand washing practices did not appear to impact the dermal contamination levels. Four factors were found to be associated with increased dermal contamination: working in an

acute care hospital, working as a porter, nurse, transport, unit clerk or other role in the drug administration unit, being female, and having had a duty to handle antineoplastic drugs.

4.2 Introduction

A number of studies have documented that occupational exposure to antineoplastic (cytotoxic) drugs can result in adverse health outcomes including genetic damage(89)(55), which could lead to cancer, and reproductive effects.(5)(65) The literature lends evidence that occupational exposure to antineoplastic drugs occurs through the transfer of surface load of these drugs to the skin(37) and therefore the primary route of exposure is via dermal contact.(38)(40)(90) This may occur by contacting the drugs or their containers directly (i.e., handling of manufacturers' vials and/or prepared drug solutions in intravenous bags) or by indirect contact via touching of drug-contaminated surfaces.

We conducted a pilot study to assess the potential dermal contamination of personnel at select British Columbian hospital pharmacies and confirmed that both pharmacists and pharmacy technicians have detectable levels of drug contamination on their hands.(42) In Chapter 3, we showed that drug contamination of work surfaces is found throughout the hospital medication system and is not limited to the drug preparation and drug administration areas.(80) As such, healthcare workers who are involved in some capacity with the hospital medication system, such as porters, unit clerks and receivers, may contact contaminated surfaces and are therefore at potential risk of exposure. Based on our review of the literature, no single study has simultaneously examined the dermal contamination levels of multiple job categories that are potentially exposed to antineoplastic drugs due to their role in the hospital medication system.

The aim of the current study was to quantify dermal contamination levels of healthcare workers in job categories identified as part of the hospital medication system.(80) In addition, we

examined various factors, including glove usage and hand washing practices, to identify potential determinants of dermal contamination. To our knowledge, this is the first study to ascertain occupational dermal exposure of a broad range of at-risk healthcare job categories and the determinants of such exposure. For the reasons described in the introductory chapter, cyclophosphamide (CP) was used as the marker drug for exposure.

4.3 Methodology

4.3.1 Selection of participants

Study participants were employed at the six healthcare facilities located in Metro Vancouver that participated in the earlier phases of this study (Chapters 2 and 3) – five sites were acute care hospitals and one site was a cancer treatment facility. Healthcare workers were selected from job categories potentially at-risk of exposure to antineoplastic drugs according to site observations described in Chapter 2.(80) Eligible participants were selected by either active recruitment via a mailed letter of invitation (Appendix C) or passive recruitment through the distribution of consent to contact forms (Appendix D) at departmental meetings. The recruitment methods were dictated by the requirements of the participating hospitals' research ethics boards. Up to three representatives of each job category at each site were invited to participate. An overview of the recruitment process is found in Figure 4-1.

Upon receiving consent from workers to participate in the study (Consent Form, Appendix E), 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 hand wipe samples. Participants were given a cash honorarium of $10 for providing a hand wipe sample.

4.3.2 Wipe sampling of hands

Participants had their hands sampled at their convenience during their work shift. Sampling dates were selected based on availability of research team members and participants' work schedules. Participants who were wearing gloves when our team member arrived to collect the samples were asked to remove them prior to the hand wipe. This was done in order to assess any permeation of drugs through the gloves.

The hand wipe sample collection method is similar to that described previously for measuring surface contamination.(80) A new pair of disposable gloves was worn by the research team member to collect hand wipes from each participant. In summary, the front and back of both hands of each participant was wiped with a Kimwipe® (Kimberly-Clark, Mississauga, ON) that was pre-moistened with 1.0 mL of 0.1 M ammonium acetate solution (Sigma Aldrich, Oakville, ON). The Kimwipe® was then placed in a 20 mL vial and kept in a portable cooler with ice packs.

All collected samples were shipped on ice to the analytical lab within 24 hours of sample collection and stored at -20^{o}C until analysis. Both travel and field blanks were collected for quality control purposes.

Sample collection took place between June 2010 and February 2011. Duplicate dermal wipe samples were collected from most participants with at least three weeks' lag between collection times (average of 97 days; range 22 to 188 days).

4.3.3 Wipe sample preparation and analysis

The methods employed for preparation and analysis of samples in the current study were the same as the surface wipes (Chapter 3). All results were corrected for blanks. Hand wipe

contamination levels were reported in nanograms per wipe (ng/wipe). The limit of detection (LOD) for the dermal wipes was 0.356 ng/wipe.

4.3.4 Supplemental data collected on site

After the hand wipe was collected, all participants were surveyed regarding the following: a) the types and frequency of contact with CP during the current work shift (e.g. mixing drugs, administering drugs, disconnecting IV line, providing physical care to patients, disposing of CP-contaminated body fluids, handling a container of CP (i.e. vial or IV bag), disposing of vial or IV bag, cleaning up leak/spill of CP, touching a CP-contaminated surface/object, and consuming food/drink in an area where CP is mixed/handled/administered), b) number of gloves worn immediately prior to sample collection, and c) hand hygiene practices immediately before sample collection as well as during the current work shift. The latter included the participants' most recent hand wash prior to sample collection, what cleaning agent they used for their most recent hand wash and the number of times they washed their hands during the work shift up to the time of sample collection. See Appendix F for a copy of "Activity-Related Questions."

4.3.5 Self-administered questionnaire

Instrument overview

Participants were also provided with a self-administered questionnaire (Appendices G and H) which was divided into nine sections. The following sections of the questionnaire were included for data analyses: a) demographic data such as age and work experience; b) degree of contact with antineoplastic drugs; c) previous education/training related to antineoplastic drugs; d) usual hand hygiene practices and use of personal protective equipment, and e) details of known previous occupational exposure to antineoplastic drugs.

The majority of the questions incorporated for analyses were in a closed-ended categorical answer format. An open-ended question was utilized for respondents to describe any direct, unintended contact to antineoplastic drugs that they may have experienced.

Theory and construct of instrument

Several sources were employed to develop the questionnaire. The questions ascertaining the type of training received by the participant were based on the Occupational Safety and Health Administration's training and information dissemination requirements for controlling occupational exposure to hazardous drugs.(91) The survey used by Geer et al. (92) in their study examining workers' knowledge, attitudes and perceptions related to dermal exposure served as a basis for questions related to hand hygiene practices and personal protective equipment usage.

Pre-testing of instrument

A total of 28 individuals at non-participating hospitals in various healthcare job categories that were representative of the study jobs were asked to answer the original draft version of the questionnaire and provide feedback on wording and clarity of the questions. Modifications to the questionnaire were made in response to the feedback and the working version of the questionnaire received research ethics approval prior to dissemination.

4.3.6 Statistical analysis

Both untransformed and ln-transformed data were used to examine the distribution of dermal contamination levels. Summary statistics (arithmetic mean (AM), geometric mean (GM), geometric standard deviation (GSD), minimum and maximum, and proportion less than limit of detection) were used to describe all hand wipe samples. When ln-transformed, the measurements more closely approximated a normal distribution than the untransformed data. As

such, all statistical analyses utilized the ln-transformed values and the GMs were compared in ANOVA. Summaries of the dermal contamination 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" respondents of the same question. Bivariate analyses were performed to examine the relationship between CP contamination level (ln-transformed) and each of the independent variables separately, using one-way ANOVA (categorical variables) or simple linear regression (continuous variables). Tukey's post-hoc tests were performed following ANOVA to determine which differences in geometric means within a categorical variable were significantly different. A paired t-test was performed to determine if there was a difference in means between the duplicate samples.

All independent variables with $p < 0.20$ from the bivariate analyses and those with a strong *a priori* hypothesis for exposure were then offered into a multiple linear regression with the ln-transformed dermal contamination level as the dependent variable. The regression model also included a random effect with independent covariance structure for subject to account for potential correlation within repeated samples of the same participant. A manual backwards stepwise approach was employed to identify those independent variables that were significantly associated with the dependent variable by removing the independent variable with the largest p value at each step. Independent variables in which one or more categories had $p < 0.05$ were retained in the final model. A residual plot was generated to assess the appropriateness of the final model. Statistical analyses were performed using R version 2.13.1 (The R Foundation for Statistical Computing).

4.3.7 Reporting of results

Similar to the surface wipe results, a large proportion of hand wipe samples had contamination levels less than the limit of detection. To alert the reader, in Tables 4-1, 4-2 and 4-3, we report the proportion of values less than the LOD. As with the surface contamination levels, laboratory-calculated concentrations below the method limit of detection were available to us. The rationale for using all laboratory-calculated concentrations for analyses is found in the Methods section of Chapter 3.

4.4 Results

4.4.1 Characteristics of study population

In total, 115 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 board; however, the proportions who participated of those contacted by each method ranged from 55% to 76% (Figure 4-1). Table 4-1 presents a summary of the characteristics of the study population. Study participants had been in their current job positions for an average of 103 months (range 0 to 433 months) and workers who had a duty to handle antineoplastic drugs (N=91) had been handling these agents for an average of 82 months (range 0 to 336 months). The results of the paired t-test found that there was a statistically significant difference in means between the two samples with wipes collected on the second occasion having a higher overall mean (less than 0.356 ng/wipe in round #1 compared to 1.09 ng/wipe in round #2).

4.4.2 Overall summary of dermal contamination levels

Of the 115 participants, 110 supplied a duplicate hand wipe sample, resulting in a total of 225 dermal wipe samples. Only 44 of all samples (20%) were above the LOD of 0.356 ng/wipe.

Overall, the dermal concentration AM was 0.360 ng/wipe, the GM < LOD, the GSD 1.98, and the range less than 0.356 to 22.8 ng/wipe. The dermal contamination levels among female participants were higher than male participants and the difference between the sexes was statistically significant. Dermal samples from acute care hospitals had a higher average contamination level than those from the cancer treatment hospital and this difference was statistically significant (Table 4-1).

4.4.3 Dermal contamination levels by individual factors

Although participants from the drug administration units had the highest AM contamination levels, the difference in GM contamination levels between departments was not statistically significant ($F(2, 222) = 2.06$, p=0.13; GMs less than detection limit). When stratified by job title, the highest average contamination level was for other workers in the drug administration unit (volunteers, oncologists, ward aide and dieticians). The highest maximum dermal concentration of 22.8 ng/wipe was recorded for a registered nurse. The difference in GM contamination levels between job titles was not statistically significant ($F(7,217) = 1.42$, p=0.20) with only two job categories, registered nurses and workers in patient units not responsible for drug administration (volunteer, oncologist, dietician, ward aide), having means greater than the limit of detection (see Table 4-1).

Those workers who reported that they had a duty to handle antineoplastic drugs had a higher average contamination level than those who did not have this responsibility and this difference was nearly statistically significant ($F(2,223) = 3.24$, p=0.07). There was no statistically significant difference in dermal contamination levels between workers who had ever received health and safety training related to antineoplastic drugs and those who never received training ($F(1,223) = 0.495$, p=0.48; GMs less than limit of detection).

Neither the duration of participants' tenure in their current position nor the length of time that an individual had been handling antineoplastic drugs had a significant association with dermal contamination levels (p=0.794 and p=0.605, respectively).

4.4.4 Dermal contamination levels by cyclophosphamide (CP) contact

Sixty-three of all participants (28%) reported that they handled or came into contact with CP at least once during their work shift on the day the hand wipe sample was collected. Every participant was asked if they were potentially exposed to CP via ten different modes of contact; the resulting average reported number of CP contact methods on the shift was 1, with a minimum of 0 and a maximum of 6 contact methods. The individual who had the maximum measured contamination level reported having no contact with CP during the work shift.

When the results were stratified by the different CP contact methods, the AM contamination level of those who indicated that they had contacted CP was higher than those who had indicated no contact (Table 4-2). Regardless of the CP contact method, in all instances where a participant reported having contacted CP during the work shift, a higher proportion of the dermal measurements were above the detection limit. However, for every contact method examined in this study, in ANOVA none of these differences were statistically significant, likely due to the small number of respondents who reported contact. When the number of contact methods was tallied and treated as a continuous variable, the results of the linear regression suggest that for every additional mode of contact, the level of dermal contamination increased by 0.05 ng/wipe (p=0.13).

Dermal contamination levels based on glove usage

Frequency of glove usage when handling antineoplastic drugs

Of those tasked with handling antineoplastic drugs, 49 of 93 (53%) participants indicated that they wore gloves all the time when handling. There was no statistically significant difference in contamination levels between those who reported using gloves all the time and those who claimed to use gloves some of the time ($F(2,222) = 1.08$, $p=0.34$; GMs less than detection limit) (Table 4-3). Of the various job titles, nurses were most likely to report wearing gloves all the time when handling hazardous drugs. However, the frequency of glove usage when handling antineoplastic drugs did not appear to have any correlation with either job title or with the percentage of time handling antineoplastic drugs.

Thirty individuals stated that they did not wear gloves all the time when handling antineoplastic drugs despite the fact that they received health and safety training related to these hazardous agents. In addition, of those who indicated that they had previous direct, unintended contact with antineoplastic drugs while at work, less than 50% (17 of 35) claimed to use gloves all the time when handling antineoplastic drugs.

Frequency of glove usage while in an area where antineoplastic drugs are handled

When the participant was simply in an area where antineoplastic drugs are handled but not assigned to manipulate the agents, the percentage of workers who wore gloves all the time decreased to 27% (31 of 115 participants). Those who indicated they wore gloves all the time when in an area where antineoplastic drugs are handled had the highest level of contamination of all response categories (Table 4-3), but the difference was not statistically significant ($F(2,222) =$

0.951, p=0.39; GMs less than detection limit). There was no association between job title and the frequency of glove usage when in an area where antineoplastic drugs are handled.

Number of gloves worn

We sampled workers at a time that was convenient according to their work schedules, and at those times, 22 of all participants (10%) were observed wearing gloves (19 wore one pair of gloves and three wore double gloves). The participants who were wearing double gloves had just finished mixing drugs and/or handling a drug vial prior to sample collection. It is not surprising then that these three individuals had a higher mean level of dermal contamination than participants who wore one pair or no gloves. However, this difference was not statistically significant ($F(2,221) = 0.607$, p=0.55) likely due to the fact that the sample size was small (see Table 4-3).

4.4.5 Dermal contamination level based on hand washing practices

Hand washing practices after glove usage

There was no statistically significant difference in dermal contamination levels between those who washed their hands all the time and some of the time after glove use ($F(1,223)=0.968$, p = 0.33); GMs less than limit of detection). The sample with the maximum reported dermal contamination belonged to a participant who reported washing his/her hands all the time after glove usage. However, at the time of sample collection, this worker was not wearing gloves, indicated no known contact with CP on the shift and his/her most recent hand wash was less than 10 minutes prior to sample collection. Of those workers who reported handling antineoplastic drugs more than 25% of the time, only 19 of 73 (26%) reported washing their hands all the time after glove use (see Table 4-3).

Twenty-five of the 35 (71%) participants who reported having previous, unintended contact with antineoplastic drugs while at work did not wash their hands all the time after glove usage. Similarly, a majority (36 of 60; 60%) of those who had received health and safety training related to antineoplastic drugs stated that they did not wash their hands all the time after glove usage.

Hand washing after being in an area where antineoplastic drugs are handled

There was no statistically significant difference in hand contamination between those who washed their hands all the time and some of the time after being in an area where antineoplastic drugs are handled ($F(1,223) = 0.227$, $p=0.63$) (see Table 4-3).

Fourteen of the 35 (40%) participants who reported having previous direct, unintended contact with antineoplastic drugs while at work stated that they washed their hands all the time after being in an area where antineoplastic drugs are handled. Of those who had received health and safety training related to antineoplastic drugs, only 20 of 60 (33%) stated that they washed their hands all the time after being in an area where antineoplastic drugs were handled.

Hand wash duration

A large proportion (60 of 74; 81%) of those who handled antineoplastic drugs for more than 25% of their time reported washing their hands for less than 15 seconds. The maximum reported concentration was for a participant who stated that they usually washed their hands for 15 seconds or less, but there was no statistically significant difference in dermal contamination levels based on hand wash duration – less than 15 seconds or at least 15 seconds ($F(1,223)=0.665$, $p=0.42$) (see Table 4-3).

Hand wash cleaning method

We asked participants to indicate their usual hand wash cleaning method and also asked about their most recent hand wash cleaning method. In both instances, there was no statistically significant difference in contamination levels between the different types of cleaning agents (water only, soap and water, alcohol hand gel and other) used for hand washing ($p=0.937$ and $p=0.978$, respectively) (see Table 4-3).

Most recent hand wash

The maximum dermal concentration level was from a participant who reported washing their hands less than ten minutes prior to the hand wipe. Collectively, individuals who reported washing their hands less than ten minutes prior to collection of the hand wipe sample had the highest average concentration but the difference was not statistically significant ($F(3,221)=1.48$, $p=0.22$; 9.1 times difference in GMs). It should be noted that a larger proportion of those who reported having had contact with CP by at least five methods on the shift indicated washing their hands less than ten minutes prior to sample collection compared to those participants with less than five CP contact methods (see Table 4-3).

Hand wash frequency

Individuals who reported washing their hands five or more times on the shift had the highest average contamination levels. This finding was statistically significant and the Tukey post-hoc test revealed that the average contamination level for those who washed five or more times on the current shift was significantly greater than those who only washed their hands one or two times on the shift. It is notable that 100% of those who indicated they had at least five different CP contact methods on the shift washed their hands at least three times before the collection of

the wipe sample. This represents a higher proportion of frequent hand washes than those with fewer CP contact methods. However, after controlling for the number of CP contact methods in linear regression, the association between dermal contamination levels and frequency of hand washing was reduced and no longer statistically significant.

4.4.6 Multiple linear regression model

The results of bivariate analyses found nine variables that had $p < 0.20$: hospital type; department; job title; sex; whether the worker had a duty to handle antineoplastic drugs; whether the worker contacted CP during the work shift; number of times hands were washed on the work shift; number of CP contact methods on the work shift; and number of job categories responsible for drug transport at the hospital. Based on *a priori* hypotheses regarding potential exposure, another five variables were selected to be offered in the regression model: whether the worker mixed CP on the shift; whether the worker administered CP on the shift; whether the worker handled a container of CP on the shift; whether the worker disposed of waste containing CP on the shift; and whether the worker touched a surface potentially-contaminated with CP on the shift.

All 14 of these independent variables[c] were offered in a multiple linear regression model to predict dermal contamination. Four independent variables remained in the final model: the type of hospital, job title, sex, and whether the worker had a duty to handle antineoplastic drugs. A review of the residual plot of the final model suggested a random distribution. Table 4-4 provides an overview of the multiple linear regression results.

[c] Department was found to be in linear combination with one or more other categorical variables and therefore was the first independent variable removed from the regression model

4.5 Discussion

This study examined the dermal contamination levels of healthcare workers throughout the hospital antineoplastic drug medication system. Although a majority of the samples (80%) were below the analytical detection limit, the maximum measured dermal contamination levels in each of the eight different job categories, including those not responsible for drug preparation and/or drug administration, were all above the LOD of 0.356 ng/wipe. This confirms our hypothesis that, since drug contamination is present on surfaces throughout the hospital medication system, numerous job categories are at risk of exposure via dermal contact (Chapter 3). This is reinforced by our finding that the maximum reported level of dermal contamination was from a worker who had no known contact with CP during his/her work shift and the second highest overall contamination level was from an individual in a drug administration unit job category *not* responsible for the actual administration (volunteers, oncologists, ward aides and dieticians)

Our results found the following four variables to be significant determinants of dermal exposure: the type of hospital, job title, sex, and whether the worker had a duty to handle antineoplastic drugs. Other studies examining determinants of dermal exposure are scarce. Both Connor et al. (7) and Fransman et al.(40) suggested that direct handling of vials is likely to result in higher dermal contamination levels. Such work is mainly performed by workers in the drug preparation area. In a recent study, Friese et al. found that organizational factors, such as adequate staffing and a check-and-balance system for drug administration, reduced the potential for skin exposure among oncology nurses; no other job categories were examined.(74) Testa et al. concluded that employment duration does not influence exposure, similar to the result we found that level of work experience was not associated with dermal contamination levels.(73)

The results of the multiple linear regression indicate that those who worked in acute care hospitals had higher dermal contamination levels than those employed at a cancer treatment hospital. This difference may be because the cancer treatment hospital has more stringent education/training with a broader range of workers being educated due to the specialized nature of the facility. However, with only one cancer treatment hospital participating in our study, additional studies are needed before we can confidently generalize this result. We do not believe that there were any differences in participant selection between the two types of hospitals; this matter is discussed in more detail in the concluding chapter.

The regression model suggests that men were less likely to have dermal contamination than women. This is consistent with the findings reported by Geer et al. with respect to demographic factors associated with occupational dermal exposures.(93) Although we are unable to provide a physiological explanation for this phenomenon, we speculate that this may be because women generally have smaller hands than men do; therefore, if both sexes were to touch the same contaminated surface, the resulting drug concentration (in ng/cm^2) would be greater on the woman's hands. In addition, women generally tend to use hand lotions more frequently than men and the lotions may cause the drugs to adhere to the hands more so than individuals who do not apply lotions.

Both job title and whether the worker had a duty to handle antineoplastic drugs were found to impact dermal contamination levels. This is not unexpected as certain job titles, based on their respective roles and responsibilities, have been deemed to be at higher risk of exposure to antineoplastic drugs. However, in our model, "pharmacist" served as the reference job category and all seven other job categories examined had positive coefficients with four job categories having significantly higher hand contamination: porters; registered nurses; transport staff; and

other job categories based in the drug administration unit (volunteers, oncologists, ward aide and dieticians). The result that porters, transport staff and other job categories within the drug administration unit have higher dermal contamination is a novel finding as pharmacists have long been considered a high-risk cohort for occupational exposure to antineoplastic drugs due performing duties within the drug preparation unit.(94) It is important to note that at all participating hospitals, pharmacy technicians, not pharmacists, were tasked with drug preparation. Those who had a duty to handle antineoplastic drugs had higher levels of dermal contamination than those who did not and, since a majority of pharmacy and nursing personnel have this duty, the hand contamination of those employees is likely reflected in this variable rather than the variable of job title.

The dermal contamination levels measured in the current study were lower than those found in the literature (see Table 4-5), with the maximum reported level consistent with the mean dermal contamination levels indicated in other studies. The reason for the difference may be that several of the published studies collected dermal samples immediately after participants performed tasks involving CP(67)(40), which would likely result in elevated contamination levels. The fact that 20% of the dermal samples in the current study had some measureable levels of drug contamination suggests that further improvements can be made to minimize occupational exposure. This includes improved compliance with glove usage when handling as well as appropriate hand hygiene after handling or being in an area where the drugs are stored/mixed/administered (discussed later on).

A review of the literature found a proposed dermal occupational exposure limit (DOEL) for CP of 4 ng/cm^2 (95) or 3360 ng/wipe using an average surface area for both hands of 840 cm^2.(96) None of the wipe samples in the current study exceeded the DOEL. However, it is important to

mention that the DOEL was calculated based on absorption of CP on a daily basis. Our study design was cross-sectional and therefore we are unable to speculate on a worker's exposure over a full day.

The fact that drug residual was found even though workers wore gloves immediately before sample collection confirms previous studies which concluded that permeation of gloves is possible.(97)(98) Although a controlled laboratory study found that various glove materials are impermeable to antineoplastic drugs(99), under actual working conditions, the durability of the gloves may change resulting in leakage.(100) It is therefore recommended that various combinations of glove material be evaluated during the course of normal duties to ensure that users are adequately protected when wearing gloves.

It is interesting to note that, of the various cleaning agents employed for washing hands at the participating facilities, none appeared to be more effective than any other in removing drug residual. We asked about cleaning agents in both the self-administered questionnaire and in the short survey of participants immediately before sample collection took place. These results are consistent with our finding that, even though a surface was reportedly cleaned, it had little impact on the residual drug contamination levels (Chapter 3). We recommend that hand cleaning protocols are reviewed to ensure that they are indeed effective in removing drug residual.

Our results also indicated that individuals had dermal contamination at the start of their work shift (i.e. 6 participants provided hand wipe samples before they officially started their shift). This suggests dermal exposure on a previous shift with measurable drug residual due to ineffective hand washing and/or that load transfer of drug is occurring prior to actual handling

activities. Additional studies examining the phenomenon of skin contamination before the start of work shift is suggested.

We found that glove usage and hand washing practices amongst healthcare workers appears to vary from person-to-person. Whether a worker had a duty to handle antineoplastic drugs, had ever received training related to the safe handling of antineoplastic drugs or had previous direct, unintended contact with antineoplastic drugs while at work were all inconsequential to complying with glove usage guidelines. The lack of adherence to hand protection is not due to availability of gloves as a majority of participants (N=196; 87%) agreed or strongly agreed that they were readily available. Nor is it likely due to the lack of knowledge surrounding glove usage as a large proportion of all participants (N=180; 81%) agreed or strongly agreed that they believed they could use the required gloves properly. Our findings support those of others who concluded that healthcare workers do not always comply with personal protective equipment usage and optimal hand hygiene practices.(101) As all agencies that have developed safe handling guidelines have indicated using gloves for protection (8)(9)(10), it is therefore recommended that barriers to compliance with glove usage and hand hygiene protocols be investigated for all at-risk job categories within the hospital medication system.

4.5.1 Limitations

Limitations of the current study need to be addressed. When the results were stratified by the independent variables, in many instances select categories within each variable had relatively small sizes and therefore we had limited power to detect differences in these groups. Another limitation is that a large proportion of the dermal contamination levels were less than the detection limit.

At least one job cohort was not represented that has potential for exposure to antineoplastic drugs – housekeepers. Housekeepers at the participating sites are responsible for removing the cytotoxic waste bins from each facility. Unfortunately, as the contract company that employed the housekeepers declined to participate, we were unable to recruit this job category.

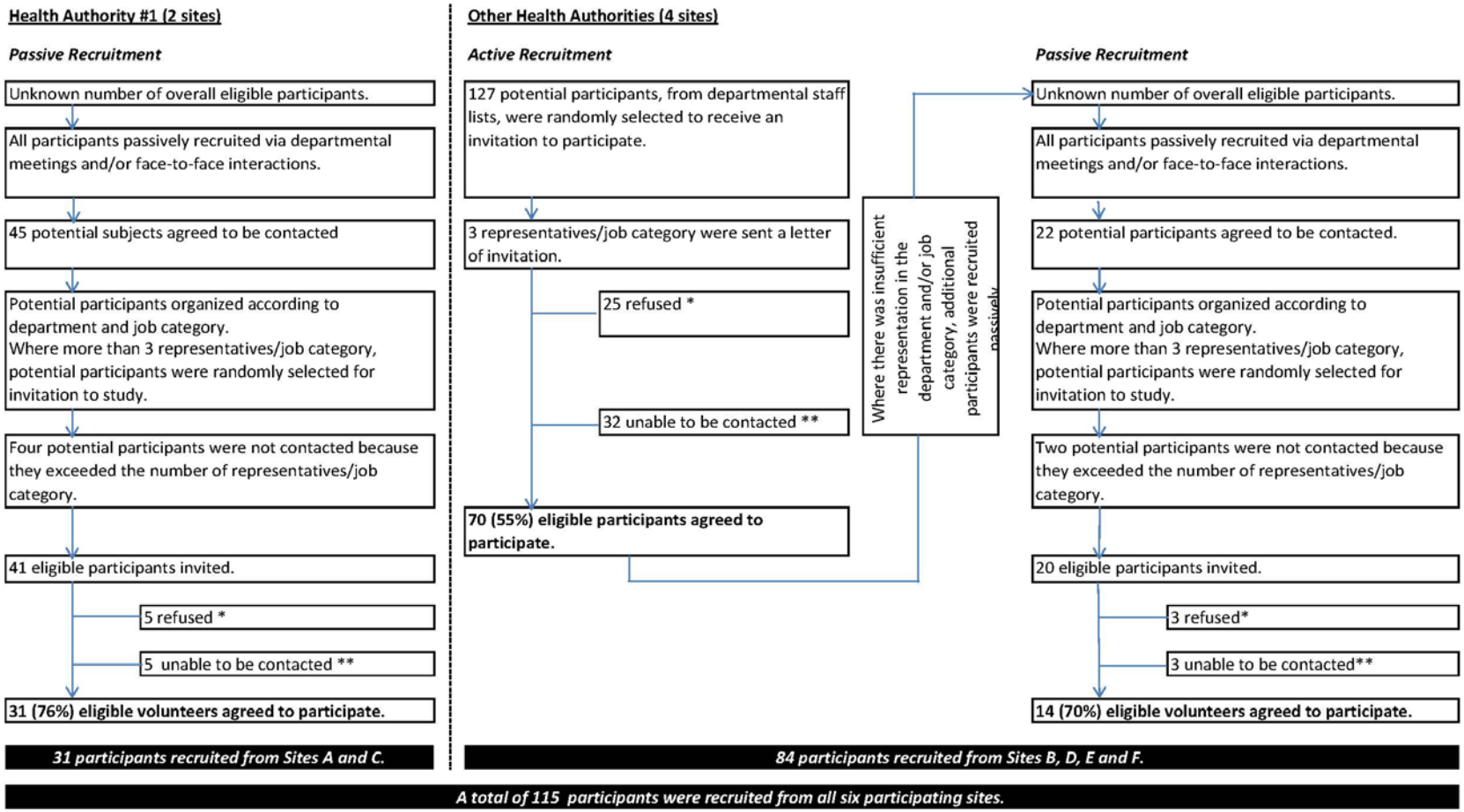
As this study was cross-sectional in nature, the findings are limited to the point in time when samples were collected; cumulative occupational exposure to antineoplastic drugs, if any, cannot be elucidated. Another temporal limitation is the fact that some of the independent variable data were collected on site while other data were gathered from the self-administered questionnaire. We were therefore unable to make certain comparisons, such as the actual frequency of glove usage when there was potential CP contact during the sampling work shift.

There is a possibility that the reported contamination levels were an underestimate of actual exposure, as CP may have been absorbed through the skin.(102) In addition, we analyzed for only one antineoplastic drug. We were also unable to quantify the amount of CP handled and/or contacted. Although we attempted to ask this information from participants, the reported amounts were not considered reliable because a majority of participants were unable to answer this question and those who did respond merely provided an estimate. Lastly, many of the independent variables were gathered via self-reports. This can result in misclassification of responses and, depending on the response, could bias the outcomes of the statistical analyses in either direction; though non-differential misclassification and bias to the null are most likely.

4.5.2 Summary

To our knowledge, this is the first study of its kind demonstrating dermal contamination to antineoplastic drugs of job categories throughout the hospital medication system. The findings are consistent with our earlier suggestion that there is likely an underestimate of the total number

of healthcare workers at risk of exposure to antineoplastic drugs.(80) We found four variables were significantly associated with dermal contamination. The determinants that were associated with increased exposure were: 1) employment at an acute care hospital, 2) work as a porter, nurse, transport staff or in the drug administration unit, 3) being female, and 4) having a duty to handle antineoplastic drugs. As this is the first study of its kind, additional studies are recommended to confirm or refute the reported associations.



** Reasons for refusal include fear of results, lack of time, perceived sample collection method as intrusive, and lack of interest in study.*
*** Reasons for non-contact include long-term illness, moved, transferred to another job within organization, did not respond to repeated call backs, or retired.*

Figure 4-1 Participant recruitment flowchart

Table 4-1 Dermal cyclophosphamide (CP) contamination levels of personnel in the hospital medication system, stratified by demographic variables: summary statistics, one-way ANOVA results and percent of samples less than detection limit

Variable	Subcategory	N	AM (ng/wipe)	SD (ng/wipe)	GM (ng/wipe)	GSD	ANOVA (p-value)¥	% < LOD
Hospital type	Cancer centre	22	0.014*	1.42	-0.863*	3.98	0.023	72.7
	Acute care hospital	93	0.444*	2.65	0.135*	1.40		82.3
Department	Pharmacy	46	-0.007*	1.36	-0.518	2.67	0.130	84.6
	Drug Administration	59	0.668	3.18	0.250*	1.46		75.7
	Other	10	0.285*	1.04	0.208*	1.18		87.0
Job title	Pharmacist	20	-0.318*	1.08	-1.123*	4.15	0.198	90.0
	Pharmacy Receiver	6	0.239*	0.395	0.224*	1.09		75.0
	Pharmacy Technician	23	0.232*	1.63	-0.001*	1.42		82.2
	Porter	6	0.404	1.37	0.280*	1.25		90.9
	Registered Nurse (includes LPN)§	33	0.767	3.13	0.363	1.46		73.4
	Transport (biopacker, shipper/receiver, and transporter)	4	0.121*	0.212	0.117*	1.05		87.5
	Unit clerk	12	-0.074*	0.978	-0.203*	1.31		83.3
	Other workers in drug admin unit (volunteer, oncologist, dietician, ward aide)	11	1.32	4.93	0.504	1.64		71.4
Sex	Female	92	0.455	2.69	0.118*	1.43	0.038	77.8
	Male	23	-0.013*	1.18	-0.792*	3.85		91.1
Age	20 to 29	12	0.254*	1.17	0.116*	1.30	0.679	79.2
	30 to 39	32	0.133*	1.37	-0.507*	3.18		77.4
	40 to 49	33	0.586	3.06	0.175*	1.48		80.3
	50 to 59	28	0.472	3.25	0.063*	1.45		83.6
	60+	10	0.119*	1.15	-0.137*	1.55		83.3
Do you directly handle, prepare and/or administer antineoplastic drugs as part of your normal duties?	Yes	91	0.433	2.70	0.096*	1.43	0.073	80.3
	No	24	0.086*	1.25	-0.689*	3.75		80.9
Percentage of time spent handling, preparing and/or administering antineoplastic drugs?	< 25%	53	0.155*	1.18	-0.006*	1.35	0.352	82.1
	> 25%	38	0.524	2.99	0.141*	1.46		78.4
	Never	24	0.575	3.56	-0.580*	3.99		80.0

** Reported values are less than the limit of detection of 0.356 ng/wipe*

¥ Where the dependent variable was the ln-transformed dermal contamination level

§ LPN = licensed practical nurse

Table 4-2 Dermal cyclophosphamide (CP) contamination levels of personnel in the hospital medication system, stratified by reported contact methods during work shift: summary statistics, one-way ANOVA results, and percent of sample less than detection

Contact query	Response	N	AM (ng/wipe)	SD (ng/wipe)	GM (ng/wipe)	GSD	ANOVA (p-value)¥	% < LOD
All participants	N/A	225	0.360	2.46	-0.081*	1.98	N/A	80.4
Did you contact CP (by any means)?	No§	162	0.291*	2.69	-0.235*	2.20	0.184	82.2
	Yes	63	0.538	1.72	0.342*	1.41		74.6
Did you mix/compound CP?	No	221	0.314*	2.40	-0.113*	1.98	0.211	81.0
	Yes	4	2.92	4.38	2.11	1.72		50.0
Did you physically handle a container of CP?	No	192	0.343*	2.54	-0.125*	2.07	0.575	80.7
	Yes	33	0.463	1.99	0.183*	1.41		78.8
Did you dispose of waste (IV bag or vial) containing CP?	No	210	0.343*	2.49	-0.112*	2.02	0.546	80.5
	Yes	15	0.602	2.01	0.369	1.34		80.0
Did you touch a surface which came into contact with a container / package of CP?	No	176	0.311	2.59	-0.176*	2.13	0.335	81.8
	Yes	49	0.538	1.94	0.279*	1.38		75.5
Did you administer CP to a patient?	No	213	0.326	2.47	-0.121*	2.01	0.373	81.7
	Yes	12	0.962	2.17	0.694	1.36		58.3
Did you disconnect an IV line containing CP?	No	216	0.330*	2.49	-0.112	2.00	0.425	81.0
	Yes	9	1.08	2.52	0.729	1.43		66.7
Did you provide physical care for a patient on CP?	No	222	0.333*	2.43	-0.100*	1.99	0.406	80.6
	Yes	3	2.37	4.45	1.52	1.86		66.7
Did you dispose of body fluids from a patient on CP?	No	225	0.360	2.46	-0.081*	1.98	N/A	80.4
Did you clean up a spill/leak containing CP?	No	225	0.360	2.46	-0.081*	1.98	N/A	80.4
Did you eat/drink in an area where CP is mixed, handled or administered?	No	197	0.335*	2.57	-0.145*	2.07	0.369	81.7
	Yes	28	0.538	1.51	0.395	1.25		71.4

** Reported values are less than the limit of detection of 0.356 ng/wipe*

¥ Where the dependent variable was the ln-transformed dermal contamination level

§ All "No" responses are actually No/Don't know combined

Table 4-3 Dermal cyclophosphamide (CP) contamination levels of personnel in the hospital medication system, stratified by protective measures employed by participants: summary statistics, one-way ANOVA and percent of samples less than detection

Variable	Subcategory	N	AM (ng/wipe)	SD (ng/wipe)	GM (ng/wipe)	GSD	ANOVA (p-value)¥	% < LOD
All participants	N/A	225	0.360	2.46	-0.081*	1.98	N/A	80.4
Frequency of glove use when handling antineoplastic drugs	Some of the time	43	0.155*	1.51	-0.140*	1.36	0.342	84.7
	All the time	49	0.442	2.53	0.140*	1.42		76.8
	Not applicable	23	0.575	3.56	-0.580*	3.99		80.0
Frequency of glove use when in an area where antineoplastics are handled	Never	29	-0.10*	0.939	-0.138*	1.31	0.388	86.0
	Some of the time	55	0.383	2.65	-0.280*	2.56		79.6
	All the time	31	0.671	3.02	0.361	1.34		76.7
Number of gloves worn immediately prior to sample collection*	0 (none)	202	0.363	2.48	-0.066*	2.01	0.546	81.2
	1 pair	19	-0.057*	1.39	-0.465*	1.76		73.7
	2 pairs	3	2.91	5.53	1.71	2.05		66.7
Frequency of hand wash after glove usage	Not all the time	78	0.188*	1.40	-0.208*	2.19	0.326	79.6
	All the time	37	0.720	3.81	0.195*	1.51		82.2
Frequency of hand wash after being in an area where antineoplastics are handled	Not all the time	83	0.412	2.83	-0.137*	2.19	0.634	82.7
	All the time	32	0.226*	1.02	0.066*	1.37		74.6
Average duration of usual hand wash	< 15 sec	87	0.343*	2.68	-0.167*	2.15	0.416	80.7
	15+ sec	28	0.415	1.59	0.202*	1.38		79.6
Usual hand wash method	Water only	1	0.000*	0.000	0.000	1.00	0.937	100.0
	Soap and water	87	0.379	2.72	-0.132*	2.15		82.2
	Alcohol hand gel	18	0.272*	1.68	-0.044*	1.53		77.8
	Other	9	0.404	0.857	0.336*	1.19		66.7
Time since most recent hand wash (prior to sample collection)§	< 10 min ago	77	0.929	3.76	0.403	1.50	0.220	75.3
	10 to 30 min ago	71	0.029*	1.21	-0.557*	2.99		88.6
	31 to 60 min ago	43	0.083*	1.72	-0.178*	1.44		79.1
	60+ min ago	34	0.116*	0.642	0.061*	1.19		79.4
Most recent hand wash method (prior to sample collection)§	Water only	8	0.126*	0.720	0.080*	1.16	0.930	87.5
	Soap and water	189	0.370	2.61	-0.131*	2.10		81.0
	Alcohol hand gel	22	0.520	1.76	0.302*	1.35		68.2
	Other	6	-0.010*	0.190	-0.075*	1.05		100.0
Number of times hands washed on shift (prior to sample collection)§	1 to 2	43	-0.197*	1.19	-1.036*	4.04	0.024	81.4
	3 to 4	64	0.002*	1.11	-0.172*	1.38		84.4
	5+	112	0.768	3.25	0.382	1.39		80.4
	0 (start of shift)	6	0.573	0.817	0.521	1.17		33.3

** Values reported are less than the limit of detection of 0.356 ng/wipe*

¥ Where the dependent variable was the ln-transformed dermal contamination level

§ Information collected from participants while on site. Total N is 225 for these questions because responses may vary between the two sampling dates

Table 4-4 Coefficients, standard errors and p-values for final multiple linear regression model showing variables associated with dermal contamination (ln-transformed)

Explanatory Variable	Subcategory	N	Coefficient	Std Error	p-value
Intercept			0.665	0.185	0.00
Type of hospital	Cancer Treatment	44	Ref		
	Acute Care	181	0.272	0.118	0.02
Job title	Pharmacist	40	Ref		
	Pharmacy receiver	12	0.309	0.220	0.16
	Pharmacy technician	45	0.200	0.147	0.17
	Porter	11	0.583	0.236	0.01
	Registered nurse	64	0.284	0.137	0.04
	Transport	8	0.874	0.286	0.00
	Unit clerk	24	0.294	0.177	0.10
	Other workers in drug admin unit	21	0.625	0.194	0.00
Sex	Female	180	Ref		
	Male	45	-0.307	0.128	0.02
Duty to handle antineoplastic drugs?	No	178	Ref		
	Yes	47	0.393	0.142	0.01

Table 4-5 Comparison of cyclophosphamide (CP) dermal contamination levels reported in the current and other published studies, in reverse chronological order

Concentration of CP	Author	Comments
AM = 0.360 ng/wipe (range of < LOD to 22.80 ng/wipe)	*Current study*	
GM = 0.98 ng/wipe (range of < LOD to 3.96 ng/wipe)	Hon et al. (2011)(42)	Pilot study; small sample size (N=9)
Concentrations in the µg range	Turci et al.(2010)(66)	Used pads for collection which are known to overestimate exposure(40)
25.2 ng/wipe[1]	van Wendel de Joode et al.(2005)(103)	Samples collected from nurses, technicians and cleaners – not stratified by job title
Not detected	Fransman et al. (2006) (104)	Small sample size (N=3); from workers in an industrial laundry facility handling hospital bed linen
13.6 ng/task - pharmacy technicians; 28.6 ng/task - nurses handling urine; 154.0 ng/task - nurses washing patients; 57.8- nurses removing bed sheets; 12.5 ng/task - cleaning personnel cleaning toilets	Fransman et al. (2005)(40)	Arithmetic means presented; units are task-based and therefore presents challenges for direct comparison
37,800 ng – Pharmacy technicians; 163.8 ng – oncology nurses[2]	Fransman et al. (2004) (67)	Samples collected immediately after the completion of tasks involving cyclophosphamide
20 to 63,400 ng/glove *(on the internal side of gloves)*	Minoia et al.(1998)(61)	Study conducted before NIOSH guidelines released; potential that gloves were contaminated during doffing resulting in elevated levels(105)

[1] *calculated using 840cm^2 as surface area of both hands*(96)
[2] *calculated using mean duration of task as per Table 3 of reference #*(67)

5 EVALUATION OF HEALTHCARE WORKERS' URINARY CONTAMINATION LEVELS THROUGHOUT THE HOSPITAL MEDICATION SYSTEM AND IDENTIFICATION OF DETERMINANTS OF SUCH EXPOSURE

5.1 Synopsis

Chapter 4 found evidence that healthcare workers involved in some capacity with the hospital medication system are at risk of dermal exposure to antineoplastic drugs. However, dermal wipe levels may not be reflective of absorbed dose nor do they not take into account other possible routes of exposure. The objective of this chapter was to measure drug contamination in the urine of healthcare workers, to overcome the shortcomings of dermal samples. As in the previous chapters, determinants associated with urinary contamination were also identified. Workers who provided hand wipe samples also participated in urine monitoring. Participants were asked to provide 24-hour urine samples which were subsequently analyzed for CP and three of its urinary metabolites using high-performance liquid chromatography-tandem mass spectrometry. Urine samples from non-hospital control subjects were collected to confirm that exposure to hospital participants occurs. Independent variables from the same survey instruments used in Chapter 4 were offered into a multiple linear regression to identify determinants associated with urinary contamination. A total of 223 urine samples were collected (115 participants with 108 providing a second sample). The mean urinary CP concentration of study participants was 17.4 nmol/L, the GM 4.16 nmol/L, and the GSD 3.60, with a range from 0.1 to 839 nmol/L. The mean, GM and maximum value from hospital participants were all greater than the corresponding values from non-hospital controls. When stratified by job title, pharmacy receivers had the highest mean contamination level as well as the maximum reported level overall. Two variables were found to be statistically significant following bivariate analysis - the number of drug transport job categories and the number of drug administration units within a site. We identified two

determinants associated with urinary contamination – jobs as a pharmacy receiver, pharmacy technician, porter, nurse, or unit clerk and having a larger number of drug transport job categories at the facility.

5.2 Introduction

The primary route of healthcare workers' exposure to antineoplastic drugs is considered to be through dermal contact.(38)(40) This can occur either: a) *directly* through handling of the drug vials or IV preparations or b) *indirectly* by contacting drug-contaminated surfaces/objects. We reported in Chapter 4 that healthcare workers are indeed at risk of exposure to antineoplastic drugs by confirming the presence of drug contamination on workers' hands. In addition, we demonstrated that an assortment of job categories throughout the hospital medication system (process flow of drugs within a facility from cradle-to-grave) have measurable levels of dermal contamination suggesting that previous occupational exposure studies have underestimated both the number and variety of healthcare workers at risk.

However, the use of dermal wipe samples is limited by the fact that they are only representative of the level of external contamination - they cannot estimate the amount that may be 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 until metabolized and can subsequently exhibit cytostatic effects.(13) Furthermore, dermal wipe samples do not take into account other potential routes of exposure such as inhalation or ingestion and, therefore, may not be the most reliable or accurate estimate of exposure. Given this, a number of occupational exposure studies have collected urine samples as a biomarker to estimate the dose of antineoplastic drug exposure.(106)(75)(107)(36)

Since we demonstrated that various job categories within the hospital medication system have antineoplastic drug contamination on their hands, it would also be sensible to determine the body burden of these hazardous agents in the same workers. Based on our review of the literature, no single study has simultaneously measured urinary drug contamination levels of all healthcare job categories across the hospital medication system potentially exposed to antineoplastic drugs.

The aim of this study was to assess the urinary contamination levels of the same job categories that were evaluated for dermal exposure. In addition to quantifying the levels of CP in urine, we also measured three of its more stable urinary metabolites, carboxyphosphamide, 4-ketocyclophosphamide, and N-dechloroethylcyclophosphamide, and summed the four analytes to ascertain contamination levels. This was done in order to obtain a more accurate indication of overall urinary contamination because a) less than 20% of the administered dose of CP is eliminated unchanged in the urine(13) and b) there is a large inter-individual variability in metabolism of CP, so the percentage of parent product excreted varies between individuals.(72)(108) In addition to quantifying the drug output, we sought to identify individual and workplace factors that may be associated with urinary contamination levels. To our knowledge, this is the first study of its kind to examine urinary contamination of a broad range of at-risk healthcare job categories and the determinants of such exposure.

5.3 Methodology

5.3.1 Selection of participants

Participants enrolled in the current study were the same individuals that provided hand wipe samples in Chapter 4. Every participant was given an honorarium of $25 each for providing a 24-hr urine sample.

5.3.2 Selection of control subjects

One control subject was recruited from a local university for approximately every 10 study participants. Control subjects were representative of the study population with respect to age and sex. A potential control subject was excluded from the study if he/she worked at or frequently visited a healthcare facility that prepares and/or administers antineoplastic drugs. Fourteen control subjects were recruited, of whom eight provided a second urine sample, for a total of 22 urine samples from control subjects.

5.3.3 Collection of urine samples

Urine sample collection took place immediately after a participant provided the hand wipe sample as outlined in the previous chapter. Participants were asked to provide 24-hour urine samples as this sampling period is recommended by the U.S. Environmental Protection Agency for biological monitoring of toxic substances(109) and is also consistent with other urinary biomarker studies of anticancer agents.(12) In addition, urinary elimination of CP and its metabolites is almost complete 24 hours after uptake.(13) (Note that the standardized collection time of 24-hours eliminates the need for creatinine correction of urine samples). Table 5-1 lists the supplies that were provided to each participant for the collection of urine samples.

Every collection jar was pre-filled with 50 mL of phosphate buffered saline solution (137 mM NaCl, 2.7 mM KCl, 1.76 mM KH_2PO_4 and 10 mM Na_2HPO_4) (Sigma Aldrich, Oakville, ON) before being furnished to participants. The buffer served to minimize the effect of pH on the stability of the urinary metabolites. To prevent potential degradation, participants were asked to keep the urine samples refrigerated whenever practical and, where a refrigerator was unavailable, it was recommended to participants to use the instant cold packs provided to facilitate the maintenance of a cool storage environment.

Due to the size limitations of the collapsible cooler, only nine polypropylene collection jars could be placed inside each cooler. To minimize the probability of participants using all the supplied collection jars, research team members collected the first urine sample of the set from every participant while on site (i.e. every participant had a total of ten jars). This first sample jar from every participant was placed into a separate portable cooler with ice packs and at the end of the sampling day was transported to the analytical laboratory where it was stored in a walk-in refrigerator (4^{o}C).

Once the 24-hour sampling period was completed, participants notified a local courier company to have the samples delivered to the laboratory. Upon receipt of the remaining samples, all collected urine from a participant was pooled, the total volume of urine estimated and three 5-mL aliquots of every participant's urine sample were placed into cryogenic tubes and subsequently stored at -80^{o}C until analysis.

Sample collection took place between June 2010 and February 2011. A second set of 24-hour urine samples were collected from most participants with at least three weeks' lag between collection times (average of 97 days; range 22 to 188 days).

5.3.4 Urine sample analysis

For every participant's urine sample, one of the 5 mL tubes 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) (University of Bielefeld, Bielefeld, Germany), 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 could be 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 urine was analyzed for CP and three of its metabolites, 4-ketocyclophosphamide (4-keto), carboxyphosphamide (carboxy), and N-dechloroethylcyclophosphamide (ethyl-CP) (Bielefeld University, Bielefeld, Germany), by high-performance liquid chromatography-tandem mass spectrometry using an Agilent Technologies 6410 Triple Quadruple LC-MS/MS (Santa Clara, CA). The instrument utilized 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% prompted reanalysis of the batch. The limit of detection (LOD) for each analyte was as follows: 4-keto 0.044 ng/mL, carboxy 0.0373 ng/mL, CP 0.0522 ng/mL and ethyl-CP 0.035 ng/mL. Any analyte concentrations that were less than the corresponding limit of detection (LOD) were substituted using LOD/2 as commonly performed on occupational exposure data.(82)

The recovery rate of each analyte was calculated, averaged following multiple trials, and the corresponding urinary concentration values were adjusted to reflect the recovery rate (4-keto 85.2%, carboxy 4.1%, CP 111% and ethyl-CP 39.9%). In addition, the molar weight of each analyte was factored into the urinary concentration levels (4-keto MW=275.07 g/mol, carboxy MW=293.08 g/mol, CP MW=261.09 g/mol, and ethyl-CP MW=198.59 g/mol). The sum of the molar concentrations of the four analytes for each sample was calculated and urinary contamination levels were reported in nanomol per liter (nmol/L).

5.3.5 Supplemental data collection and questionnaire

As detailed in Chapter 4, all participants were interviewed on-site using the "Activity-Related Questionnaire" and were asked to complete the self-administered "Cytotoxic (Antineoplastic) Drug Exposure Questionnaire".

5.3.6 Statistical analysis

Both untransformed and ln-transformed data were used to examine the distribution of urinary contamination levels. Summary statistics (arithmetic mean (AM), geometric mean (GM), geometric standard deviation (GSD), minimum and maximum) were used to describe all urine samples. When ln-transformed, the measurements more closely approximated a normal distribution than the corresponding untransformed data. As such, all statistical analyses utilized the ln-transformed values and the GMs were compared in ANOVA. Summaries of the urinary contamination 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" respondents of the same question. A paired t-test was conducted to determine if there was a statistical difference in mean urinary contamination between the two sample collection times.

To determine which factors were associated with urinary contamination levels, a multiple linear regression analysis was conducted in several steps. First, we considered whether there was plausible support for a relationship between the factor and exposure. Second, we examined whether the variables were associated with exposure (ln-transformed urinary contamination level) in bivariate analyses (one-way ANOVA for categorical variables and simple linear regression for continuous variables). Tukey's post-hoc tests were performed following ANOVA to determine which differences in geometric means within a categorical variable were

significantly different. Those independent variables with $p < 0.20$ in the bivariate analyses and for which the direction of association could be logically interpreted, as well as variables with a strong *a priori* hypotheses for exposure were then offered into a multiple linear regression model with the ln-transformed molar urinary contamination of all four analytes combined serving as the dependent variable. The model also included a random effect with independent covariance structure for subject to account for potential correlation within repeated samples of the same subject. A manual backwards stepwise approach was utilized to identify those independent variables with $p < 0.10$; these were retained in the final model. A residual plot was generated to determine the appropriateness of the final model. Statistical analyses were performed using R version 2.13.1 (The R Foundation for Statistical Computing).

5.4 Results

5.4.1 Characteristics of study population

The participants for the current study were the same as those who provided dermal wipe samples from Chapter 4.

5.4.2 Summary of urinary contamination levels – participants and controls

Of the 115 participants, 108 provided a second sample, resulting in a total of 223 urine samples. The mean urinary concentration of CP and its metabolites in study participants was 17.4 nmol/L, the GM 4.16 nmol/L, and the GSD 3.60, with a range from 0.1 to 839 nmol/L.[d] In comparison, the mean urinary contamination for control subjects was 6.80 nmol/L, the GM 3.98 nmol/L, and the GSD 2.58 with a range from 1 to 45.8 nmol/L. The paired t-test found a statistically

[d] Our dataset had one very large outlier that skewed the summary statistics. For quality assurance purposes, this sample was re-analyzed along with other randomly-selected samples. All re-analyzed results reflected the original urinary concentrations except for this outlier. In addition, the re-analyzed result of the outlier was found to be more consistent with the other sample concentrations as well as with the second sample from the same participant. Therefore, the re-analyzed result for this one sample was employed for all statistical analyses.

significant difference between the two sample collection periods with the second collection period having a higher mean (3.73 nmol/L in round #1 compared to 31.9 nmol/L in round #2).

5.4.3 Urinary contamination levels by individual factors

Table 5-2 presents a summary of the urinary contamination levels grouped by various characteristics of the study population. When stratified by job title, the highest mean concentration belonged to the pharmacy receivers, one of whom had the maximum reported concentration. The difference in contamination levels between job titles was not statistically significant ($F(7,215)=1.74$, $p=0.10$; largest difference in job means was 2.7 times).

As expected, participants who reportedly handled antineoplastic drugs as part of their normal duties had higher urinary contamination levels (both AM and GM) than those who did not ($F(1,221)=2.58$, $p=0.11$; difference in means of 1.28 nmol/L). Similarly, those who regularly worked in an area where antineoplastic drugs were handled, prepared or administered had higher urinary contamination levels ($F(1,221)=0.10$, $p=0.75$; difference in means of 0.250 nmol/L). Those who handled antineoplastic drugs less than 25% of the time had higher urinary contamination levels (both AM and GM) than those who handled the drugs more frequently ($F(1,176)=0.29$, $p=0.06$; difference in means of 0.465 nmol/L). The cohort that handled antineoplastic drugs less than 25% of the time had a smaller proportion of individuals who received training related to safe handling of antineoplastic drugs (21% vs. 61%) (see below). None of the ANOVA results of the three drug-handling variables were statistically significant.

Participants who indicated they received training related to antineoplastic drugs had lower levels of urinary contamination. The difference between those who received training compared to those who did not was nearly statistically significant ($F(1,221)=3.23$, $p=0.07$; difference in means of 1.29 nmol/L).

Neither the duration of participants' tenure in their current position nor the length of time that participants had been handling antineoplastic drugs had a significant association with urinary contamination levels (p=0.98 and p=0.49, respectively)

5.4.4 Urinary contamination levels by hospital characteristics

Table 5-3 is a summary of urinary contamination levels based on the categorical variables associated with characteristics of the hospital. A review of this table indicates that, although the maximum recorded contamination level was from an individual working at an acute care hospital, participants from the cancer treatment hospital had higher AM and GM urinary contamination levels than participants from acute care hospitals. This difference was not statistically significant ($F(1,221)=2.23$, p=0.14; difference in means of 1.50 nmol/L).

An individual from the Pharmacy department had the highest overall urinary contamination level. However, there was no statistically significant difference in GM contamination levels between departments ($F(2,220)=1.18$; p=0.31; largest difference in groups means was 1.96 nmol/L). Similarly, there was no statistically significant difference in urinary contamination levels between sites that had an isolated room to prepare antineoplastic drugs compared to the site that had no isolated room ($F(1,221)=0.38$, p=0.54; difference in means of 0.573 nmol/L).

Both the AM and GM were higher at facilities where antineoplastic drugs were initially delivered to the shipping/receiving department; this difference was not statistically significant ($F(1,221)=2.51$; p=0.11; difference in means of 1.123 nmol/L).

Table 5-4 presents the results for those hospital characteristics that are continuous in nature and have a logical association with urinary contamination levels. Urinary contamination levels increased with increases in either the number of job categories responsible for drug transport or

the number of drug administration units in a facility. Both of these variables were statistically significant.

5.4.5 Urinary contamination levels by contact with cyclophosphamide (CP)

We asked participants regarding their potential CP contact method within the past 24 hours (to allow for absorption and metabolism of CP) as well as on the current shift. There was no apparent association between urinary contamination levels and the methods by which an individual came into contact with CP within the past 24 hours and on the work shift (see table in Appendix I).

5.4.6 Multiple linear regression model

The results of bivariate analyses identified ten variables with $p < 0.20$ and a logical direction of association: health authority; hospital type; job title; whether the worker had a duty to handle antineoplastic drugs; frequency of gloves use when handling antineoplastic drugs; where the drugs were initially delivered to the facility; whether the worker ever received training related to workplace health and safety of antineoplastic drugs; whether the individual had previous, unintended contact with antineoplastic drugs while at work; the number of job categories responsible for drug transport within a facility; and the number of drug administration units at the facility. Based on *a priori* hypotheses regarding potential exposure, another two variables were selected to be offered in the regression model: dermal contamination levels (from Chapter 4); and the number of chemotherapy patients with whom the participant was directly involved with in the past seven days.

All 12 of the aforementioned independent variables were offered into a multiple linear regression model to predict urinary contamination levels.[e] Two variables remained in the final model: job title and the number of job categories responsible for drug transport. With respect to the job title variable, five categories exhibited relatively large differences in urinary contamination levels compared with pharmacists (reference category): pharmacy receivers; pharmacy technicians; porters; registered nurses; and unit clerks. A review of the residual plot suggested a random distribution. Table 5-5 provides an overview of the multiple linear regression results.

5.5 Discussion

Until now, little attention has been paid to the body burden of healthcare workers who are part of the hospital medication system other than pharmacy personnel and drug administration nurses. Our results demonstrate that, collectively, the healthcare workers examined have increased levels of CP and its metabolites in their urine compared to control subjects. When stratified by job title, pharmacy receivers (individuals responsible for ordering and stocking drugs) had the highest mean exposure and the maximum urinary contamination level measured.

Twelve independent variables were offered into the regression model to identify determinants of urinary exposure for healthcare workers at risk throughout the hospital medication system. Two variables, job title and the number of job categories responsible for drug transport within a facility, proved to be statistically significant at $p < 0.10$. Of note, job title was found to be significantly associated with dermal contamination as well as in this urinary contamination study. In the urinary contamination model, "pharmacists" served as the reference job category and all seven of the other categories had positive coefficients with five job categories having relatively large differences – pharmacy receivers, pharmacy technicians, porters, registered

[e] Number of drug administration units was identified to be in linear combination with one or more other variables and therefore was the first independent variable removed from the regression model

nurses and unit clerks. It was surprising that all other job categories had positive coefficients relative to pharmacists as the latter have long been considered a high-risk cohort with respect to occupational exposure to antineoplastic drugs.(94) However, unlike other studies, pharmacy technicians, not pharmacists, at participating sites were responsible for preparing the drugs. Therefore, it was not unexpected to find that pharmacy technicians had statistically significant elevated urinary contamination levels compared with pharmacists. Other studies have had varying conclusions regarding the urinary CP levels of pharmacists. Connor et al. reported urinary contamination was found in pharmacists only, with no measurable levels in the urine of nurses, pharmacy technicians or nurse assistants.(36) Sugiura et al. did not detect CP in the urine of any pharmacists and observed that urinary contamination levels varied considerably amongst the healthcare workers that participated in their study.(35)

With respect to the second determinant identified in the current study, it is not clear why the number of job categories responsible for drug transport within a facility was associated with urinary contamination levels. This same variable was found to be associated with surface contamination levels (Chapter 3). As with the surface contamination, we speculate that the more job categories involved, the more drug handling activities are performed by various individuals – a large proportion of whom are not formally trained regarding the hazards of these agents or the associated safe handling requirements (based on questionnaire responses). This is supported by the fact that porters and unit clerks (proportion not trained was 82% and 74%, respectively), two of the three job categories responsible for drug transport at participating sites, had the highest GM urinary contamination levels when stratified by job title. As we are the first to identify this determinant, we suggest that future studies examine this phenomenon more closely.

There have been other determinants of urinary contamination reported in the literature. Rekhadevi et al. found that age, years of exposure and duration of handling antineoplastic drugs

per day were positively associated with urinary CP concentrations, though age was the lone variable that was statistically significant. None of the exposed nurses in their study employed protective measures such as gloves nor did they work within safety cabinets, whereas nurses in the current study do not mix drugs and are required to wear gloves when administering.(64) Another study concluded that the amount of CP compounded was significantly correlated with urinary CP concentration despite the implementation of a revised compounding standard operating procedure at the facility(48) (based in part on the National Institute for Occupational Safety and Health (NIOSH) "Alert" aimed at protecting healthcare workers from exposure to cytotoxic compounds(9)). This same study also observed measureable levels of CP in morning urine samples even before pharmacists began compounding and, according to the authors, suggests that these workers may have been exposed through skin contact due to environmental contamination from compounding activities the day before.(48) This finding supports the conclusions from our two earlier chapters that surface contamination is widespread and, in turn, the drug residual can lead to dermal exposure. Lastly, Schreiber et al. concluded that the amount processed and the number of CP preparations resulted in an increase in the number of reportable urinary CP results for those tasked with drug preparation.(75) In addition, the authors found the use of a garbage can with a removable lid increased the number of positive samples of urinary CP.(75) We did not record the type of waste containers so could not examine this variable.

Other studies examined determinants within more restricted cohorts and could not examine differences between the range of jobs involved in the hospital medication system. Rekhadevi et al. studied nurses only (tasked with drug preparation, drug administration and disposal of drug-contaminated body fluids)(64), Tanimura et al. looked solely at pharmacists responsible for compounding(48), and Schreiber et al. examined pharmacy technicians and pharmacists.(75)

The current study reported urinary contamination levels in molar concentration of CP and three of its urinary metabolites. However, the literature primarily presents urinary concentration of the parent product, CP, only. Given this, Table 5-6 compares the CP urinary levels in the current study to the results reported by others since 2004, the year that NIOSH initially released their "Alert." We therefore believe that most of these studies would have comparable control measures implemented at the participating sites.(9) A review of the Table indicates that the urinary contamination levels in the current study are consistent with the findings of others; however, for all studies cited, there is a great deal of variability with respect to the proportion of samples above detection limits as well as the range of reported contamination levels. Differences in urinary CP concentrations within and between studies are likely due to variations in handling practices including personal protective equipment usage as well variability in metabolic rates amongst individuals. The latter is suspected to be due, in part, to genetic polymorphisms of the enzymes responsible for metabolizing xenobiotics.(17) This variability is supported by the low correlation between CP and sum of molar concentrations found in the current study (Pearson $r = 0.22$). In addition, liver function may influence the metabolism of CP. Where liver function is impaired, a smaller fraction of the CP dose is metabolized and a higher fraction of CP may be eliminated in the urine.(71) Of concern is the fact that we detected drug residual despite workers reporting not having any contact with CP. Long-term urinary excretion of CP (continuously positive urine samples) may signify continuous absorption of CP.(43) This may be due, in part, to the fact that the skin has a reservoir function whereby internal exposure may continue despite the cessation of external exposure.(95)

Sargent et al. indicated a no-significant-risk level (NSRL) of 1000 ng/day for CP,[f] the level at which no increase in cancer risk and no adverse effects on organ systems or the developing fetus are expected.(110) A review of our data shows that ten participants (4.5%) had exposure levels which exceeded the NSRL. Of these, four were nurses, two were unit clerks, two were pharmacy technicians, one was a pharmacist and the final sample was from an individual who worked in the drug administration unit but was not responsible for drug administration.

Our results found no correlation between the dermal contamination levels (from Chapter 4) and urinary CP contamination. This could be due to the fact that we collected hand wipes at a single point in time which is not reflective of the day's exposure. It could also suggest that other routes of exposure, such as inhalation and accidental ingestion, may play a role in the body burden of antineoplastic drugs.

We performed bivariate analyses (ANOVA or linear regression) on 65 variables and only ten variables had a $p < 0.20$ that also demonstrated a logical direction of association. These 65 variables included environmental and organizational factors which have been associated with better safety practices in the workplace and, presumably, lower exposure levels.(111) However, we were unable to detect any association between the environmental and organizational factors examined and the urinary contamination levels. We believe that the lack of statistically significant results following bivariate analysis is related to the small numbers in each category and/or small differences in the exposure concentrations between groups. Further discussion on this matter is found in the concluding chapter.

[f] Assumed that "day" is equivalent to 24 hours

5.5.1 Limitations

Additional limitations of this study are described here. We were unable to accurately determine the amount of antineoplastic drug handled by each participant; therefore, we could not evaluate if this factor is associated with urinary CP contamination levels. We did not obtain information on participants' contact with CP during the 24-hour sample collection period; this information may have allowed us to identify other variables associated with exposure. This study was cross-sectional in nature and therefore cumulative exposures to antineoplastic drugs cannot be determined. We only examined CP but other antineoplastic drugs are handled at the sites and we measured three urinary metabolites of CP but there are other, less stable metabolites that may have been present(13). Both of these factors likely lead to an underestimate of the true exposure levels. Lastly, a multitude of the independent variables were gathered via self-reports. This can result in misclassification of responses, and depending on the response, could bias the outcomes of the statistical analyses in either direction; though non-differential misclassification and bias to the null are most likely.

5.5.2 Summary

To our knowledge, this is the first study of its kind demonstrating urinary contamination with antineoplastic drugs among individuals with jobs throughout the hospital medication system. From our regression model, job title and the number of drug transport job categories were found to be correlated with urinary contamination levels. Of note, the regression model suggests that other job categories may be more at risk than pharmacists – traditionally believed to be a high-risk cohort**.** Future studies are recommended to ensure that all at risk job categories throughout the hospital medication system are examined independently to identify specific determinants of exposure to antineoplastic drugs applicable for each category. In addition, we are in agreement

with others(44)(66) that measuring for CP and one or more of its urinary metabolites, as opposed to quantifying CP only, is a more accurate reflection of body burden.[g]

[g] Based on the laboratory results, the proportion of analytes in the current study was as follows: ethyl-CP > 4-keto > CP > carboxy

Table 5-1 Supplies provided to each participant for collecting urine samples

Number of units	Supplied item (Manufacturer/Supplier)
1	Written instructions for collecting and returning urine sample (Appendix J)
10	250mL straight-side wide-mouth polypropylene jars with lids (Thermo Scientific)
1	12-can capacity collapsible cooler (Escort)
2	Ice gel liners (Cole-Palmer)
1	5” x 8” ice pack (Rapid-Aide)
1	Permanent marker
3	Large re-sealable plastic storage bags
4	Instant cold packs (Ardes Medical)

Table 5-2 Urinary contamination levels of cyclophosphamide (CP) and its metabolites of personnel in the hospital medication system, stratified by demographic variables: summary statistics and one-way ANOVA results

Variable	Subcategory	N	AM (nmol/L)	SD (nmol/L)	Max (nmol/L)	GM (nmol/L)	GSD	ANOVA (p-value)*
Overall		223	17.3	75.2	839	4.16	3.60	
Job titles	Pharmacist	20	3.83	3.41	18.3	2.57	2.74	0.10
	Pharmacy Receiver	6	79.4	240	839	5.83	6.97	
	Pharmacy Technician	23	13.7	49.0	332	4.47	3.24	
	Porter	6	14.4	29.9	105	6.84	2.59	
	RN (includes LPN)	33	24.3	82.5	565	4.26	4.41	
	Transport (biopacker, transporter, and shipper/receiver)	4	5.54	2.76	9.84	5.01	1.60	
	Unit clerk	12	12.9	24.4	114	6.26	2.91	
	Other workers in drug admin unit (volunteer, oncologist, dietitian, and ward aide)	11	4.98	4.85	22.8	3.07	3.42	
Sex	Female	92	18.1	80.1	839	4.10	3.72	0.72
	Male	23	14.4	51.3	332	4.43	3.16	
Age	20 to 29	12	47.3	132	565	6.74	5.45	0.24
	30 to 39	32	21.7	107	839	4.39	3.54	
	40 to 49	33	9.63	36.4	299	3.80	2.92	
	50 to 59	28	13.8	32.5	172	4.13	4.13	
	60+	10	3.59	2.18	9.35	2.75	2.44	
Do you directly handle, prepare and/or administer antineoplastic drugs as part of your normal duties?	Yes	91	20.3	84.1	839	4.47	3.67	0.11
	No	24	6.39	14.9	105	3.19	3.26	
Percentage of time handling spent handling, preparing and/or administering antineoplastic drugs?	< 25%	54	23.1	98.8	839	4.58	3.85	0.59
	> 25%	38	15.5	53.7	332	4.11	3.48	
Do you regularly work in an area where antineoplastics are handled, prepared and/or administered?	Yes	82	19.5	84.4	839	4.23	3.74	0.75
	No	33	11.9	42.9	332	3.98	3.29	
Have you ever received training related to workplace health and safety of antineoplastic drugs?	Ever	60	15.5	61.7	565	3.59	3.71	0.07
	Never	55	19.5	88.0	839	4.89	3.44	
Have you ever had previous, unintended contact with antineoplastic drugs while at work?	Yes	18	26.3	60.9	299	5.48	5.03	0.17
	No	97	15.7	77.6	839	3.95	3.35	

** where the dependent variable was the ln-transformed urinary concentration level*

Table 5-3 Urinary contamination levels of cyclophosphamide (CP) and its metabolites of personnel in the hospital medication system, stratified by categorical hospital characteristics: summary statistics and one-way ANOVA results

Categorical variable	Subcategory	N	AM (nmol/L)	SD (nmol/L)	Max (nmol/L)	GM (nmol/L)	GSD	ANOVA* (p-value)
Overall	N/A	223	17.4	75.2	839	4.16	3.60	
Hospital	A	18	7.37	21.5	128	2.71	3.66	0.11
	B	16	6.97	14.3	80.5	3.33	3.18	
	C	13	6.19	7.79	34.0	3.38	3.23	
	D	23	12.7	29.2	172	4.63	3.48	
	E	23	31.5	130	839	5.25	3.59	
	F	22	29.0	98.7	565	5.40	3.99	
Health Authority	1	31	6.87	17.0	128	2.98	3.46	0.10
	2	23	12.7	29.2	172	4.63	3.48	
	3	39	21.7	101	839	4.37	3.47	
	4	22	29.0	98.7	565	5.40	3.99	
Hospital type	Cancer centre	22	29.0	98.7	565	5.40	3.99	0.14
	Acute care hospital	93	14.6	68.4	839	3.91	3.50	
Department	Pharmacy	46	18.6	94.5	839	3.64	3.55	0.31
	Drug Administration	57	18.0	64.2	565	4.36	3.92	
	Other	12	9.78	20.8	105	5.60	2.26	
Does the facility have an isolated room for antineoplastic drug preparation?	Yes	92	18.6	82.7	839	4.05	3.64	0.54
	No	23	12.7	29.2	172	4.63	3.48	
Where are the drugs received at the facility?	Pharmacy	54	9.35	23.0	172	3.59	3.52	0.11
	Shipping/receiving	61	24.3	99.9	839	4.72	3.65	

** where the dependent variable was the ln-transformed urinary concentration level*

Table 5-4 Urinary contamination levels of cyclophosphamide (CP) and its metabolites of personnel in hospital medication system, stratified by continuous variables of hospital characteristics: linear regression results

Variable	Intercept	β	Std Error	p-value*
No. transport job categories (range 1 – 3)	-6.03	0.301	0.114	0.007
No. drug admin units (range 1-3)	-5.95	0.233	0.095	0.014

** where the dependent variable was the ln-transformed urinary contamination level*

Table 5-5 Coefficients, standard errors and p-values for final multiple linear regression model showing variables associated with urinary contamination levels (ln-transformed)

Explanatory variable	Subcategory	N	Coefficient	Std Error	p-value
Intercept			-6.47	0.312	< 0.001
Job title	Pharmacist	39	Ref		
	Pharmacy receiver	12	0.666	0.452	0.14
	Pharmacy technician	45	0.580	0.296	0.05
	Porter	11	0.772	0.470	0.10
	Registered nurse	64	0.455	0.277	0.10
	Transport	8	0.327	0.544	0.55
	Unit clerk	23	0.597	0.375	0.11
	Other workers in drug administration unit	21	0.053	0.392	0.89
Number of drug transport categories			0.240	0.132	0.07

Table 5-6 Comparison of cyclophosphamide (CP) urinary contamination levels reported in current study and other published studies in reverse chronological order since 2004

Proportion of samples > LOD (LOD)	Cyclophosphamide concentration Mean in µg/L (range)	Mean in ng/24hrs (range)	Comments	Author and Country
202/223 *(0.052 ng/mL)*	*0.14* *(< LOD – 2.37)*	*232.1* *(< LOD – 7069)*	*24-hr urine samples from at-risk job categories throughout hospital medication system*	*Current study*
0/36 (0.2 ng/mL)	None reported		Pre- and post-shift urine samples from pharmacy technicians and nurses	Sottani (2011); Italy(44)
1/1 (0.01 ng/mL)	N/A	13.5	24-hr urine sample from pharmacist (not wearing PPE)	Hama (2011)(52); Japan
7/40 (0.1 ng/mL)	(0.1–1.2)	N/A	Post-shift urine samples from pharmacy techs, nurses and attendants	Villarini (2011)(17); Italy
90/226 (None reported)	N/A	(2.7 to 462.8)	Examined physicians, pharmacists and nurses.	Sugiura (2011)(43); Japan
11/62 (0.01 ng/mL)	N/A	29.3	Positive results from nurses administering drugs and a medical doctor.	Sugiura (2011)(35); Japan
3/17 (0.1 ng)	N/A	(6.7 to 52)	Sampled pharmacists responsible for mixing and checking	Yoshida (2011)(62); Japan
0/35 (0.4 ng/mL)	None reported		Varying urine sampling times; urine samples from 6 pharmacists and 2 nurses.	Maeda (2010)(112); Japan
2/67 (0.015 ng/mL)	(0.000043 - 0.000079)	N/A	Results from two pharmacists that prepared drugs.	Connor (2010)(36); USA
4/4 (None reported)	N/A	165.3 [*before* changes to SOP]; 47.4 [after *changes* to SOP]	Examined pharmacists responsible for compounding	Tanimura (2009)(48); Japan
0/22 (0.01 ng/mL)	None reported		Pre- and post-shift samples from pharmacy workers, nurses, assistant nurses and cleaners.	Hedmer (2008)(31); Sweden
42/52 (0.04 ng/mL)	440 (80 – 900)	N/A	Pre-shift samples from nurses exposed to antineoplastic drugs (not wearing PPE)	Rekhadevi (2007)(64); India
0/50 (~ 1 nM)	None reported		Pre- and post-shift samples from pharmacy personnel	Mason (2005)(45); UK

LOD = limit of detection; N/A= not applicable; PPE = personal protective equipment

6 CONCLUDING CHAPTER

6.1 Study overview and objectives

A review of the literature regarding healthcare workers' exposure to antineoplastic drugs reveals that the drug preparation and drug administration units are most often examined. However, there have been evidence suggesting that drug contamination of surfaces is found beyond these two areas(20)(57) while others have argued that additional healthcare cohorts, besides pharmacy personnel and drug administration nurses, are potentially exposed to antineoplastic drugs, such as drug transport personnel and other hospital staff in the drug administration units.(68)(70)

These theories are plausible because antineoplastic drugs follow a site-specific pathway known as the hospital medication system (process flow of drugs from receipt to disposal).(79)(10) In order to test the theory that surface contamination and occupational exposure occurs throughout the hospital medication system, the current study was undertaken with cyclophosphamide (CP) as the marker drug of exposure. The following is an outline of the four objectives of the study:

Objective 1: Identify surfaces most likely contaminated and the job categories potentially at risk of exposure to antineoplastic drugs throughout the hospital medication system;

Objective 2: Quantify the surface contamination levels throughout the hospital medication system and identify determinants associated with surface contamination;

Objective 3: Assess the dermal CP contamination levels of at-risk healthcare job categories and identify determinants associated with dermal exposure; and

Objective 4: Determine the urinary contamination levels of CP and three of its metabolites of at-risk healthcare job categories and identify determinants associated with urinary contamination.

6.2 Key findings

The study took place at six hospitals (five were acute care facilities and one was a cancer treatment centre) within Metro Vancouver in the province of British Columbia. Every participating site frequently prepares and administers CP, a known human carcinogen.(15) The study objectives and the respective results of each were presented in separate chapters and below is a review of the key findings from each chapter.

6.2.1 Chapter 2 (Objective 1)

Using repeated site observations, I identified 55 potentially drug-contaminated categories of surfaces located throughout the hospital medication system that were contacted frequently by healthcare personnel. Some of the more frequently contacted surfaces include a box cutter (delivery stage), writing instrument (drug preparation, delivery and drug administration stages), bin where drugs are held for pick up (transport to ward stage) and IV pump (drug administration stage).

For the purposes of the study, exposure potential was defined as physically manipulating the drugs, contacting a potentially contaminated surface/object, or using an instrument that was touched by someone suspected of having drug-contaminated hands/gloves. Site observations found that an exposure potential exists at all five stages of the hospital medication system. Up to 11 job categories per site were potentially at risk of exposure. Job categories that were found to be at risk of exposure common to all participating sites were: pharmacy receivers, pharmacy technicians, pharmacists and nurses. In addition to pharmacy receivers, other novel job categories that were identified to be at risk that have not been mentioned in the literature or guidelines include volunteers, unit clerks, dieticians (in the drug administration stage), porters (transport to ward stage) and biopackers (waste disposal).(9)

6.2.2 Chapter 3 (Objective 2)

Wipes samples were collected from those surfaces identified in Chapter 2 as potentially contaminated and analyzed using high-performance liquid chromatography-tandem mass spectrometry to quantify the level of CP. Four-hundred thirty-eight samples were collected (229 surfaces with 209 duplicates). The mean CP surface concentration was 0.201 nanograms per square centimeter (ng/cm^2), the geometric mean 0.019 ng/cm^2 and the geometric standard deviation 2.54 with a range of less than detection (0.356 ng/wipe; LOD in ng/cm^2 varied with surface area) to 26.1 ng/cm^2 (64% of surface wipe samples were less than the limit of detection). Measureable levels of CP were found at every stage of the hospital medication system with the highest average contamination found in the drug preparation stage. Of note, reported handling of CP and cleaning of surfaces did not appear to be associated with contamination. I identified two factors associated with surface contamination: the stage of the hospital medication system and the number of job categories responsible for drug transport. In particular, the drug preparation and drug administration stages had significantly higher surface contamination than the delivery stage and the more job categories tasked with drug transport at a facility, the higher the levels of surface contamination.

6.2.3 Chapter 4 (Objective 3)

As surface contamination was detected at all stages of the hospital medication system, it was deemed important to confirm if an occupational exposure potential exists. Personnel selected for inclusion in the study were those job categories found in Chapter 2 that had a high probability of touching either the drugs directly or drug-contaminated surfaces. One-hundred fifteen workers agreed to participate with 110 able to provide a duplicate sample. The mean dermal CP concentration was 0.360 ng/wipe, the geometric mean was less than limit of detection (0.356

ng/wipe), the geometric standard deviation was 1.98 with a range of less than 0.356 to 22.8 ng/wipe (80% of dermal wipe samples were less than the detection limit). Female participants had statistically significant higher dermal contamination levels than males. When stratified by department, personnel working in the drug administration unit had the highest average contamination levels. When stratified by job titles, the maximum value in each job category exceeded the detection limit and the cohort with the highest average dermal CP concentrations were other workers in the drug administration unit (volunteers, oncologists, ward aides and dieticians). Despite glove use, measurable levels of drugs were found on the hands of workers. This could be due to contamination prior to donning of gloves or permeation of drugs through gloves or both. Variables that were not associated with dermal contamination included previous safe drug handling training, job tenure and experience handling antineoplastic drugs.

With respect to determinants associated with dermal contamination, we identified four factors: type of hospital, job title, sex and whether the worker had a duty to handle antineoplastic drugs. Specifically, workers in acute care facilities had higher levels of contamination than workers in cancer treatment facilities; all examined job categories had higher CP concentration levels on their hands relative to pharmacists; males had lower dermal contamination levels; and having a duty to handle antineoplastic drugs resulted in higher CP concentrations on one's hands. Interestingly, hand washing practices and contact with CP on the shift were not found to be significant variables in the final model for dermal contamination. In addition, the surface contamination levels from Chapter 3 were not correlated with dermal contamination.

6.2.4 Chapter 5 (Objective 4)

Although measurable levels of CP were detected on the hands of individuals in jobs across all stages of the hospital medication system, whether individuals absorbed CP remained unknown.

Therefore, urine samples were collected from the same workers who provided dermal wipes to ascertain if a body burden exists. As approximately 20% of CP remains unchanged in the urine(13), we also measured for three of its metabolites and tallied all four analytes to determine urinary contamination levels. Non-hospital subjects were enrolled as controls for evaluating exposure potential of healthcare workers. A total of 223 urine samples were collected from participants (115 participants, 108 of whom provided a second sample). The mean urinary concentration for study participants was 17.4 nanomols per liter (nmol/L), the geometric mean was 4.16 nmol/L, the geometric standard deviation was 3.60 with a range of 0.1 to 839 nmol/L. In comparison, the non-hospital control subjects had lower values for all corresponding summary statistics providing evidence that the study participants were occupationally exposed to antineoplastic drugs. When stratified by job title, pharmacy receivers had the highest arithmetic mean urinary CP contamination levels. Both the number of job categories responsible for drug transport and the number of drug administration units within a facility were found to be associated with urinary contamination levels. Reported contact with CP did not appear to influence CP levels in urine. Variables that were not associated with urinary contamination included job tenure and experience handling antineoplastic drugs.

With respect to determinants associated with urinary contamination, the job title and the number of job categories responsible for drug transport were significant. More precisely, all evaluated job titles had higher urinary contamination levels relative to pharmacists and the more job categories responsible for drug transport within a facility, the higher the urinary contamination levels. Of note, dermal contamination levels from Chapter 4 were not correlated with urinary contamination levels.

6.3 Conclusions and implications of research

To date, no other body of work (i.e. single report/document) has examined drug contamination on work surfaces or occupational exposure of at-risk healthcare workers throughout all stages of the hospital medication system. Specifically, the drug delivery, drug transport and waste disposal stages of the hospital medication system had not been evaluated concurrently with the drug preparation and administration stages. In the current study, although levels were generally low, I found evidence that environmental contamination is present on various surfaces throughout the hospital medication system. As a result of this widespread contamination, I demonstrated that several healthcare job categories had measurable levels of dermal and urinary drug contamination. This implies that the number of healthcare workers at risk of exposure to antineoplastic drugs is higher than previously believed as the list of occupations exposed should, based on the current study, be extended from pharmacy and nursing personnel to include unit clerks, pharmacy receivers, porters, volunteers, biopackers and dieticians.(70) A national carcinogen exposure surveillance project, CAREX Canada, recently estimated that 17,000 Canadians are occupationally exposed to antineoplastic drugs; but this estimate considered only nurses and pharmacists as potentially exposed.(16) The results found here indicate that this estimate will need to be updated to include the additional at-risk job categories identified in the current study. Based on our estimates, the number of Canadian healthcare workers at risk of exposure to antineoplastic drugs could exceed 100,000. Furthermore, the study suggests that current control measures are not 100% effective in minimizing contamination and/or occupational exposure and that additional control efforts, through the identification of factors associated with contamination or exposure, are necessary to reduce the risk.

With respect to the risks associated with the contamination levels found, only 2% of the surfaces sampled exceeded the United States Pharmacopeia maximum suggested level of 1 ng/cm^2(33) and none of the hand wipe samples exceeded a published dermal occupational exposure limit of 4 ng/cm^2 per day.(95) However, as we collected wipe samples at a point in time only, it cannot be confirmed if cumulative exposure is likely to exceed either referenced threshold level.

Ten participants (4.5%) had urinary CP contamination levels that exceeded a published no-significant-risk level (NSRL) of 1000 ng/day.(110) Individuals with drug levels greater than the NSRL have an increased risk of developing cancer. Based on the risk assessment reported by Sessink et al.(108), an individual exposed to the average urinary CP contamination levels in our study of 232 ng/24 hours has a lifetime cancer risk of 7.78 per million (see Table 6-1). Alternatively, if one were to use the cancer slope factor referenced by Sargent et al.(110), then the lifetime cancer risk would be 1.89 per million using our average urinary CP concentration (see Table 6-2). Regardless of the quantitative risk assessment method used for the calculations, both models suggest a slight increase in the number of cancer cases among healthcare workers who have absorbed CP. [For comparison purposes, urinary CP levels in patients 24-hours after treatment ranged from 1.75 ng/day to 190,000 ng/day(71), which translates to a maximum cancer risk of 636 per 100,000 using Sessink et al.'s calculation.(108)]

6.4 Recommendations to minimize occupational exposure to antineoplastic drugs

The findings in the current study are in agreement with others that an exposure potential exists despite the implementation of control measures.(34)(36)(43)(44)(47) The objective of determining factors associated with surface contamination and occupational exposure was to allow for the identification of control initiatives that specifically address these factors.

With respect to determinants associated with surface contamination, reducing the number of job categories responsible for drug transport may minimize surface contamination levels. This can be achieved through configuration of the facility so that the drug preparation unit is closer to the patient administration areas or employing only dedicated staff for drug transport. I identified that the drug preparation area was the most contaminated stage in the hospital medication system at the participating sites. This area is likely the primary source of contamination for the remaining hospital medication stages of transport, drug administration and waste disposal. The use of closed system drug transfer devices during drug preparation has proven to be effective in other studies and it is recommended that they be adopted at the participating facilities.(113)(114)(115) Given that external contamination on vials was detected, another recommendation is to clean the drug vials prior to handling to minimize the level of external contamination.(51)(54) It is also suggested that every site perform routine surface monitoring to confirm reduction in contamination. This can be achieved using a recently developed rapid analytical technique.(116)

Regarding factors that were identified as being associated with dermal contamination (hospital type, job title, sex, and whether the worker had a duty to handling antineoplastic drugs), little can be done to actually modify any of these factors. However, these factors do indicate the jobs and facilities where monitoring and training should be ongoing, and where effective control measures need to be sought. As I found that compliance with personal protective equipment and hand hygiene varied from individual-to-individual, enhancement of the safety culture/climate, as suggested by McDiarmid and Condon(70), may improve workers' compliance with safe drug handling guidelines which advocates glove usage and regular hand washing. Whether increased compliance with these recommendations leads to reduced exposure will need to be tested.

The two determinants associated with urinary contamination, job title and number of job categories responsible for drug transport, were also found to be factors for dermal contamination and surface contamination, respectively. The same recommendations suggested earlier for these two factors apply for urinary contamination as well.

6.5 Knowledge translation

Research findings will be sent to all participants who requested this information on the consent form. Individual dermal and urinary contamination levels will be reported in relation to other participants as well as to comparable results in the literature. Participants will also be provided with a summary of the key study findings and a website address for additional information regarding the study.

A non-scientific report will be drafted and provided to the funding agency (WorkSafeBC Research Secretariat); after external review, the report will be posted on their website. Study results will also be shared in presentations with the affected departments, health and safety departments and joint health and safety committees at the six participating hospitals.

Other study stakeholders will be sent a summary of the key study findings, the study's website address and, in addition, be given the option to request a presentation. These stakeholders include the following groups: Health Sciences Association of British Columbia (HSA), British Columbia Nurses' Union (BCNU), Hospital Employees' Union (HEU), Health Care Safety Professionals Association of British Columbia (HCSPA), and Health Employers' Association of British Columbia (HEABC). Stakeholders can use the study results to raise awareness of the issue of healthcare workers' exposure to antineoplastic drugs and, in turn, lead to discussions surrounding changes to practices and policies. In addition, the drug levels found in this

document can serve as a baseline to gauge the effectiveness of any future control initiatives aimed at reducing surface contamination and/or occupational exposure.

6.6 Study strengths and limitations

The predominant strength of the study was examination of surfaces and healthcare workers throughout the hospital medication system to ascertain the extent of environmental contamination and exposure potential within a hospital. This, in turn, allowed us to identify determinants of surface contamination as well as occupational exposure throughout the hospital medication system.

Another strength of the study was the sample size. To my knowledge, this study had the largest number of surface wipes and personal samples compared to other similar studies.(36) This study also evaluated surfaces whereby the probability of worker contact is known. In comparison, published studies sampled surfaces where frequency of contact is unknown e.g. floors (59)(60) while in other instances no rationale was provided for inclusion of surfaces.(43)(55)(48) Furthermore, I collected duplicate samples to ascertain the variability of contamination/exposure over two sampling periods.

For the laboratory analyses, highly sensitive instrumentation was used resulting in detection limits in the nanogram per wipe (surface and dermal) or nanogram per milliliter (urine) range. Regarding the urine analyses, we measured for the parent product as well as three of its urinary metabolites. This results in a more accurate reflection of urinary contamination levels as the current study found that 25% of the absorbed CP was excreted unchanged (similar to literature reports of 20% of parent product excreted unchanged (72)).

This study is not without its limitations, however. This study was cross-sectional in nature and, therefore, we are unable to comment about cumulative exposures. With only CP being measured, the results are likely to be an underestimate of contamination/exposure to all antineoplastic drugs that are found at the participating facilities. I was unable to obtain accurate quantities of CP handled/contacted by participants on the work shift (asked during collection of dermal wipes) and during the 24-hour urine sampling period. Although various types of surfaces were sampled, I only had wipe recovery information for stainless steel surfaces (recovery rate of 99.65%). Due to the fact that cleaning services at participating facilities were provided by a contractor who declined to participate in the study, we did not have representation from housekeepers which are known to be at risk of exposure.(31)(67)(40)

The relevant ethics boards dictated the manner in which workers were recruited for inclusion in the study. Some workers were actively recruited via random sampling from employee lists, while others were passively recruited via volunteering their contact information after formal and informal meetings at the hospital site (non-random). As such, whether the differing recruitment methods resulted in a bias of the findings needs to be explored. One of the recruitment methods was based on potential participants agreeing to be contacted after introduction to the study via department or face-to-face meetings (passive recruitment). This might result in a volunteer effect, where individuals who are more likely to be exposed (those who are concerned) might preferentially participate. However, it is unlikely that any of the potential participants had concerns related to previous measurement data, because none of the healthcare workers at any of the participating sites have ever been asked to provide samples for exposure assessment to antineoplastic drugs. There was still potential for people who routinely handle antineoplastic drugs to be more concerned and to preferentially volunteer. I was able to examine this potential,

because 63% of participants were recruited actively (i.e. randomly selected based on staff lists of job titles that were considered at potential risk of exposure). I compared contamination levels between those who were actively versus passively recruited and found no statistically significant difference (t-test results of p=0.46 and p=0.11 for dermal and urine contamination levels, respectively). Breaking down the comparison even further, we examined the results between the recruitment methods for two specific independent variables – hospital and job title. A majority (95%) of the 20 t-tests conducted were found to be not statistically significant and no trends in mean contamination levels were evident. I also compared the risk perception scores (with respect to hazards associated with antineoplastic drugs) of those recruited by the two methods and did not find a statistically significant difference (p=0.42). These comparisons provide some comfort that the participant recruitment method was not likely to have biased the contamination levels.

Throughout this study, results of analyses examining factors that might be associated with exposure levels were often not statistically significant. This issue was explored further to determine whether important differences in ln of the exposure concentration (dependent variable) were missed because of the study design. Based on a significance level of 0.05 and a power of 80%, the difference in ln of the exposure concentration that we could detect using a one-way ANOVA balanced design was 0.257 (for 8 categories with 28 participants in each) or 0.188 (for 2 categories with 112 participants in each). [Note 8 was chosen because it represents the most categories of a variable in the current study i.e. job title]. This represents a 1.29 or 29% ($e^{0.257}$ = 1.29) and 1.21 or 21% ($e^{0.188}$ = 1.21) times difference in GM concentrations, respectively. This suggests that study power was very good, more than adequate to detect a doubling of exposure levels. Reviewing the dermal results, a majority of the GM values were less than the detection

limit. As a result, many of the one-way ANOVAs were found to be not statistically significant. With respect to the one-way ANOVAs for the urine contamination levels, some categories had relatively small numbers (<10) and/or the difference in contamination levels were less than 21% resulting in non-statistically significant findings.

Another way to consider whether the study design, in particular the sensitivity of the laboratory analyses, was sufficient to identify differences in the dependent variable is to compare the lowest concentration values and the referenced exposure thresholds. The dermal limit of detection was 0.356 ng/wipe and a proposed dermal occupational exposure limit is 3360 ng/wipe, almost a 10,000X difference. For urine samples, the detection limit for CP was 0.052 ng/mL or 91 ng/24 hrs (assuming an average urinary volume of 1.75 L per day) and a proposed limit is 1000 ng/day. This represents more than a 10X difference. Based on these calculations, I believe that the study design was appropriate to detect meaningful differences in the ln of the exposure concentrations.

Lastly, there exists the possibility of misclassification of measurements of contamination levels and responses to questionnaires. Any analytical measurement error in drug contamination levels is expected to be non-differential and therefore bias towards the null. With respect to self-reported responses to questionnaires, depending on the response, the bias either could be in either direction, though non-differential misclassification and bias to the null are most likely.

6.7 Future direction/work

As mentioned earlier, novel findings of the current study include the fact that measureable levels of drug contamination were found on surfaces throughout the hospital medication system and that more job categories than previously believed face an exposure potential. Despite these novel findings, questions remain surrounding the matter of surface contamination and

occupational exposure to antineoplastic drugs. These outstanding questions should be addressed in future work as outlined below.

6.7.1 Surface cleaning

In Chapter 3 I found that a majority of participants were unaware if a potentially-contaminated surface/object was cleaned, making it difficult to determine the impact of surface cleaning. However, even where cleaning was reported, measurable levels of drug residual were still found. This suggests that cleaning of surfaces may not be effective, and raises the possibility that accumulation of contamination may occur, as suggested by Touzin et al.(86) This is noteworthy as antineoplastic drugs have been found to be environmentally stable for up to two months.(117) Therefore, in order to ensure the efficacy of surface cleaning, we agree with others that the type of cleaning agent used(87) and the time of action of the cleaning agent(86) need to be examined.

6.7.2 Evaluate health risks

This was an occupational exposure study whereby we discovered novel information that a number of healthcare job categories, besides pharmacy and nursing personnel, have measurable levels of drug contamination on their hands as well as in their urine. The next logical step would be to ascertain if these newly-identified job cohorts face health risks due to this exposure. This includes damage to genetic material (17)(118), reproductive effects (including spontaneous abortions, still births and ectopic pregnancies) as well as cancer.(5) Information about chronic health risks, especially cancer, in conjunction with the exposure levels reported in the current study can then lead to the establishment of an updated quantitative risk assessment for CP, the most recent of which was in 2002.(110)

6.7.3 Determine mechanism of spread of contamination

Although we identified that drug residual was found on surfaces situated throughout the hospital medication system, we are unable to explain the mechanism of spread. By understanding the mechanism, one can then apply specific control measures to prevent dissemination of antineoplastic drugs. One method to track the spread of contamination is to use a tracer (119)(85) and, concurrently, systematically analyze tasks/processes where contamination may occur (i.e. critical control points) as suggested by Bonan et al.(120)

6.7.4 Identify determinants for each stage/job category separately

Although we have identified determinants associated with contamination or exposure throughout the hospital medication system, it may be worthwhile to break down this process and ascertain the determinants by stage of the medication system and/or healthcare job categories at risk of exposure. This is suggested for two reasons: a) when stratified by job title, some of the categories had relatively small sample sizes ($N < 10$) and b) different processes take place in each stage and therefore certain determinants may only be applicable to specific tasks. By examining each stage separately, it may provide some additional insight into the matter of environmental contamination and/or occupational exposure.

6.7.5 Association between environmental monitoring and biological monitoring

There was a time lag between the collection of surface wipes and the collection of personal samples (dermal wipe and urine samples). This may be one reason we did not find an association between the two matrices. It is therefore recommended to collect the environmental samples concurrently with the personal samples as the former can demonstrate how, where and

possibly when contamination occurred while the biological samples indicates if exposure occurred.(66)

Table 6-1 Risk assessment for bladder cancer based on Sessink et al.

	Variable	Calculation	Value
A	Lowest dose with significant increase in tumors		1.25 (mg/kg)/day
B	Bladder tumour incidence		14.3%
C	Exposure period (Median survival period – age when started x days/week exposed)	(646-100) x 5/7	390 days
D	Total cumulative dose *(A x C)*	1.25 x 390	487.5 mg/kg
E	Cancer risk *(B / C)*	0.143/487.5	$293x10^{-6}$ per mg CP
F	Average cumulative dose from urine chapter (average dose in mg x 200 days/yr x 40 yrs)*	$2.32x10^{-4}$ x 200 x 40	1.86 mg
G	Lifetime cancer risk *(1/average mass x E x F)*	1/70 x $293x10^{-6}$ x 1.86	7.78 per million
H	Population at risk of exposure**		6,893,979
I	Excess cases of cancer in this population *(G x H)*	$7.78x10^{-6}$ x 6,893,979	54

** time periods used are those utilized by the author*
*** based on number of US healthcare workers estimated by McDiarmid and Condon*(70)*; note that not all job categories found to be at risk of exposure in the current study are included in the equation*

Table 6-2 Risk assessment for bladder cancer based on Sargent et al.

	Variable	Calculation	Value
A	Cancer slope factor		0.57 (mg/kg)/day
B	Lifetime average daily dose (average does in mg/70kg)	$2.32x10^{-4}$ / 70	$3.31x10^{-6}$ (mg/kg)/day
C	Population at risk of exposure[±]		6,893,979
D	Lifetime cancer risk *(A x B)*	0.57 x 3.31x10-*6*	1.89 per million
E	Excess cases of cancers in this population *(C x D)*	$1.89x10^{-6}$ x 6,893,979	13

[±]*based on number of US healthcare workers estimated by McDiarmid and Condon*(70)*; note that not all job categories found to be at risk of exposure in the current study are included in the equation*

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APPENDICES

APPENDIX A PASSIVE OBSERVATIONAL CHECKLIST

PASSIVE OBSERVATIONAL CHECKLIST

FACILITY:	**OBSERVED BY:**
ROOM/DEPT:	**DATE (mm/dd/yy):**
TIME OF OBSERVATION (from – to):	

Contacted Surfaces	**Workers at Risk of Exposure**				
Surface/object ↓	**Worker #1**	**Worker #2**	**Worker #3**	**Worker #4**	**Worker #5**
Job Title → →					

Page ____ of ____

Notes:

Page ____ of ____

APPENDIX B DRUG HANDLING AND CLEANING QUESTIONS

Studying healthcare workers' exposure to antineoplastic drugs

A collaborative study involving UBC, Fraser Health, OHSAH, PHC and VCH

Drug Handling and Cleaning Questions

(To be asked immediately before collection of surface/object wipe sample)

Site:	Date:
Sample collected by:	Sample ID:
Sample Description – be as specific as possible (type of surface/object, specific location, colour, room number, etc.):	
Surface area of sample*:	Time of sample collection:

** draw schematic on back of page if necessary*

The following section is to be completed by interviewing a healthcare worker:

Job title:	HCW's department:

Please answer the following questions based on processes related to cyclophosphamide (CP)

To your knowledge, was CP handled, prepared and/or administered prior to collection of the wipe sample? □ Yes □ No □ Don't know	If "yes", do you know approximately how much CP was handled, prepared and/or administered prior to collection of wipe sample? *(check <u>all</u> that apply)* □ Number of shipped boxes: _____ □ Number of vials: _____ □ Number of waste containers: ____ □ Number of tablets: _____ □ Number of syringes: _____ □ Number of IV bags: _____ □ Don't know/Don't recall
To you knowledge, was the surface/object cleaned prior to collection of wipe sample? □ Yes □ No □ Don't know	If "yes", can you provide the approximate time of the last cleaning? □ Don't know □ Time when last cleaned: _____ □ Time difference (btw last clean and collection of sample): _____
To your knowledge, was there a spill/leak of CP earlier in the day on this surface? *(check one response only)* □ Yes □ No □ Don't know	

For Research Team Only. *If information could be not be obtained for the wipe sample, please indicate the reason(s):*

Sample ID: _____ Page 1 of 1

APPENDIX C LETTER OF INITIAL CONTACT (FOR RAMDOMLY SELECTED PARTICIPANTS)

THE UNIVERSITY OF BRITISH COLUMBIA

School of Environmental Health
Room 372 – 2206 East Mall.
Vancouver, BC V6T 1Z3
tel: 604 822 2041
email: kay.teschke@ubc.ca

[date]

[name]
[address]
[city, province, postal code]

Dear M.

Re: Healthcare workers' and antineoplastic drugs

We are inviting you to participate in a study about occupational exposure to antineoplastic drugs. We are trying to understand the degree of spread of drug contamination as well as the variety of healthcare job categories that are potentially exposed. We hope to determine the various factors which influence exposure to these drugs and, subsequently, strengthen control measures to reduce occupational exposure.

The study is a joint venture of Vancouver Coastal Health, Providence Health Care, Fraser Health, and the University of British Columbia. This study has also received the support of union groups (BCNU, HEU and HSA) as well as the Occupational Health and Safety Agency for Healthcare in BC (OHSAH).

How were you selected for this study?

You were selected because your job title is considered to be potentially exposed based on initial observations of the process flow of the drugs throughout the hospital as well as through discussions with key contacts at your site.

What will you need to do to participate?

To conduct this research, we will ask you to
1. provide two hand wipe samples,
2. provide two urine samples, and
3. complete a questionnaire.

We expect the total time involved to be approximately 60 minutes.

Is your participation voluntary and how will your consent to participate be requested?

Your participation in this study is entirely voluntary. This is described in more detail in the attached consent form. Our study coordinator, Chun-Yip Hon, will telephone you in the next week or so. He will ask if you are willing to participate and, if you are, a date will be arranged for sample collection.

If you have any questions about this study, or if you do not wish to be contacted, please feel free to contact me at 604.822.2401, kay.teschke@ubc.ca, or via the address on this letterhead.

Yours sincerely,

Kay Teschke, PhD
Professor, University of British Columbia

APPENDIX D CONSENT TO CONTACT FORM (FOR PASSIVELY RECRUITED PARTICIPANTS)

THE UNIVERSITY OF BRITISH COLUMBIA

School of Environmental Health
University of British Columbia
Room 372 – 2206 East Mall
Vancouver, BC V6T 1Z3
Tel: 604 822 9595

CONSENT TO CONTACT re: Healthcare Employees and Antineoplastic Drugs

We would like to be able to contact you, so we can invite you to participate in a study about occupational exposure to chemotherapy drugs. We are trying to understand the degree of spread of drug contamination as well as the variety of healthcare job categories that are potentially exposed. We hope to determine factors which influence exposure to these drugs and, subsequently, strengthen control measures to reduce exposures.

The study is a joint venture of Vancouver Coastal Health, Providence Health Care, Fraser Health, and the University of British Columbia. It has received the support of union groups as well as the Occupational Health and Safety Agency for Healthcare in BC (OHSAH).

We would like your permission for a member of our UBC research team to contact you about this study, to answer any questions you may have, and to invite your participation. Any contact information you provide below will be used exclusively to contact you for this project, only in the manner you provide.

- You do not need to complete this form if you do not wish to be contacted.
- If you agree to be contacted, you may change your mind at any time without affecting current or future employment or privileges with Fraser Health.

Kay Teschke
Professor and Principal Investigator
kay.teschke@ubc.ca
604 822 2041 . . . please feel free to contact me with questions at any time.

CONSENT TO CONTACT ABOUT PARTICIPATION IN RESEARCH

Are you willing to be contacted? ☐ YES

If yes, please provide information below on whichever contact methods are acceptable to you:

Mailing address: _____

Phone number: _____

Email address: _____

By signing I confirm that I have read and understand this consent-to-contact form. I also understand that I can refuse to be contacted by research personnel and this will not affect my employment in any way.

I hereby give consent for the UBC research team for this project to contact me for the purposes indicated above, within the 24-month period from the date of signing this consent.

Name (*please print*): _____

Signature: _____ Date: _____

Please fax completed form to 604 822 9588

APPENDIX E CONSENT FORM

THE UNIVERSITY OF BRITISH COLUMBIA

School of Environmental Health
University of British Columbia
Room 372 – 2206 East Mall
Vancouver, BC V6T 1Z3
Tel: 604.822.9595

Consent Form

Healthcare workers and antineoplastic drugs: Identifying the determinants of occupational exposure and current challenges to reducing exposure

Principal Investigator:
Dr. Kay Teschke, University of British Columbia 604 822 2041 kay.teschke@ubc.ca

Study Coordinator:
Chun-Yip Hon, University of British Columbia @interchange.ubc.ca

Co-Investigators:
Dr. Winnie Chu, University of British Columbia Prescillia Chua, Fraser Health
Robin Ensom, Vancouver Coastal Health/Providence Health
George Astrakianakis, Occupational Health and Safety Agency for Healthcare in BC

What is the purpose of this study?

We are inviting you to participate in this study because your job category may involve occupational exposure to antineoplastic drugs, which are cytotoxic agents. We are studying up to 150 healthcare workers in the Metro Vancouver area to better understand the degree of spread of drug contamination within a hospital as well as the exposure levels of those job categories that are at risk of skin contact with the drugs. The goal is to determine the various factors which influence exposure to antineoplastic drugs and, ultimately, strengthen control measures for all hospital staff.

Who is conducting this study?

The principal investigator in this study is a researcher from the University of British Columbia affiliated with the School of Environmental Health. The WorkSafeBC Research Secretariat is funding the study. They provide funding for studies that aim to improve health and safety in BC workplaces.

What does the study involve?

This study will take place at three health authorities within the BC Lower Mainland: Vancouver Coastal Health, Providence Health Care, and Fraser Health. Two hospitals each from Vancouver Coastal Health and Fraser Health and one facility within Providence Health Care will be involved.

For managers/supervisors of those departments where antineoplastic drugs are prepared, handled and/or administered, you will be interviewed about current procedures, staffing levels and existing health and safety policies related to antineoplastic drugs.

For all healthcare workers, your daily routine will be observed to determine if your job is potentially at risk of exposure to antineoplastics during their process flow within the hospital. That is, we want to assess if you have contact with antineoplastics directly through handling or indirectly by touching surfaces that have been in contact with antineoplastics or their containers.

You will be asked to provide two to four hand wipe samples, which involves wiping the top and bottom of both of your hands with a moistened wipe. The wipes will be analyzed for the amount of antineoplastics present. It will take approximately 5 minutes to collect one hand wipe sample.

You will also be asked to provide two to four urine samples. You will be given clean plastic bottles and written instructions for collecting the samples. Urine samples will be collected over a 24-hour period and analyzed for the amount of antineoplastics present.

Lastly, you will be asked to complete a questionnaire. The questionnaire will inquire about your experience, knowledge about antineoplastic drugs and use of personal protective equipment. The questionnaire will also ask about workplace environmental and organizational factors. The questionnaire will take approximately 20 minutes to complete. You do not have to answer any questions that you do not feel comfortable answering.

What are the possible harms and side effects of participating?

- You may experience feelings of nervousness and anxiety when being observed by the research team member regarding the surfaces/objects that you contact. Note that the findings during the observations will not be used to evaluate job performance.
- If you are asked to provide a hand wipe sample, your hands will be exposed to a very dilute solvent. Your hands may become red immediately after because of the friction from the wipe. You may experience dryness or irritation of the hands due to exposure to the mild solvent. Hand washing and moisturizing immediately after the wipe sample will minimize this.

What are the benefits of participating in this study?

There may be no direct benefits to participating in this study. However, if you do decide to participate, you will gain insight into whether you are at exposed to antineoplastic drugs.

Is my participation voluntary?

Yes. You may choose not to be in this study and you may choose not to participate in any part of the study. You may decline to participate or withdraw from the study at any time, without penalty or loss of benefits to which you are otherwise entitled.

What will the study cost me?

There is no cost to you if you agree to participate in the study. For your time and any inconvenience, you will receive a cash honorarium after completing each of the three tasks – providing a hand wipe sample ($10/sample), submitting a urine sample ($15/sample), and completing the questionnaire ($25/questionnaire).

Confidentiality

Your confidentiality will be respected. No information that discloses your identity will be released or published without your specific consent to the disclosure. However, research records and medical records identifying you may be inspected in the presence of the Investigator or her designate by representatives of WorkSafeBC and the UBC Research Ethics Board for the purpose of monitoring the research. However, no records which identify you by name or initials will be allowed to leave the Investigators' offices.

Who will have access to the data?

All the observations, measurements and questionnaires will be coded with a number, not your name. We will keep a record of the number we assign to you, but will not release that record to anyone else. Only members of the research team will have access to information about you. All published reports will include only aggregate data and will not include your name or other identifying information.

Where can you get more information about the study?

If you have any questions or would like further information about this study before, during or after participation, **you can contact the Project Coordinator at 604** . You may also call or email one of the people listed on the front page of this consent form. You may also want to visit the study's website at www.cher.ubc.ca/antineoplasticdrugs/.

If you have any concerns about your rights as a research subject and/or your experiences while participating in this study, contact the Research Subject Information Line in the University of British Columbia Office of Research Services at 604 822 8598.

Consent to Participate:

- ☐ I have read and understood this subject information and consent form.
- ☐ I have had sufficient time to consider the information provided.
- ☐ I have had the opportunity to ask questions and have had satisfactory responses to my questions.
- ☐ I understand that all of the information collected will be kept confidential and that the results will only be used for scientific objectives.
- ☐ I do not waive my legal rights by signing this consent form.
- ☐ I understand that my participation in this study is voluntary and that I am completely free to refuse to participate or to withdraw from this study at any time.
- ☐ I have read this form and I freely consent to participate in this study.
- ☐ *I would like to be informed of the results of this study. (Please let us know if you move.)*

Printed name of subject	Signature	Date
Printed name of witness	Signature	Date
Printed name of principal investigator/designated representative	Signature	Date

Copies to: 1) Participant
2) AND study file

APPENDIX F ACTIVITY-RELATED QUESTIONS

Studying healthcare workers' exposure to antineoplastic drugs

A collaborative study involving UBC, Fraser Health, OHSAH, PHC and VCH

Activity-Related Questions

(To be asked immediately after collecting dermal wipe and before 1st urine sample)

We would like to ask you questions about your exposure to cyclophosphamide (CP) over various time periods. Two common trade names for cyclophosphamide are CYTOXAN® and PROCYTOX®. We will ask you questions related to your tasks and your potential exposure: a) within the past 7 days, b) within the past 24 hours and c) on your current shift. Please make every effort to answer the questions for the time period indicated because these are critical for comparing your dermal and urine results.

Job Title:	**Your shift time today:**
Department:	**Time of sample collection:**

Task	*Weekly Exposure Frequency* **within the past 7 days?**		*To compare with urine results* **within the past 24 hours?**		*To compare with dermal wipe results* **on this shift only?**	
Did you mix / compound cyclophosphamide**	☐ Yes ☐ No ☐ Don't know	If "Yes", # of times:	☐ Yes ☐ No ☐ Don't know	If "Yes", # of times:	☐ Yes ☐ No ☐ Don't know	If "Yes", # of times:
Did you administer cyclophosphamide to a patient**	☐ Yes ☐ No ☐ Don't know	If "Yes", # of times:	☐ Yes ☐ No ☐ Don't know	If "Yes", # of times:	☐ Yes ☐ No ☐ Don't know	If "Yes", # of times:
Did you disconnect an IV line containing CP**	☐ Yes ☐ No ☐ Don't know	If "Yes", # of times:	☐ Yes ☐ No ☐ Don't know	If "Yes", # of times:	☐ Yes ☐ No ☐ Don't know	If "Yes", # of times:
Did you provide physical care for a patient on CP, e.g. washing, changing dressing, mouth care**	☐ Yes ☐ No ☐ Don't know	If "Yes", # of times:	☐ Yes ☐ No ☐ Don't know	If "Yes", # of times:	☐ Yes ☐ No ☐ Don't know	If "Yes", # of times:
Did you dispose of body fluids from a patient on CP, e.g. urine, soiled diaper**	☐ Yes ☐ No ☐ Don't know	If "Yes", # of times:	☐ Yes ☐ No ☐ Don't know	If "Yes", # of times:	☐ Yes ☐ No ☐ Don't know	If "Yes", # of times:

***If respondent answered, "yes" to any of the five tasks indicated above, please be reminded to ask questions found on page 4*

Subject ID: _____

Studying healthcare workers' exposure to antineoplastic drugs

A collaborative study involving UBC, Fraser Health, OHSAH, PHC and VCH

Task	*Weekly Exposure Frequency* **within the past 7 days?**		*To compare with urine results* **within the past 24 hours?**		*To compare with dermal wipe results* **on this shift only?**	
Did you physically handle a container of CP e.g. transport/deliver, set up drug preparations, open shipments, check compounds, etc.	☐ Yes ☐ No ☐ Don't know	If "Yes", # of times:	☐ Yes ☐ No ☐ Don't know	If "Yes", # of times:	☐ Yes ☐ No ☐ Don't know	If "Yes", # of times:
Did you dispose of waste (IV bag or vial) containing CP	☐ Yes ☐ No ☐ Don't know	If "Yes", # of times:	☐ Yes ☐ No ☐ Don't know	If "Yes", # of times:	☐ Yes ☐ No ☐ Don't know	If "Yes", # of times:
Did you clean up a leak or spill containing CP	☐ Yes ☐ No ☐ Don't know	If "Yes", # of times:	☐ Yes ☐ No ☐ Don't know	If "Yes", # of times:	☐ Yes ☐ No ☐ Don't know	If "Yes", # of times:
Did you touch a surface/object which came into contact with a container/package of CP e.g. counter, tray, Ziploc, etc.	☐ Yes ☐ No ☐ Don't know	If "Yes", # of times:	☐ Yes ☐ No ☐ Don't know	If "Yes", # of times:	☐ Yes ☐ No ☐ Don't know	If "Yes", # of times:
Did you consume food or drink in an area where CP is mixed, handled or administered	☐ Yes ☐ No ☐ Don't know	If "Yes", # of times:	☐ Yes ☐ No ☐ Don't know	If "Yes", # of times:	☐ Yes ☐ No ☐ Don't know	If "Yes", # of times:
Do you recall in engaging in any other activities/tasks that may have resulted in exposure to cyclophosphamide within the past 7 days? ☐ No ☐ Yes If "yes", please list in row(s) below:						
Other task (specify):	☐ Yes ☐ No ☐ Don't know	If "Yes", # of times:	☐ Yes ☐ No ☐ Don't know	If "Yes", # of times:	☐ Yes ☐ No ☐ Don't know	If "Yes", # of times:

Subject ID: _____

If you answered "yes" to any of the questions above, please indicate the amount that you were exposed to

Dosage Form	*Weekly Exposure Amount* **Within past 7 days**		*To compare with urine results* **Within past 24 hours**		*To compare with dermal wipe results* **This shift only**	
Total dose of cyclophosphamide (in milligrams)	☐ Don't know / don't recall*	Dose (in milligrams):	☐ Don't know / don't recall*	Dose (in milligrams):	☐ Don't know / don't recall*	Dose (in milligrams):
* If you don't know or don't recall the exact dose, please provide estimates of the following *(check all that apply)*:						
Number of CP vials	☐ N/A ☐ Don't know	# of CP vials:	☐ N/A ☐ Don't know	# of CP vials:	☐ N/A ☐ Don't know	# of CP vials:
Number of IV bags with CP	☐ N/A ☐ Don't know	# IV bags with CP:	☐ N/A ☐ Don't know	# IV bags with CP:	☐ N/A ☐ Don't know	# IV bags with CP:
Number of CP tablets	☐ N/A ☐ Don't know	# CP tablets:	☐ N/A ☐ Don't know	# CP tablets:	☐ N/A ☐ Don't know	# CP tablets:
Number of syringes with CP	☐ N/A ☐ Don't know	# syringes with CP:	☐ N/A ☐ Don't know	# syringes with CP:	☐ N/A ☐ Don't know	# syringes with CP:

The following questions all relate to practices prior to collecting the hand wipe sample

Number of gloves worn <u>immediately prior</u> to the collection of the hand wipe sample?

☐ Single (one pair) ☐ Double (two pairs) ☐ None

If glove(s) were worn prior to collecting hand wipe sample, indicate type(s) of glove material *(check all that apply)*

☐ Latex *Inner* Outer* ☐ Nitrile *Inner* Outer* ☐ Chemotherapy-specific *Inner* Outer* ☐ Other(specify): _____ *Inner* Outer* ☐ Don't know

When was the **last time** you washed your hands (by any method)?

☐ Less than 10 minutes ago ☐ 10 to 30 minutes ago ☐ 31 to 60 minutes ago ☐ More than 60 minutes ago

With respect to your **most recent** hand wash, how did you wash your hands?

☐ Water only ☐ Soap and water ☐ Alcohol-based hand gel ☐ Other: _____ ☐ Don't know/don't recall

How many times **on this current shift** did you wash your hands (up until now)?

☐ 1 to 2 ☐ 3 to 4 ☐ 5 or more ☐ Don't know/don't recall

** indicate whether the glove type was the inner or outer glove if double gloves were worn*

Subject ID: _____

If subject responded "yes" to any of the tasks found on page 1, please ask the following questions about patient load:

Approximately how many patients on cytotoxic drugs, not just cyclophosphamide, were you directly involved with in the past 7 days (includes mixing cytotoxic drugs, checking drug preparations, administering cytotoxic drugs, disconnecting an IV line, providing physical care, and handling body fluids)?

□ # of patients receiving cytotoxic drugs: □ Don't know/don't recall

Approximately how many patients on a cyclophosphamide regimen were you directly involved with in the past 7 days (includes preparing CP, checking drug preparations, administering CP, disconnecting an IV line containing CP, providing physical care, and handling body fluids)?

□ # of patients receiving CP: □ Don't know/don't recall

Indicate the number and type of patient(s) you were directly involved with in the past 7 days ((includes preparing chemotherapy, administering chemotherapy, disconnecting an IV line, providing physical, and handling body fluids)? Place the estimate number beside the type of disease/treatment. *(if none, indicate as zero or '0')*

□ Breast cancer: _____ □ Leukemia: _____

□ Lung cancer: _____ □ Lymphoma: _____

□ Multiple myeloma: _____ □ Stem cell transplant: _____

□ Lymphoproliferative disease: _____ □ Myelodysplastic syndrome (MDS): ____

□ Renal transplant: ____ □ Lupus nephritis: ____

□ Other (specify): _____ #_____ □ Other (specify): _____ #_____

□ Don't know/don't recall

APPENDIX G INTRODUCTION LETTER SENT WITH QUESTIONNAIRES

THE UNIVERSITY OF BRITISH COLUMBIA

School of Environmental Health
Room 372 – 2206 East Mall
Vancouver, BC V6T 1Z3
604 822 2041
kay.teschke@ubc.ca

February 9, 2012

Name, Title
Site/Department
Address
City, Prov

Dear {},

Re: Studying healthcare workers' exposure to antineoplastic drugs

Thank you so much for agreeing to participate in our study. The goal is to determine what factors influence occupational exposure to antineoplastic drugs and, subsequently, strengthen control measures to reduce exposure.

We are enclosing the first part of the study: a **questionnaire**. We would be most grateful if you would **complete it within three weeks** of receiving it. Some information about completing and returning it is listed below.

COMPLETING THE QUESTIONNAIRE

- Please use a pen to fill it out.
- Where you are asked to print an answer, please print as clearly as possible.
- Please ensure you have completed all 8 pages (single-sided) of the questionnaire.
- You do not have to answer any questions that you do not feel comfortable answering.

RETURNING THE COMPLETED QUESTIONNAIRE

- Please place all 8 pages into the postage-paid return envelope provided and put it in the mail.
- Once we receive your completed questionnaire, an **honorarium cheque of $25** will be sent to your mailing address above. *Please let us know if you want the cheque sent to an alternate address.*

If you have questions about the questionnaire or about the study itself, please contact the Project Coordinator, Chun-Yip Hon, at 604- or via email at @interchange.ubc.ca.

Thanks again for your help with this important study.

Kay Teschke, PhD
Professor

APPENDIX H SELF-ADMINISTERED QUESTIONNAIRE

CYTOTOXIC (ANTINEOPLASTIC) DRUG EXPOSURE QUESTIONNAIRE

Cytotoxic drugs are used for treating cancer in patients. Some of these drugs do not distinguish between normal and cancerous cells. As a result, it is important to determine whether healthcare workers are exposed to these drugs in areas where they are prepared and administered. We hope to determine factors which increase or reduce staff exposure to cytotoxic drugs in the workplace. The results of this study will be used to identify exposure risk factors within a hospital (i.e. not individual risks) in order to strengthen safety measures, where required. On behalf of the research team, thank you for agreeing to answer this confidential questionnaire. This questionnaire should take approximately 30 minutes to complete.

A . Information about You and Your Work

1. Hospital *(check one only)*:
   - ☐ Burnaby General
   - ☐ Lions Gate
   - ☐ Royal Columbian
   - ☐ St. Paul's
   - ☐ Vancouver General
2. Health Authority *(check one only)*:
   - ☐ Fraser Health
   - ☐ Providence Health Care
   - ☐ Vancouver Coastal Health
3. Your department *(where you work 75% of your time)*: _____
4. Your current job title: _____
5. I have worked in this job for: _ _ years _ _ months.
6. Overall, I have been in healthcare for: _ _ years _ _ months.
7. My gender is *(check one only)*
   - ☐ Female
   - ☐ Male
8. My age is *(check one only)*
   - ☐ < 20
   - ☐ 20-29
   - ☐ 30-39
   - ☐ 40-49
   - ☐ 50-59
   - ☐ 60+

Subject ID# _____

B. Your Work with Cytotoxic Drugs *(Check only one response for each question.)*

9. As part of your normal job duties, do you directly handle, prepare and/or administer cytotoxic drugs? For the purposes of this questionnaire, "directly handle" includes transporting the drugs and opening packages containing cytotoxic drugs.

- ☐ Yes *(answer next three questions; a to c)*
- ☐ No *(go to question #10)*

a. How long have you been handling, preparing and/or administering cytotoxic drugs?

__ years __ months

b. What percentage of time do you spend handling, preparing and/or administering cytotoxic drugs?

- ☐ Less than 25%
- ☐ 25 to 50%
- ☐ 51 to 75%
- ☐ More than 75%

c. How often do you wear gloves when directly handling, preparing and/or administering cytotoxic drugs?

- ☐ Never
- ☐ Some of the time
- ☐ Most of the time
- ☐ All the time

10. Do you regularly work (i.e. daily) in an area where cytotoxic drugs are handled, prepared and/or administered?

- ☐ Yes
- ☐ No
- ☐ Don't know

11. How often do you wear gloves in an area where cytotoxic drugs have been handled, prepared and/or administered?

- ☐ Never
- ☐ Some of the time
- ☐ Most of the time
- ☐ All the time
- ☐ Don't know/Don't recall

C. Information about Risks and Control Measures *(Check only one response for each question.)*

12. Cytotoxic drugs can enter the body through skin contact with drug-contaminated surfaces.

- ☐ True
- ☐ False
- ☐ Don't know

13. One of the possible health effects due to workplace exposure to cytotoxic drugs is cancer.

- ☐ True
- ☐ False
- ☐ Don't know

14. Surfaces in a room where a patient was given cytotoxic drugs may be potentially contaminated with residual drug.

- ☐ True
- ☐ False
- ☐ Don't know

15. Is there a designated preparation area (i.e. isolation room) for pharmacy to mix cytotoxic drugs in your hospital?

- ☐ Yes
- ☐ No
- ☐ Don't know

16. Is there a separate method for disposing of cytotoxic drugs and/or those items contaminated with cytotoxic drugs in your hospital?

- ☐ Yes
- ☐ No
- ☐ Don't know

17. Is there a safe handling policy/procedure for cytotoxic drugs at your hospital?

- ☐ Yes
- ☐ No
- ☐ Don't know

18. Is there a cytotoxic drug spill clean up policy/procedure at your hospital?

- ☐ Yes
- ☐ No
- ☐ Don't know

D. Your Thoughts about Exposure and Risk

Please circle the number that best corresponds to your response *(circle one only)*.

	Strongly Agree	Agree	Disagree	Strongly Disagree	Don't Know
19. My risk of exposure to cytotoxic drugs in the hospital is very low.	1	2	3	4	0
20. I am afraid of working with or near cytotoxic drugs.	1	2	3	4	0
21. Safety measures currently in place are suitable in reducing cytotoxic drug contamination.	1	2	3	4	0
22. Workers around me are handling cytotoxic drugs safely.	1	2	3	4	0
23. I am confident that I can handle all situations where there is a potential for cytotoxic drug exposure, including spills, leaks, contaminated urine, and patients' vomit.	1	2	3	4	0

E. Organizational Support and Communication in Your Work Setting

Please circle the number that best corresponds to your response *(circle one only)*.

	Strongly Agree	Agree	Disagree	Strongly Disagree	Don't Know
24. The protection of workers from exposure to hazardous agents is a high priority in my department.	1	2	3	4	0
25. My immediate supervisor/manager shows concern for my safety on the job.	1	2	3	4	0
26. In my department, employees are encouraged to become involved in workplace health and safety matters (e.g. safety meetings, reporting incidents)	1	2	3	4	0
27. There are good relations amongst all staff (both management and workers) in my department.	1	2	3	4	0

E. Organizational Support and Communication in Your Work Setting (cont'd)

	Strongly Agree	Agree	Disagree	Strongly Disagree	Don't Know
28. Management and workers in my department support one another.	1	2	3	4	0
29. In my department, there is open communication between management and workers.	1	2	3	4	0

F. Training about Cytotoxic Drugs

The following questions ask about the training that you have received with respect to workplace exposure to cytotoxic drugs and the specific topics that were covered.

30. How often do you receive training related to the workplace health and safety of cytotoxic drugs e.g. workplace exposure risks and ways to minimize the risk *(check one only)*?
    - ☐ At least every 6 months
    - ☐ Annually
    - ☐ Every few years
    - ☐ Never *(go to question #33)*

31. If you have previously received training related to the workplace health and safety of cytotoxic drugs, did you learn about *(answer all four questions: a to d)*:
    a. Potential health effects if exposed to cytotoxic drugs *(check one only)*?
       - ☐ Yes
       - ☐ No
       - ☐ Don't know

    b. The type and variety surfaces or objects which may be contaminated with cytotoxic drugs or their residue *(check one only)*?
       - ☐ Yes
       - ☐ No
       - ☐ Don't know

    c. Safety measures to use in order to reduce potential workplace exposure *(check one only)*?
       - ☐ Yes
       - ☐ No
       - ☐ Don't know

F. Training about Cytotoxic Drugs (cont'd)

d. Personal protective equipment (e.g. gloves, gown, eye protection and/or respirator) to be worn when in potential contact with cytotoxic drugs *(check one only)*?

- ☐ Yes
- ☐ No
- ☐ Don't know

32. The training provided on cytotoxic drugs is adequate to protect myself. *(check one only)*

- ☐ Strongly Agree
- ☐ Agree
- ☐ Disagree
- ☐ Strongly Disagree
- ☐ Don't know

G. Overall Stress of Your Job

The following questions ask about your day-to-day responsibilities. Please circle the number that best corresponds to your response *(circle one only)*.

	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
33. My job requires me to work very fast.	1	2	3	4	5
34. In this job, I am asked to do an excessive amount of work.	1	2	3	4	5
35. In this job, I have enough time to get the job done.	1	2	3	4	5
36. In this job, I am free from conflicting demands (e.g. interruptions).	1	2	3	4	5

H. Handwashing and Personal Protective Equipment

The following questions ask about your perceptions of personal protective equipment (i.e. gloves, gowns, eye protection and/or respirator) and your usual handwashing practices.

Please circle the number that best corresponds to your response *(circle one only)*.

	Strongly Agree	Agree	Disagree	Strongly Disagree	Don't Know
37. I feel that the personal protective equipment required to protect me from cytotoxic drugs is readily available for my use.	1	2	3	4	0

Subject ID# _____

H. Handwashing and Personal Protective Equipment (cont'd)

	Strongly Agree	Agree	Disagree	Strongly Disagree	Don't Know
38. In general, I feel that I am able to use the required personal protective equipment properly.	1	2	3	4	0

39. If you use gloves, do you wash your hands immediately after removing your gloves *(check one only)*?

- ☐ Never
- ☐ Some of the time
- ☐ Most of the time
- ☐ All the time
- ☐ Not applicable

40. Do you wash your hands immediately after being in an area where cytotoxic drugs were handled, prepared and/or administered *(check one only)*?

- ☐ Never
- ☐ Some of the time
- ☐ Most of the time
- ☐ All the time
- ☐ Don't know

41. On average, what is the length you time you spend washing your hands (each time) *(check one only)*?

- ☐ 5 seconds or less
- ☐ 6 to 10 seconds
- ☐ 11 to 15 seconds
- ☐ More than 15 seconds

42. What do you usually use to wash your hands while at work *(check one only)*?

- ☐ Water only
- ☐ Soap and water
- ☐ Alcohol hand gel/foam
- ☐ Other (specify): _____

I. Previous Exposure(s)

43. Have you ever had *direct, unintended* contact with cytotoxic drugs while at work *(check one only)*?

- ☐ Yes (provide details below in box below)
- ☐ No *(go to question #44)*
- ☐ Don't know *(go to question #44)*

If "yes", please describe the circumstances:

44. If you have any additional comments related to cytotoxic (antineoplastic) drug exposure in the workplace, please enter into box below:

THANK YOU FOR TAKING THE TIME TO COMPLETE THE QUESTIONNAIRE!

Please return the completed questionnaire (all 8 pages) using the pre-paid envelope provided.

Once we have received your questionnaire, we will send you the honorarium cheque of $25 to the address we used to send you the survey. *Please let us know if you want the cheque sent to an alternate address.*

Subject ID# _____

APPENDIX I URINARY CONTAMINATION LEVELS STRATIFIED BY REPORTED CONTACT METHODS DURING WORK SHIFT: SUMMARY STATISTICS AND ONE-WAY ANOVA RESULTS

Method of contact	Time	Response	N	AM (nmol/L)	Max (nmol/L)	GM (nmol/L)	GSD
Contact with CP by any means…	past 24 hrs	Yes	81	20.79	839.14	3.83	3.73
		No/DK	142	15.44	565.29	4.36	3.54
	on shift	Yes	64	20.10	839.14	3.74	3.47
		No/DK	159	16.29	565.29	4.34	3.66
Mix CP…	past 24 hrs	Yes	10	9.90	32.32	6.27	2.74
		No/DK	213	17.74	839.14	4.08	3.64
	on shift	Yes	4	11.85	22.56	9.20	2.38
		No/DK	219	17.49	839.14	4.10	3.61
Administer CP…	past 24 hrs	Yes	17	20.48	298.87	3.34	3.89
		No/DK	206	17.13	839.14	4.24	3.59
	on shift	Yes	12	3.23	5.10	2.81	1.90
		No/DK	211	18.19	839.14	4.25	3.69
Disconnect IV line containing CP…	past 24 hrs	Yes	14	24.09	298.87	3.33	4.47
		No/DK	209	16.94	839.14	4.22	3.56
	on shift	Yes	9	3.11	5.10	2.64	2.03
		No/DK	214	17.99	839.14	4.24	3.66
Provide physical care to a patient on CP…	past 24 hrs	Yes	5	62.43	298.87	6.72	9.74
		No/DK	218	16.35	839.14	4.11	3.52
	on shift	Yes	3	4.21	5.10	4.16	1.21
		No/DK	220	17.56	839.14	4.16	3.63
Handle a container of CP…	past 24 hrs	Yes	49	12.32	298.87	3.70	3.55
		No/DK	174	18.81	839.14	4.30	3.63
	on shift	Yes	32	6.61	50.37	3.82	2.70
		No/DK	191	19.19	839.14	4.22	3.77
Dispose of waste containing CP…	past 24 hrs	Yes	27	15.97	298.87	3.86	3.52
		No/DK	196	17.58	839.14	4.20	3.63
	on shift	Yes	14	4.21	18.28	3.06	2.28
		No/DK	209	18.27	839.14	4.25	3.69
Touch a CP-contaminated surface…	past 24 hrs	Yes	66	22.73	839.14	3.77	3.84
		No/DK	157	15.14	565.29	4.33	3.51
	on shift	Yes	48	21.97	839.14	3.48	3.37
		No/DK	175	16.13	565.29	4.37	3.66
Consume food/water…	past 24 hrs	Yes	33	34.27	839.14	4.05	4.47
		No/DK	190	14.45	565.29	4.18	3.47
	on shift	Yes	27	39.49	839.14	4.17	4.57
		No/DK	196	14.34	565.29	4.16	3.49

APPENDIX J WRITTEN INSTRUCTIONS FOR COLLECTING URINE

Studying healthcare workers' exposure to antineoplastic drugs

Instructions for Collecting and Returning Urine Samples

REMINDER: The study requires that you provide urine over a 24-hour period. You previously provided one urine sample while at the hospital. Please collect all voided urine for the next 24-hours (since the initial urine sample).

IMPORTANT: Please make every effort to keep collected urine samples cold. This may include placing the cooler and its contents into a refrigerator while the rest of the samples are collected and/or placing ice packs in the cooler with the filled containers.

Collecting Urine Samples:

1. Before going to the washroom, take two new (clean) urine sample containers with you. Note that each container has 50 mL of a non-hazardous liquid (phosphate buffer) in it to ensure that the urine remains neutral i.e., neither basic or acidic.
2. Wash your hands prior to urinating. You do **not** need to clean the genitals prior to sample collection.
3. Unscrew lid of container and place lid upside down on a clean, flat surface to avoid contamination.
4. Collect the entire stream of urine (i.e. NOT mid-stream) into the container. Do not fill past the line of the container (this line is only visible when lid is removed and sits just below the threads for the lid). If necessary, use the second urine container to collect all the urine.
5. Once you have emptied your bladder, replace the lid securely after each collection. Do not over-tighten lid. If the outside of the container is wet, wipe the outside of the container after sample collection.
6. Use the permanent marker provided to write the **time and date** of urine collection **on the side and top** of the container. Example: 7:00 AM Oct 23.
7. Keep the container upright and place in the cooler with ice pack (provided) to keep samples cool. Try to keep ice gel liners in the same configuration as given. Where necessary, use one (1) instant ice pack to quickly reduce temperature of urine samples (please follow instructions on back of instant ice pack to activate). Note that only 6 containers can be placed upright in the cooler. If you use the final 3 containers, please secure lid and place the closed container into a Ziploc bag (provided) and then place on its side in the cooler.

8. If you have access to a refrigerator (either at work or home), place cooler and collected sample containers in the refrigerator.
9. If you are concerned about privacy, place cooler into a shopping bag (provided).
10. Dispose of the instant ice pack once it is no longer cool to the touch.
11. Repeat steps 1 to 7 until you have collected **all** voided urine for a complete 24-hour period.
12. For your final urine sample, try to collect it **at the same time as the first sample was taken** (on-site by research team member), *even if* you do not feel the urge to urinate. Empty your bladder completely. Use the permanent marker to write the **time and date on the side and top** of the container. Example: 7:00 AM Oct 24 (exactly 24 hours from the first urine sample).
13. Once you have collected urine for the 24-hour period, please proceed to "Returning urine samples" below.

Returning urine samples (after collecting 24-hour urine):

A. Place all urine sample containers (from the past 24-hours) into the cooler provided. Also, place any unused containers and the permanent marker into the cooler. Place ice packs into cooler to keep samples cool. Zip the cooler closed.

B. Make arrangements with the courier company, Novex, for pick up (weekdays only).

> **IMPORTANT**: In order for the cooler to arrive at the laboratory before it closes at 5:00 PM, you must call the courier company to arrange pick up **before 2:00 PM**. If you are unable to arrange a pick up before 2:00 PM, please place cooler and its contents in a refrigerator and make delivery arrangements as soon as possible the next business day.

C. Call **Novex** at **604-278-1935** and specify the pick up location. When they ask where the package will be delivered, the destination address is as follows:

School of Environmental Health Laboratory
UBC
370A – 2206 East Mall
Vancouver, BC V6T 1Z3

D. Provide Novex with the following information to ensure proper delivery: ***Account number: 15939. Reference field: AND.***

E. Write the confirmation number provided by Novex on label found on the outside of cooler.

F. Place the cooler and its contents in the specified pick up location.

G. Your honorarium of $15 will be sent to your mailing address shortly after the urine samples have been received by our staff at UBC.

Thank you for participating in the study. If you have questions about this sample collection or any other questions about the study itself, please call the Project Coordinator at 604- .