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EXPOSURE AND HANDLING PRACTICES OF HEALTHCARE PROFESSIONALS FOR CYTOTOXIC DRUGS IN THE WORKPLACE ENVIRONMENT

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This dissertation is submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy

Under the Supervision of Dr. Elpidoforos S. Soteriades

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Declaration of Original Work

I, Laila Masoud Ali Masoud Al Alawi, the undersigned, a graduate student at the United Arab Emirates University (UAEU), and the author of this dissertation entitled "*Exposure and Handling Practices of Healthcare Professionals for Cytotoxic Drugs in the Workplace Environment*", hereby, solemnly declare that this dissertation is my own original research work that has been done and prepared by me under the supervision of Dr. Elpidoforos S. Soteriades, in the College of Medicine and Health Sciences at UAEU. This work has not previously formed the basis for the award of any academic degree, diploma or a similar title at this or any other university. Any materials borrowed from other sources (whether published or unpublished) and relied upon or included in my dissertation have been properly cited and acknowledged in accordance with appropriate academic conventions. I further declare that there is no potential conflict of interest with respect to the research, data collection, authorship, presentation and/or publication of this dissertation.

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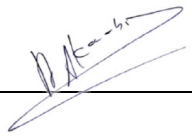
Signature  Date 04/08/2021

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Abstract

Introduction: Occupational exposure to cytotoxic drugs is associated with various unfavorable health outcomes. There is currently no safe level for occupational exposure to cytotoxic agents. Healthcare workers' adherence to cytotoxics control measures is of primary importance to minimize the risk from exposure to these agents.

Aims: To develop a protocol for a systematic review and meta-analysis on environmental assessment of cytotoxic drugs in healthcare settings and conduct an environmental assessment study of cytotoxic drugs in two Oncology centers of Abu Dhabi, United Arab Emirates (UAE). In addition to evaluate pharmacists' and nurses' Knowledge, Attitudes, and Practices (KAP) towards handling of cytotoxic drugs.

Method: This research project comprised of three studies. The first study developed a protocol on environmental assessment of cytotoxic drugs in healthcare settings. The protocol was developed in line with PRISMA-P guidelines. The second study evaluated workplace contamination with 10 cytotoxic drugs by collecting 79 surface wipe samples from preparation and administration areas of two Abu Dhabi Oncology centers. The third study was a cross-sectional survey using an online self-administrated questionnaire to assess pharmacists' and nurses' KAP regarding the handling of cytotoxic drugs.

Results: In the first study**,** the protocol was registered (ID CRD42020162780) on The International Prospective Register of Systematic Reviews (PROSPERO). In the second study, a total of 79 surface samples were analyzed. Of these, 20 samples (25%) were positive for cytotoxic drug residues. Moreover, 10 samples (13%) indicated contamination by more than one cytotoxic drug, mainly in the oncology pharmacy department in both hospitals. The levels of contamination in the positive samples ranged from 0.003 to 50 ng/cm^2. In the third study, 113 oncology healthcare professionals participated in the survey (23 Male and 90 Female). Most of them were aware of the potential hazards associated with handling of cytotoxic medications. The mean score of the participants' knowledge was 74.04 out of 100. The majority of the participants reported high adherence levels to the use of personal protective equipment such as gloves, protective gown, and mask (98.14%, 97.22%, and 96.29%),

respectively, while handling these agents. All the participants (100%) had received training on the safe handling of cytotoxic drugs during the past year.

Significant contributions: The findings of this research provide important baseline data about exposure and handling practices of healthcare professionals for cytotoxic drugs in the workplace environment. The findings may be used to develop programs about cytotoxic drugs handling that will help to minimize the risk of these agents. The results also point out that it is vital to healthcare facilities to assess environmental contamination with cytotoxics. Such initiatives will contribute to raise both knowledge and practices of healthcare professionals regarding the handling of cytotoxic drugs.

Gap filled: The environmental assessment study is the first study in the Middle East and North Africa (MENA) region, and in UAE in particular, that evaluated the potential environmental contamination with ten cytotoxic drugs in preparation and administration areas. Furthermore, the KAP study is also the first in the UAE to assess oncology healthcare professionals' KAP towards handling of cytotoxic drugs.

Keywords: Cytotoxic drugs, environmental assessment, occupational exposure, knowledge, attitude, practices.

Title and Abstract (in Arabic)

تعرض ممارسي الرعاية الصحية لأدوية العلاج الكيميائي في بيئة العمل وممارسات تعاملهم مع هذه الأدوية

الملخص

المقدمة: يرتبط التعرض المهني لأدوية العلاج الكيميائي بأثار صحية عديدة. حيث لا يوجد حاليًا مستوى آمن للتعرض المهني لهذه الأدوية. كما يعد إلتزام ممارسي الرعاية الصحية العاملين في مراكز علاج الأورام بإجراءات السلامة والوقاية الخاصة للتعامل مع هذه الأدوية ذا أهمية قصوى لتقليل مخاطر التعرض لها.

الأهداف: يهدف هذا البحث إلى تطوير برتوكول لـ (a systematic review and meta-analysis) للتقييم البيئي لكمية أدوية العلاج الكيميائي في المنشآت الصحية، ودراسة التقييم البيئي لإحتمال تلوث مراكز علاج الأورام بإمارة أبوظبي بأدوية العلاج الكيميائي، بالإضافة إلى دراسة معرفة وممارسات وتصورات الصيادلة والممرضين العاملين في تلك المراكز تجاه التعامل مع أدوية العلاج الكيميائي.

الطريقة: يتضمن هذا المشروع البحثي 3 دراسات، من خلال الدراسة الأولى تم تطوير بروتكول للتقييم البيئي لكمية أدوية العلاج الكيميائي في المنشآت الصحية، والذي تم تطويره وفقاً لتوجيهات (PRISMA-P)، هذا وقد قيمت الدراسة الثانية تلوث أماكن العمل لعدد (10) أدوية تستخدم للعلاج الكيميائي من خلال جمع (79) عينة مسح لأسطح وحدة الصيدلية ووحدة علاج المرضى بمركزين للأورام بإمارة أبوظبي. أما بالنسبة للدراسة الثالثة، فقد كانت عباره عن دراسة مقطعية بإستخدام استبيان تم تعبأته ذاتيا من قبل المشاركين في الدراسة، بهدف تقييم معرفتهم وتصوراتهم وممارساتهم حول التعامل مع أدوية العلاج الكيميائي.

النتائج: من خلال الدراسة الأولى، تم تسجيل البروتكول في منصة (PROSPERO) تحت رقم (CRD42020162780)، كما وجدت الدراسة الثانية 20 عينة (25%) ملوثة بأدوية العلاج الكيميائي. علاوة على ذلك، تلوث 10 عينات (13%) بعدد من أدوية العلاج الكيميائي، خاصة في وحدة صيدلية الأورام في المستشفيين. تراوحت مستويات التلوث في العينات الإيجابية من 0.003 إلى 50 نانوغرام/ سنتيمتر مربع. أما بالنسبة للدراسة الثالثة، فقد شارك فيها عدد (113) مشارك من الصيادلة والممرضين العاملين في مراكز علاج الأورام (23 ذكر و 90 أنثى). حيث أشارت الدراسة أن معظم المشاركين بالدراسة على دراية بالمخاطر المرتبطة بالتعامل مع أدوية العلاج الكيميائي. كما كان متوسط درجة معرفة المشاركين 74.04 من 100. هذا وقد أبدى غالبية المشاركين التزامهم بمستويات عالية لاستخدام معدات الحماية الشخصية مثل القفازات، وملابس الوقاية وأقنعة الحماية بنسبة (98.14%، 97.22%، 96.29%) على التوالي، أثناء التعامل مع هذه الأدوية. هذا بالإضافة إلى تلقى جميع المشاركين (100%) تدريبات متعلقة بالتعامل الآمن مع أدوية العلاج الكيميائي خلال العام الماضي.

المساهمات الإضافية المميزة للدراسة: توفر نتائج هذا البحث بيانات أساسية مهمة حول مدى تعرض ممارسي الرعاية الصحية لأدوية العلاج الكيميائي في بيئة العمل وممارسات تعاملهم مع هذه الأدوية. كما يمكن استخدام نتائج هذا البحث لتطوير برامج حول التعامل الآمن مع أدوية العلاج الكيميائي، والتي من شأنها أن تساهم في الحد من مخاطر التعرض المهني لهذه الأدوية. كما تشير النتائج أيضاً إلى أهمية عمل المنشآت الصحية لتقييم بيئي لأدوية العلاج الكيميائي في منشآتها، والذي سيساهم إلى رفع مستوى كلاً من معرفة وممارسات ممارسي الرعاية الصحية العاملين في مراكز الأورام بهذا الموضوع.

الفجوات المعرفية التي أغلقتها الدراسة: دراسة التقييم البيئي لإحتمال تلوث بيئة العمل بأدوية العلاج الكيميائي هي الدراسة الأولى في منطقة الشرق الأوسط وشمال إفريقيا (MENA)، وفي دولة الإمارات العربية المتحدة على وجه الخصوص، والتي قيمت التلوث البيئي المحتمل لعشرة أدوية علاج كيميائي في وحدات الصيدليات وعلاج المرضى في مراكز علاج الأورام. هذا بالإضافة، إلى أن دراسة المعرفة والتصورات والممارسات (KAP) هي الدراسة الأولى في دولة الإمارات العربية المتحدة، والتي قيمت مستوى معرفة وتصورات وممارسات ممارسي الرعاية الصحية العاملين في مراكز علاج الأورام تجاه التعامل مع هذه الأدوية.

كلمات البحث الرئيسية: أدوية العلاج الكيميائي، التقييم البيئي، التعرض المهني، المعرفة، التصور، الممارسة.

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Dedication

To my beloved parents, brothers and sisters

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List of Abbreviations

AD DOH	Abu Dhabi-Department of Health
ASCO	American Society of Clinical Oncology
CDs	Cytotoxic Drugs
CP	Cyclophosphamide
CSTD	Closed System Drug Transfer Devices
CUPE	Canadian Union of Public Employees
ETUI	European Trade Union Institute
HFs	Healthcare Facilities
HPRT	Hypoxanthine-guanine phosphoribosyltransferase
HSE	Health and Safety Executive
IARC	International Agency for Research on Cancer
KAP	Knowledge, Attitudes and Practices
LOD	Limit of Detection
NIDDK	Nattional Institute of Diabetes and Digestive and Kidney Diseases
NIOSH	National Institute for Occupational Safety and Health
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
OSHAD	Abu Dhabi Occupational Safety and Health Center
PPE	Personal Protective Equipment
UAE	United Arab Emirates
USP	United States Pharmacopeia
WHO	World Health Organization
WHSQ	Workplace Health and Safety Queensland

Chapter 1: Introduction

1.1 Overview

Cancer is a major public health concern worldwide (Siegel et al., 2015), accounted for nearly 9.6 million deaths in 2018 (WHO, 2018). The global burden of cancer is projected to continue to rise with, 27.5 million new cases expected to be diagnosed annually by the year 2040 (American Cancer Society, 2018). In the United Arab Emirates (UAE), cancer was ranked the third leading cause of death following cardiovascular diseases and injuries, responsible for 9.2% of the total fatalities in 2014 (MOHAP, 2014) and 12.8% of the total fatalities in the Emirate of Abu Dhabi during the same year (AD DOH, 2017). Moreover, the number of cancer cases in the UAE nearly doubled from 2011 to 2017, according to the UAE Ministry of Health and Prevention (MOHAP, 2017). With cancer cases on the rise, the overall use of Cytotoxic Drugs (CDs) and other treatment modalities is expected to rise proportionately in order to cater for the new cancer cases.

Cytotoxic agents have extensively been used in cancer patients' treatment, which has led to occupational hazards associated with exposure of Healthcare Workers (HCWs) to such drugs leading to different adverse health outcomes (Lawson et al., 2012; Connor et al., 2014; NIOSH, 2020). According to the United Kingdom (UK) Health and Safety Executive (HSE), occupational exposure to cytotoxic drugs may occur through several routes, including dermal absorption, inhalation of drug particles or aerosols, ingestion, and accidental injection (e.g. needlestick injuries) (HSE, 2020). Whereas levels of such exposures are usually much lower than those used for cancer patients (Lawson et al., 2012), occupational exposure probably includes a concurrent exposure to multiple cytotoxic drugs, and it occurs more frequently over a prolonged

period of time, leading to mixed cumulative exposures (NTP, 2019). Exposure can occur at any step of the medication circuit, where cytotoxic drugs are handled in shipping and receiving areas, prepared in pharmacies, administered in wards, and contacted through sanitary services such as laundry, cleaning, and waste disposal (Hon et al., 2013; WHSQ, 2017). Furthermore, several studies have demonstrated widespread contamination of working areas in healthcare settings which lead to healthcare workers' exposure to these hazardous drugs (Sugiura, Asano et al., 2011; Sugiura, Nakanishi et al., 2011; Kopp et al., 2013; Viegas et al., 2014; Sessink et al., 2015; Muller-Ramirez et al., 2017; Verscheure et al., 2020).

1.2 Statement of the problem

Studies involving environmental assessment of hospital working environments and biological monitoring of staff involved in the handling of such hazards have demonstrated cytotoxic drugs residues on the work surfaces as well as exposure of employees to cytotoxic drugs along with the development of adverse health effects among healthcare workers (Elshamy et al., 2010; Hanafi et al., 2015). In particular, pharmacists who prepare these drugs or nurses who administer them to patients are the two professional groups who have the highest risk of potentially being exposed to cytotoxic drugs (Hon et al., 2011; Hon et al., 2014) where no precautions exist.

Pharmacists' and nurses' knowledge of the handling of cytotoxic medications remains a concern because it has been associated with continuous improvement of safety standards. Educational intervention is a potent instrument for improving nurses' knowledge level (Shrestha et al., 2015; Keat et al., 2013). The higher the pharmacists' and nurses' knowledge, the more they adhere to safety precautions in their workplace, which in turn enhances their sense of well-being. Knowledge and safe practices of

healthcare workers in handling cytotoxic drugs is therefore of paramount importance to help prevent exposure to occupational hazards for themselves, patients, and people who visit the oncology departments in the hospitals. However, there is a gap between the HCWs' knowledge and their behavior when handling cytotoxic agents (Ibrahim et al., 2018).

In UAE, cytotoxic therapies are mainly prepared by pharmacists in designated pharmacy, and it is administered to patients by nurses in the oncology wards. However, assessing the oncology settings' contamination with cytotoxic drugs has not been previously reported. Moreover, there have been no studies to evaluate Abu Dhabi healthcare professionals' Knowledge, Attitudes and Practices (KAP) regarding the handling of cytotoxic drugs in oncology healthcare settings. Therefore, it is vital to identify the magnitudes of workplace contamination with cytotoxic agents and evaluate oncology healthcare workers' knowledge, attitude, and practices towards handling these hazardous agents.

1.3 Research questions

The present research specifically addresses the following questions:

1. Is there any surface contamination of Oncology Departments with cytotoxic drugs?
2. What is the level of nurses' and pharmacists' (KAP) regarding cytotoxic drugs handling at Abu Dhabi's Hospitals?
3. Are there any challenges faced by healthcare workers when handling cytotoxic drugs in Abu Dhabi Hospitals?

1.4 Aim and objectives

This research is aimed to measure the potential environmental exposure to cytotoxic drugs and the level of nurses' and pharmacists' KAP towards handling cytotoxic drugs. To achieve this aim, therefore, the research had formulated the following objectives:

a. To develop a protocol for a systematic review and meta-analysis on environmental assessment of cytotoxic drugs in healthcare settings.
b. To assess the workplace contamination of the oncology departments of Abu Dhabi with the frequently used cytotoxic agents.
c. To evaluate the level of nurses' and pharmacists' KAP regarding the handling of cytotoxic drugs.
d. To recommend additional preventive measures and associated policies base on the finding of this research.

1.5 Significance of the study

The concern for persistence of workplace contamination and healthcare workers' exposure to cytotoxic agents is well documented. Yet, in the UAE and in Abu Dhabi (AD) in particular, information on the potential workplace contamination of the oncology departments with cytotoxic drugs and the level of nurses' and pharmacists' KAP towards handling of cytotoxic drugs is not documented. The outcomes of this research will add to the existing literature and help in developing interventions to reduce healthcare workers' exposure to these hazardous agents. It will also help policymakers in UAE to come with a better plan to increase knowledge, create a positive attitude, and improve proper practice related to cytotoxic drug handling.

1.6 Summary

This research sought to develop a protocol for a systematic review and meta-analysis regarding environmental assessment of cytotoxic drugs in healthcare settings and assess the oncology departments' workplace contamination with the widely used cytotoxic agents. Additionally, evaluate the level of nurses' and pharmacists' KAP on the safe handling of cytotoxic drugs. The results of this research may serve multiple stakeholders such as the Department of Health-Abu Dhabi, Abu Dhabi Public Health Center, oncology healthcare providers, managers, and healthcare workers, especially oncology nurses and pharmacists.

1.7 Relevant literature

In this section, the literature is reviewed. It compares studies in the context of the research questions. It starts by defining the cytotoxic drugs, their classifications, and related uses. Then present the environmental and biological monitoring techniques used for these agents. Then explore the different health hazards related to cytotoxic drugs. The section also sheds light on the healthcare workers' KAP regarding the handling of cytotoxic drugs. Moreover, it presents the different factors influencing the adoption of protective behaviours and the effect of interventional programs in improving the KAP of healthcare workers.

1.7.1 Cytotoxic drugs definitions, classifications, and uses

Cytotoxic agents are medications used, in combination or alone, to treat a wide variety of cancers. These agents are also known as chemotherapeutic, anti-neoplastic, or hazardous drugs. Cytotoxic drugs work on the cell level, interfering with the process of cell growth and division. Unfortunately, most cytotoxic drugs are generally non-

selective and, therefore, when administered, may also damage healthy cells resulting in adverse toxic effects (Pavlica et al., 2015; ETUI, 2020).

Numerous classification schemes have been established to categorize cytotoxic agents. Historically, based on the source and mechanisms of action, these agents are divided into alkylating agents, antimetabolites, natural products, hormones and antagonists, and miscellaneous agents (Livshits et al., 2014; NIDDK, 2020). Cytotoxic agents can also be classified on the basis of their mechanisms of action (alkylating agents, biological response modifiers, antibiotics, antiandrogens, topoisomerase inhibitors, or protein kinase inhibitors), their indication (lymphoma, melanoma, leukemia, solid tumor), their chemical structures (purine or pyrimidine analog, folic acid analog, platinum coordination complex, monoclonal antibody) or grouped as cytotoxic or non-specific versus non-cytotoxic or targeted drugs (NIDDK, 2020). The WHO/International Agency for Research on Cancer (IARC) has grouped twelve cytotoxic drugs, and two combined chemotherapies in group 1 as carcinogenic to humans, eleven drugs are classified as probably carcinogenic (Group 2A), nine drugs as possibly carcinogenic to humans (Group 2B), and the rest of the agents has classified as not classifiable as to carcinogenic to humans (Group 3) (Table 1.1) (IARC, 2020). However, most CDs are classified by NIOSH as hazardous drugs, which were defined as the agents that are associated with carcinogenicity, genotoxicity, teratogenicity (fertility impairment) or other developmental toxicity, organ toxicity at low doses, reproductive toxicity, structure, and toxicity profiles of new drugs that mimic existing hazardous agents (NIOSH, 2016).

Table 1.1: IARC classification of cytotoxic drugs

Group 1 (carcinogenic to humans)	Group 2A (probably carcinogenic to humans)
Azathioprine N,N-Bis(2-chloroethyl)-2-naphthylamine (Chlornaphazine) 1,4-Butanediol dimethanesulfonate (Busulfan; Myleran) Chlorambucil Semustine Cyclophosphamide Etoposide Etoposide in combination with cisplatin and bleomycin Melphalan MOPP and other combined chemotherapy including alkylating agents Thiotepa Treosulfan Tamoxifen Diethylstilbestrol	Azacitidine Bischloroethyl Nitrosourea (BCNU) Cisplatin Lomustine N-Methyl-N-nitrosourea N-Ethyl-N-nitrosourea Nitrogen mustard (Mechlorethamine) Procarbazine hydrochloride Teniposide (Vumon) Adriamycin Chlorozotocin
Group 2B (possibly carcinogenic to humans)	**Group 3 (not classifiable as to carcinogenic to humans**
Bleomycins Dacarbazine Daunomycin Mitomycin C Mitoxantrone Streptozotocin Merphalan Amsacrine Aziridine	5-Fluorouracil Isophosphamide 6-Mercaptopurine Methotrexate Prednisone Vinblastine sulfate Vincristine sulfate

Cytotoxic drugs are used in various settings, including healthcare facilities, laboratories, manufacturing, and research settings. Apart from their cancer treatment application, cytotoxic drugs are also used to treat other illnesses such as psoriasis,

multiple sclerosis, and systemic lupus erythematosus. These drugs are also applied topically in ophthalmology for an increasing number of indications (WHSQ, 2017). Furthermore, these drugs are also increasingly used in veterinary clinics to treat companion animals (Elliot & Mayer, 2009).

1.7.2 Environmental assessment

Occupational exposure to cytotoxic drugs may occur from one or more of the common routes of exposure. Whereas dermal and inhalation routes are the most likely routes of exposure to cytotoxic drugs in health care settings, hand to-mouth exposure or accidental needle sticks may also contribute to exposure (McDiarmid et al., 2013; Connor & McDiarmid, 2006; Kromhout et al., 2000). Consequently, surface wipe sampling and airborne sampling have been considered the two main methods for determining workplace contamination with cytotoxic drugs. Several environmental studies have measured airborne concentrations of cytotoxic drugs in health care settings (McDiarmid et al., 1986; Pyy et al., 1988; Sessink, Boer et al., 1992; Larson et al., 2003). Overall, most of these studies have detected little to no airborne contamination with the cytotoxic agents (McDiarmid et al., 1986; NIOSH, 2004). These results are probably due to the inefficient sampling and analytical techniques employed in the past (Larson et al., 2003). The most frequently measured drugs in air sampling studies include cyclophosphamide, 5-fluorouracil, ifosfamide, and methotrexate (Turci et al., 2003).

Surface wipe sampling, combined with surface wipe analysis, is the method of choice for determining the level of workplace surface contamination with cytotoxic drugs (Connor & Smith, 2016). Surface wipe sampling can help quantify the effects of improved work practices and identify the need for effective engineering controls and

Personal Protective Equipment (PPE) (Ashley et al., 2011; Connor et al., 2016; Böhlandt & Schierl, 2016).

1.7.2.1 Surface contamination with cytotoxic drugs

Since the first studies of environmental monitoring of cytotoxic drugs in healthcare settings (McDiarmid et al., 1986; Pyy et al., 1988; Sorsa et al., 1988; Sessink, Boer et al., 1992), various surveys have been published worldwide. Notably, environmental assessment studies of healthcare settings have continually reported measurables levels of cytotoxic agents on surfaces. A recent study analyzed 5,842 surface wipe samples from 338 pharmacies, mostly in the United States, over six years. Evidence showed that between 3.94% and 25.96% of samples had high cytotoxic drugs contamination levels (Salch et al., 2019). The recently published study by Chauchat and others presented the results of hazardous drugs surface contamination in 83 Canadian hospitals. It demonstrated 36% of the samples were positive for Cyclophosphamide (CP), with contamination found in both pharmacy and administration areas (Chauchat et al., 2018). A multi-hospital study in Europe revealed surface contamination in drug preparation and administration sites in all hospitals, with measurable levels of at least one drug detected on sampled surfaces. The investigators concluded that improving standard work procedures could dramatically reduce workplace contamination levels (Korczowska et al., 2020). In Italy, a study of cytotoxic drugs environmental monitoring was carried out in nine hospitals between 2008 and 2017 and included 74,565 measurements in 4,814 wipe samples. Cytotoxic drug contamination was found in 3,081 samples, confirming potential healthcare professionals' exposure (Dugheri et al., 2018). In Japan, multicenter field studies were performed by Sugiura, Asano et al. (2011) and Sugiura, Nakanishi et al. (2011)

evaluating cyclophosphamide exposure. The outcomes showed contamination levels with cyclophosphamide ranging from 50% to 80% among all samples collected (Sugiura, Asano et al., 2011; Sugiura, Nakanishi et al., 2011). In the Middle East and North Africa (MENA) region, there is limited data assessing the level of workplace contamination with CDs. A study in two Iranian hospitals by Azari et al. (2017) reported contamination of the workplace with cyclophosphamide. Furthermore, a recent Algerian study analyzed 39 surface wipe samples from 6 different departments, including dermatology, oncology, nephrology, hematology, and rehabilitation. Evidence showed that all surfaces' samples tested positive with one or more cytotoxic drugs. More than half of the samples were positive for cyclophosphamide (79.5%), 5-Fluorouracil (66.7%), and methotrexate (56.4%). Cyclophosphamide was the highest measured concentration per cm^2 (208.85 ng/cm^2) (Verscheure et al., 2020). Both studies conclude that regular environmental monitoring of CDs is essential to protect healthcare workers from the potential risk of occupational exposure. Table 1.2 summarizes studies published on environmental monitoring of cytotoxic drugs in healthcare settings in the MENA region.

Evidence of cytotoxic agent contamination has been detected inside and outside biological safety cabinets, work surfaces, floors (Davis et al., 2011; Call et al., 2017), and gloves (Wallemacq et al., 2006; Call et al., 2017). In addition to these sources of contamination, multiple studies have demonstrated that the exterior surfaces of drug vials supplied by pharmaceutical companies contain cytotoxic drug residues on their external parts (Hama et al., 2013; Power et al., 2014; Moretti et al., 2015; Cotteret et al., 2020). These findings show that oncology pharmacists and nurses are at risk for dermal exposure if they do not comply with the safety measures while handling drug vials.

Table 1.2: Studies on environmental monitoring of cytotoxic drugs in healthcare settings in the MENA region

Region	Country	Author(s)/year of pub	Study purpose	Population	Sampled Areas	Total Samples	Measured CDs	Total positive samples	Main results
Middle East	Iran	Azari et al. (2017)	Investigate the contamination of surfaces with cyclophosphamide	Two hospitals	Preparation room, in patient bed rooms, out patient bed rooms, office area	89	Cyclophosphamide	27	Cyclophosphamide was detected in some wipe surfaces at two hospitals.
North Africa	Algeria	Verscheure et al. (2020)	Evaluate surface contamination with cyclophosphamide, ifosfamide, 5-fluorouracil, and methotrexate	One hospital	Rehabilitation, nephrology, oncology, hematology, maternity oncology, dermatology	39	Cyclophosphamide, ifosfamide, 5-fluorouracil, and methotrexate	39	All samples tested positive for one or more drugs.

1.7.3 Controlling exposure

Various control measures and strategies are employed to limit surface contamination and workers' exposure, such as using biological safety cabinets, providing training, priming intravenous tubing in the pharmacy, using personnel protective equipment (NIOSH, 2004), implementing cleaning techniques (Federici et al., 2019; Adé et al., 2017), using automatic compounding devices (e.g., robotic system), etc. (Kramer et al., 2018). All these measures have a common aim to provide maximum protection for healthcare workers handling these drugs.

Closed System Drug Transfer Devices (CSTDs) can be used for preparing and administering cytotoxic drugs in conjunction with other safety control measures. These devices create a 'closed' environment that prevents aerosols from escaping (NIOSH, 2004). Although CSTDs provide additional protection, they must be used inside the biological safety cabinet to prepare cytotoxic agents (USP, 2017).

Some studies have addressed the benefits of CSTD to reduce the cytotoxic contamination of surfaces and biological fluids of handlers (Wick et al., 2003; Yoshida et al., 2011; Siderov et al., 2010; Bartel et al., 2018). Both studies by Sessink in American hospitals documented a reduction in surface contamination. In a 2011 study, the reduction cited was 95%, 90%, and 65% for cyclophosphamide, ifosfamide, and 5-fluorouracil, respectively (Sessink et al., 2011). While in a 2013 study, the reduction in the contamination amounts was 86% for cyclophosphamide after six months of using the closed system (Sessink et al., 2013). The outcomes of the study by Miyake et al. (2013) indicated that four out of the six surfaces tested positive for cyclophosphamide before the introduction of the closed system, and seven months

after implementing it, only one of the six surfaces tested positive with almost undetectable levels (0.001 ng/cm^2).

Compounding robot has been introduced in 51 hospitals in 14 countries to improve both patients' and workers' safety (Yaniv & Knoer, 2013; Masini et al., 2014). Importantly, robotic drug preparation helps to solve the problem of exposure or contact with hazardous drugs. Few studies have been published on workplace contamination during the use of automated compounding devices (Schierl et al., 2014; Iwamoto et al., 2017; Sessink et al., 2015; Krämer et al., 2018).

A study in a hospital pharmacy in Amsterdam compared environmental and external cross-contamination (from one preparation to the next) of traces of cytotoxic drugs, during cyclophosphamide preparation using a robotic system or the conventional manual compounding procedure. The study concluded that external cross-contamination of infusion bags with cyclophosphamide was lower for robotic compounding, both in the number of contaminated samples and in the observed levels of cyclophosphamide (Buning et al., 2020).

Overall, the application of safety control measures reduces, but does not entirely eliminate, CD exposure in the workplace environment (Power & Coyne, 2018). Hence, implementing methods to detect workplace surface contamination is prudent while developing and evaluating organizational policies and procedures intended to mitigate occupational risk (Hodson et al., 2020). Because there is no safe cytotoxic agent level, exposure to these agents should be kept as low as reasonably achievable based on the ALARA principle (Verscheure et al., 2020; Connor et al., 2016).

1.7.4 Biological monitoring

Numerous bio-monitoring techniques have been developed to assess cytotoxic drugs in the biological samples. These techniques include: detecting the CD or its metabolite in the workers' urine, determining the mutagenicity of urine of workers, or measuring endpoints such as sister chromatid exchanges, chromosomal aberrations, and micronuclei induction in white blood cells of the handlers. Other studies have measured Hypoxanthine-Guanine Phosphoribosyltransferase (HPRT) mutations and damage to the DNA. Most of these endpoints measure different types of genotoxic damage (NIOSH, 2019).

Urinary levels of cytotoxic drugs and their metabolites are widely assessed in healthcare personal as a tool of detecting occupational uptake of these agents, provide biomarkers for exposure, and measure workers' real risk. A cross sectional study from the US by Connor et al. (2010), including 68 urine samples from healthcare workers, revealed that 4% of the urine samples tested positive for one cytotoxic drug (Connor et al., 2010). Hone et al. quantified the urine concentration of non-metabolized cyclophosphamide in 201 urine samples from 103 Canadian healthcare workers, 55% of which were above the Limit of Detection (LOD) for cyclophosphamide. Interestingly, the same study found the highest average level of cyclophosphamide in the urine of workers who were not handling these agents (Hon et al., 2015). A 2018 study in Iran reported 46.66%, and 16.66% of the healthcare workers′ urine samples were positive for cyclophosphamide and ifosfamide, respectively (Baniasadi et al., 2018). A minireview of 20 studies by Suspiro & Prista reported that 17 studies found cytotoxic drugs in healthcare workers' urine (Suspiro & Prista, 2011). Conversely, other studies did not find any evidence of trace levels of cytotoxic drugs in the urine

samples of healthcare staff. For instance, Palamini and others found no urine samples testing positive for cyclophosphamide, ifosfamide, methotrexate, or 5-fluorouracil with 24 h sampling (Palamini et al., 2020). Moreover, a study in 2 Canadian adult hospitals by Chauchat et al. revealed that no cytotoxic drug was detected in any of the worker's urine samples (Chauchat et al., 2019).

Urinary mutagenicity was first used as marker of occupational exposure to cytotoxic drugs in 1979 by Falck and his colleagues using bacterial mutagenicity assays. Nurses who prepared and administered cytotoxic drugs had higher indicators of mutagenic substances in their urine than non-exposed healthcare workers. A dose response was also detected in the urine mutagenicity frequency with additive exposure over the workweek that decreased during the weekend (Falck et al., 1979). Since then, several studies have confirmed the genotoxic risk of working with these agents using different genotoxicity tests.

Some studies found a significant increase in Micronuclei (MN), Sister Chromatid Exchanges (SCEs), Chromosome Aberrations (CAs) and comet tail length of individual exposed to cytotoxic drugs, although negative results have also been cited. A study conducted in two Portuguese hospitals included 27 nurses occupationally exposed to cytotoxic agents and 111 unexposed personals revealed a significant increase in MN frequency with peripheral blood lymphocytes in exposed nurses versus controls (Ladeira et al., 2014). Another study by Moretti et al. (2015) based on occupationally CD-exposed as cases (n=71) and CD-unexposed as control reported a significant increase in MN frequency (5.30 ± 2.99 and 3.29 ± 1.97; $p<0.0001$) in exposed nurses compared with controls, as well as in chromosome aberration detection (3.30+2.05 and 1.84+1.67; $p<0.0001$) exposed workers versus controls

(Moretti et al., 2015). Measuring chromosomal aberration or micronuclei in peripheral blood cells are effective tools for evaluating occupation exposure-related genotoxicity (Roussel et al., 2019). Association between occupational exposure to CDs and genotoxic effects has been reported in various studies. A meta-analysis of 16 studies by Roussel and his colleagues reported a significant association between occupational exposure to cytotoxics over the course of a normal workday and increases in chromosomal aberrations in exposed healthcare workers (Roussel et al., 2019). A recent systematic review and meta-analysis also observed a significant association between occupational exposure to CDs and DNA damage in healthcare workers (Gianfredi et al., 2020).

In general, these studies suggest that occupational exposure to CDs may induce genotoxic effects and even be a risk to human health.

1.7.5 Hazardous effects of cytotoxic drugs

Although the potential therapeutic benefits of cytotoxic drugs exceed the risks of side effects for cancer patients, exposed healthcare professionals may experience adverse health effects with no gain (NIOSH, 2004).

Since cytotoxic drugs are extremely effective active compounds, even exposure to doses lower than those received by cancer patient can produce health effects, especially in chronically exposed healthcare workers (Moretti et al., 2015; Viegas et al., 2018; Yoshida et al., 2011; Zhang et al., 2016). The health risk is influenced by various factors such as dose and frequency of exposure, drug toxicity, the existence of proper work practices, and others (NIOSH, 2004; Villarini et al., 2011).

Considering all these aspects, there is concern that healthcare professionals continuously exposed to cytotoxic drugs may have adverse acute and chronic health effects, raising a need to reduce this exposure as much as possible. Various acute side effects of cytotoxic agents are well documented in healthcare workers exposed to these drugs. These include such effect as skin, eye, mouth and throat irritations, as well as nausea, headaches, and dizziness (Ivanova & Avota, 2016; CUPE, 2020). Cases of abdominal pain and hair loss related to cytotoxic drug exposure have also been reported (Keat et al., 2013). An interesting Egyptian study found almost more than half of the nurses frequently complained from recurrent headache, skin and eye irritation, and hair loss (El Hosseini et al., 2019). Similar health outcomes have been evidenced in previous studies (Constantindis et al., 2011; Kyprianou et al., 2010; Unsar et al., 2016). Chronic health effects linked with exposure have included damage to multiple organs (e.g., liver, kidney, bone marrow, lungs and heart) (NIOSH, 2017), reproductive harms such as infertility and birth defects, genotoxic changes, and potential cancer development (NIOSH, 2004).

However, the clinical significance of low-level exposure to cytotoxic agents is not fully recognized, especially when workers are exposed to a combination of cytotoxic drugs over long periods of time (Kibby, 2017; Marie et al., 2017).

1.7.5.1 Reproductive and developmental effects

Adverse reproductive outcomes have been observed in healthcare professionals handling cytotoxic drugs, including spontaneous abortions (Lawson et al., 2012), miscarriage, infertility (Martin, 2003; Connor et al., 2014), longer time to conception (Nassan et al., 2019), premature labor (Elshamy et al., 2010), low birth weight (Fransman et al., 2007) and learning disabilities in offspring of nurses exposed

during pregnancy (Martin, 2005; Elshamy et al., 2010). In a literature review study by Connor et al. (2014), researchers found that healthcare workers with chronic, long-term exposure to low levels of cytotoxic drugs appear to have an increased risk of adverse reproductive effects such as congenital malformation and abortions. An extensive American study published in 2012 documented increased spontaneous abortions in nurses exposed to cytotoxic drugs in the workplace environment (Lawson et al., 2012). Furthermore, it is noteworthy that similar results were found in a systematic review study by the US National Toxicology Program (NTP). They reported that workplace exposure to cytotoxic drugs is associated with elevated incidence of spontaneous miscarriage among nurses and pharmacists (NTP, 2019).

1.7.5.2 Genetic effects

Cytotoxic drugs have the capability to bind DNA, thus cause genotoxic damage (Aristizabal-Pachon & Castillo, 2019). The genotoxicity of cytotoxic drugs has been evaluated using different endpoints including chromosomal aberrations, primary DNA damage, and micronuclei in peripheral blood lymphocytes (Suspiro & Prista, 2011; Villarini et al., 2016; Roussel et al., 2019; NIOSH, 2019). A significant genotoxic effect for many cytotoxic drugs has been observed in cancer patients treated with cytotoxic agents (Kopjar et al., 2006; Padjas et al., 2005; Torres-Bugarı´n et al., 2004). The genotoxic risk in healthcare workers exposed to cytotoxic drugs has been evaluated in various studies, and it has been shown that some studies have no statistically significant risk of genotoxicity (Buschini et al., 2013; Ladeira et al., 2015; Oltulu, et al., 2019) and some studies have a statistically significant effect on DNA damage compared to the control group (Rekhadevi et al., 2007; Villarini, et al., 2011).

However, a recent systematic review and meta-analysis by Roussel and colleagues in 2019 reported a significantly higher level of chromosomal aberrations in health workers exposed to cytotoxic drugs compared with controls, with a pooled standardized mean difference = 1.006, $z = 4.25$, $p < 0.001$) (Roussel et al., 2019).

Another recent meta-analysis conducted by Gianfredi et al. (2020) included 19 studies in quantitative evaluation and 20 in the qualitative analysis that evaluated whether or not there is an association between occupational exposure to cytotoxic drugs and the extent of primary DNA damage in health professionals. The authors found a positive association between duration of exposure and primary DNA damage. The authors also concluded that the literature clearly shows a significant association between occupational exposure to cytotoxic drugs and the extent of primary DNA damage in healthcare personnel (Polled effect size: 1.27, 95% CI:0.66-1.88, p=0.000) (Gianfredi et al., 2020).

These recent studies, along with the historical evidence, conclude that there is a risk of genotoxic damage to healthcare workers occupationally exposed to cytotoxic agents.

1.7.5.3 Cancer development

The International Agency for Research on Cancer (IARC) has classified many cytotoxic drugs as group 1 (human carcinogens) such as etoposide, cyclophosphamide, melphalan, busulfan, group 2A (probably carcinogenic to humans) such as cisplatin, azacitidine, clorozotocin, and group 2B (possibly carcinogenic to humans) such as, dacarbazine, bleomycin, mitomycin, mitoxantrone (Table 1.1) (IRAC, 2020). Secondary tumor risks for patients receiving chemotherapy treatment have been

confirmed by several studies (Lyman et al., 2018). Relatively few studies have addressed the link between cancer occurrence and healthcare workers' exposures to cytotoxic agents. Skov et al. (1990) reported a nonsignificant increased risk of developing leukemia among physicians who handled chemotherapy (relative risk [RR] = 2.85; 95% CI = 0.51–16.02). A further study by the same group found a significant increase risk for leukemia among oncology nurses who handled cytotoxic agents (RR = 10.65; 95% CI = 1.29–38.5) (Skov et al., 1992). Ratner and colleagues (2010) have concluded that nurses potentially exposed to cytotoxic drugs through their employment had an increased risk of rectal and breast cancer (Ratner et al., 2010). However, a recent systematic review and meta-analysis reported that there was insufficient evidence to reach conclusions on occupational exposure to cytotoxic agents and cancer development (NTP, 2019).

1.7.6 KAP regarding safe handling of cytotoxic drugs

Due to the adverse health outcomes of exposure with cytotoxic drugs, organizations such as the International Society of Oncology Pharmacy Practitioners (ISOPP) (Connor et al., 2007), the CDC/National Institute for Occupational Safety and Health administration (NIOSH), the American Society of Hospital Pharmacist (ASHP), the US Oncology Nursing Society (Constantinidis et al., 2011), the American Society of Clinical Oncology (ASCO), and US Occupational Safety and Health Administration (OSHA) have recommended safe handling guidelines for cytotoxic drugs (Al-Azzam et al., 2015; Connor & McDiarmid, 2006). These guidelines recommend the application of the hierarchy of controls to mitigate workplace hazards, which include engineering controls, administrative controls, work practice controls, and Personal Protective Equipment (PPE) (Boiano et al., 2014). All healthcare workers

who work with cytotoxic drugs have also been advised to comply with these safety guidelines (Al-Azzam et al., 2015).

1.7.6.1 Knowledge regarding safe handling of cytotoxic drugs

The high levels of knowledge regarding cytotoxic drugs and their adverse health outcomes are critically important to improve healthcare workers' adherence to occupational preventive measures. Inadequate knowledge levels about handling of cytotoxic drugs, where observed in several studies. Polovich and Martin (2011) reported that only 32.7% nurses had sufficient knowledge concerning handling of cytotoxic drugs wording in a Turkey hospital (Polovich & Martin, 2011). A study of 60 Indian oncology nurses by Sarita et al. (2019) concluded that the level of nurses' knowledge regarding cytotoxic drugs was poor (Sarita et al., 2019). A study from Taiwan on evaluating nurses' knowledge of cytotoxic agents, found that most of the nurses (63.5%) had a knowledge score of less than 70% (Yu et al., 2013). Studies in Egypt also indicated that oncology nurses had insufficient knowledge regarding handling of cytotoxic drugs (Mohsen et al., 2011; Bolbol et al., 2016; Ibrahim et al., 2018). Similar results were found in studies that took place in Pakistan (Khan et al., 2012). In Saudi Arabia, a cross-sectional descriptive study was conducted to assess the knowledge of pharmacy staff and oncology nurses about safe handling of cytotoxic agents. Ibrahim et al. (2019) reported that there is a lack of knowledge among pharmacists, pharmacy technicians and oncology nurses about the risk of harm related to cytotoxic agents. In other studies, it was also found that the oncology nurses had adequate knowledge about the safe handling of cytotoxic drugs (Sheikh, 2016; Callahan et al., 2016).

1.7.6.2 Is knowledge applied in practice?

Existing evidence indicates that there is a mismatch between oncology healthcare workers' knowledge of occupational exposure risks and their actual practices while handling these agents (Boiano et al., 2014, 2015; Ben-Ami et al., 2001; Polovich & Clark, 2012). In other words, having sufficient knowledge about safe handling of cytotoxic drugs and their associated risks does not automatically generate commensurate precautionary action. For example, a study of 185 U.S oncology nurses by Polovich & Clark (2012) found that although perceived risk of harm from CDs exposure, self-efficacy for using PPE, and exposure knowledge were high, total precaution use during CDs handling was low. Another study from US concluded that oncology nurses had high exposure knowledge. However, total mean CD safety precaution use demonstrated greatest while CD administration and least for handling patient excreta at 48 hrs (Callahan et al., 2016). In 2017, DeJoy and colleagues examined the predictors of consistent PPE use, safe-handling components, and adverse events associated with CD exposure in 1,814 nurses and revealed that adherence to CD safe handling guidelines is inconsistent (DeJoy et al., 2017). A recent study conducted in Egypt hospitals to assess the KAP of oncology nursing staff towards the safe handling of CDs reported that nurses' knowledge was satisfactory but there was inadequate practice of safe handling of CDs and defective implementation of guidelines (Zayed et al., 2019). Similar findings were also reported by Al-Azzam et al. (2015). The authors evaluated the compliance of 252 healthcare workers with safe handling guidelines of cytotoxic drugs in Jordanian hospitals and revealed that 46.4% of HCWs reported full knowledge and compliance with the guidelines. However, only 10.7% reported full compliance with eye protection (goggles), hair cover, and shoe cover (Al-Azzam et al., 2015). Table 1.3 represents KAP studies towards handling of

CDs in the MENA region. All in all, 40% of these studies demonstrated that the HCWs' knowledge on handling of CDs was not satisfactory.

Table 1.3: KAP studies towards handling of cytotoxic drugs in the MENA region

Region	Country	Author(s)	Year of publication	Study purpose	Geographic area and time frame	Population	Sample size	Main results
Middle East	KSA	Ibrahim N, Al Mutairi M, & Al Onazi M.	2019	Assess the knowledge of pharmacy staff and oncology nurses about safe handling of oral CDs	KSA, Riyadh Jul.-Sept. 2014	Pharmacists, pharmacy technicians and oncology nurses	1000	Lack of knowledge among oncology HCWs regarding the risk of harm related to oral CDs versus intravenous form of cytotoxics.
	Jordan	Al-Azaam et al.	2015	Evaluate the compliance of HCWs with standard safety guidelines during the preparation and administrations of CDs.	Jordan Nov. 2011-Mar. 2012	HCWs form 15 Hospitals (pharmacists, pharmacy technicians, and nurses)	252	46.4% of participants reported full compliance with healthcare workers' guidelines. 10.7% of participants reported full compliance with PPE use
	Iraq	Hussein D. & Omed H.	2018	Assess nurses' knowledge concerning safe CDs administration	Iraq, Kirkuk Feb.-Sept. 2017	Nurses	40	Nurses' knowledge regarding to safe CDs administration was inadequate
	Iraq	Esmail et al.	2016	Evaluate knowledge and practices of nurses for safe handling CDs	Iraq, Erbil Jun.-Oct. 2015	Nurses	27	Majority of nurses were fair knowledge and practices of safe handling CDs. There was significant negative association between knowledge and practices (r=-0.469, p=0.014)
	Israel	Ben-Ami et al.	2001	Examine the influence of the nurses' knowledge, attitudes, and health beliefs on their behavior and their actual usage of safety measures while handling CDs	Israel	Nurses	61	A gap was found between the nurses' knowledge and their actual behavior concerning the potential risks of cytotoxic drugs and their use of PPE ($p < .005$)

Table 1.3: KAP studies towards handling of cytotoxic drugs in the MENA region (Continued)

Region	Country	Author(s)	Year of publication	Study purpose	Geographic area and time frame	Population	Sample size	Main results
	Iran	Alehasem M & Baniasadi S	2018	Assess the KAP of oncology nurses towards the safe handling of CDs as well determine the educational needs for the promotion of safe behaviours	Iran Nov. 2014-Aug. 2015	Nurses	80	The KAP scores of oncology nurses on the safe handling of CDs were fairly satisfactory.
	Iran	Orujlu et al.	2016	Evaluate the KAP of oncology nurses	Iran Jun.-Aug. 2015	Nurses	54	All nurses prepared CDs in BSC but 85.5% and 37% of nurses used the eye and respirator protection while drug preparation. The mean score of knowledge, attitude, and performance of nurses was 9.43±1.5 out of 12, 39.14±6.5 out of 60, and 13.41±4.7 out of 23, respectively.
	Iran	Shahrasbi et al.	2014	Evaluate the KAP of nurses' handling CDs	Tehran	Nurses	225	Nurses' level of knowledge was satisfactory, but the usages of safety measures are not in line with guidelines recommendations
	Turkey	Kyprianou et al.	2010	Evaluate the knowledge, attitudes and safe behaviours of nurses' handling cytotoxic drugs	Nicosia	Nurses	88	The mean score of the participants' knowledge was 79.43 out of 100. Most of the participants reported high levels of compliance with the use of PPE

Table 1.3: KAP studies towards handling of cytotoxic drugs in the MENA region (Continued)

Region	Country	Author(s)	Year of publication	Study purpose	Geographic area and time frame	Population	Sample size	Main results
	Turkey	Türk et al.	2004	Evaluate the KAP of nurses' handling CDs	Turkey, Ege Feb. 2003	Nurses	120	Nurses' level of knowledge was not satisfactory. Nurses' safety behaviours and usage of recommended health safety measures showed that, not with the rules and regulations related to CDs
North Africa	Egypt	Zayed et al.	2019	Assess the KAP of oncology nursing staff towards the safe handling of CDs	Egypt, Tanta From Feb. to April. 2018	Oncology nursing staff	55	The total KAP scores of nurses towards the safe handling of CDs were satisfactory among 63.6% of the studied group. Defective use of PPE
	Egypt	Ibrahim A., Zain Eldin Y. & Mohamed, E.	2018	Investigate Oncology Nurses' Knowledge About Handling of CDs	Egypt, Damanhour	Nurses	52	Nurses' level of knowledge was very low (less than 50%).
	Egypt	Mahdy N, Rahman A, & Hassan H.	2017	Evaluate the effect of CDs safety guidelines on KAP of oncology nurses	Egypt, Cairo	Nurses	65	There were highly statistically significant differences between mean scores of the pre and post guidelines intervention of nurses' KAP towards safe handling of CDs.
	Egypt	Bolbol et al.	2016	Evaluate the effect of health education program on improving the knowledge and practice of nurses exposed to CDs.	Egypt, Zagazig Jun.-Dec. 2014	Nurses	50	The level of knowledge of nurses about CDs was not satisfactory. However, there was a significant improvement of knowledge and practices among the studied nurses handling CDs following intervention
	Egypt	Waheida S.M, Abd-ELgaffar S.I, & Atia G. A.	2015	Evaluate the nurse's practice during CDs preparation and administration	Egypt, Menofia Jul.-Dec. 2012	Nurses	30	The nurses did not comply with recommended safety behavior due to workload, lack of knowledge and lack of equipment and facilities

1.7.6.3 Factors influencing adoption of protective behaviours

According to the literature, major reported factors influencing oncology healthcare workers to adhere to PPE use and other safety measures include, but are not limited to, knowledge of health hazards implicated when handling cytotoxics, comfortability of Personal Protective Equipment (PPE) (Boiano et al., 2014; Callahan et al., 2016), belief (Ali et al., 2015; Topçu & Beşer, 2017), and workload (He et al., 2017). Other reasons cited include availability, and access to protective equipment (Boiano et al., 2014). Callahan et al. (2016) have also reported a conflict of interest between caring for the patient and adhering to safe-handling recommendations. A study by Kim et al. (2019) concluded that the workplace safety climate, particularly feedback/training and the absence of job hindrances, are significantly associate with adherence to the safety guidelines for cytotoxics administration (Kim et al., 2019). In a recent study, Lin et al. (2019) performed an integrative literature review, ultimately finding that perceived barriers to PPE use, perceived safety climate, and work pressure were common factors related to the use of CDs safe handling precautions (Lin et al., 2019).

1.7.6.4 Education and training

Education refers to offering information, whereas training is defined as forming by “discipline, instruction, or drill” (Mish, 2004). Education and training of healthcare workers handling cytotoxic drugs are crucial to improve adherence to safe handling guidelines and cytotoxic drugs precaution in general (Polovich & Clark, 2012; Chan et al., 2013; Hennessy & Dynan, 2014; Al-Azzam et al., 2015; Crickman & Finnell, 2017). A published study by Silver and his colleagues found that training in CDs safe handling practices were associated with more reported PPE use (Silver et

al., 2016). A cross sectional study of 163 oncology healthcare workers indicated that PPE use was lower than recommended and improved slightly following the intervention (Graeve et al., 2017). Similar results were noted in other studies conducted in Asia (Keat et al., 2013; Shrestha et al., 2015). For example, a Malaysian study by Keat et al. (2013) revealed the mean score of nurses' knowledge raised from 45.5 to 73.7 out of 100 after completion of pharmacist-base intervention that includes courses and training programs, and guideline update (Keat et al., 2013). Another interventional study among two Pakistani hospitals highlighted that although nurses' knowledge about chemotherapy administration and management improved following the intervention, there was no significant change in their attitudes (Khan et al., 2012). A short educational course in Iran was designed in 2013 for evaluating the effect of this course on nurses' knowledge and attitude. Data revealed that nurses significantly improved their knowledge and attitude after the intervention (Kermani et al., 2015). Also, Samir et al. (2016) carried out a study on thirty Egyptian oncology nurses to assess the impact of a tailored teaching program concerning the safe handling of cytotoxic drugs. They found significant differences in nurses' knowledge and performance mean scores between the pre-test and post-test (Samir et al., 2016). However, other experts disagree with these results. A recent randomized controlled trial study, from 2015 to 2017, involved 12 ambulatory oncology settings in the United States and included 396 nurses who handled cytotoxic drugs. In this study, 136 nurses in control settings received a one-hour educational module on PPE use with quarterly reminders, while 121 nurses in the treatment setting received the control intervention plus tailored messages to address perceived barriers and quarterly data gathered on hazardous drug spills across all study settings. However, the intervention did not enhance compliance among nurses. Therefore, the authors suggested that nurse leaders

should standardize education and hazardous drugs policies/procedures and enforce personal accountability regarding safe handling processes and PPE use (Friese et al., 2019).

An association between knowledge and practice has been reported in some studies. A Cypriot study indicated that nurses who had higher knowledge scores reported using at least one personal protective equipment significantly more frequently than the nurses who had lower knowledge scores (Kyprianou et al., 2010). A recent study by Simegn and others has also shown a consistent association between knowledge and practice (Simegn et al., 2020). However, in a study of safe handling knowledge and practices of CDs among oncology nurses in Erbil city in Iraq, results from the study indicated a significant negative association between knowledge and practices ($r=-0.469$, $p=0.014$). Moreover, the study showed that a significant negative association existed between practices and barriers to PPE compliance ($r = 0.475$; $P = 0.012$) (Esmail et al., 2016).

In the United Arab Emirates (UAE), there has been no previous study evaluating oncology healthcare workers' KAP of on the handling of cytotoxic medications. Therefore, the KAP study's objective was to assess the knowledge, attitudes and practices of oncology nurses and pharmacists regarding the safe handling of cytotoxic drugs.

Chapter 2: Methods

2.1 Introduction

This chapter describes the methodology and research design used in the study. The research aims to fulfil the following objectives: develop a protocol for a systematic review and meta-analysis on environmental assessment of cytotoxic drugs in healthcare settings and assess the potential workplace contamination of the oncology departments of Abu Dhabi with the most widely used cytotoxic drugs. The research additionally aims to evaluate the level of KAP of Abu Dhabi healthcare professionals regarding safe handling of cytotoxic drugs.

To find answers to the research questions of the research, the researcher included the following three studies: study no. 1: environmental assessment of cytotoxic drugs in healthcare settings: protocol for a systematic review and meta-analysis, study no. 2: environmental assessment of cytotoxic drugs in oncology department of UAE hospitals; and study no. 3: KAP of oncology healthcare professionals on the handling of cytotoxic drugs.

2.2 Study No. 1: Environmental assessment of cytotoxic drugs in healthcare settings: protocol for a systematic review and meta-analysis

2.2.1 Data synthesis

The review to be carried out following this protocol will be reported in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Liberati et al., 2009).

2.2.1.1 Outcome

The main outcome measure in the study will be the pooled prevalence of positive samples of cytotoxic drugs in the tested environmental samples, and the mean concentration of cytotoxic drugs in environmental samples collected from healthcare settings.

2.2.1.2 Protocol design and registration

The development of this protocol is in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA-P) guidelines (Appendix A) (Moher et al., 2015). The protocol was registered (ID CRD42020162780) on The International Prospective Register of Systematic Reviews (PROSPERO). Registration reduces duplication of reviews and provides transparency in the review process, with the aim of minimizing reporting bias. In Table 1.1, an indicative International Agency is provided for Research on Cancer (IARC) classification of cytotoxic drugs that have been adopted and will be used in this planned review (IARC, 2019; Fransman, 2006).

2.2.1.3 Eligibility criteria

Studies will be included that are conducted in healthcare settings with no restriction on publication or study period. All studies including samples from settings involved in the preparation, transport, administration, and waste disposal of cytotoxic drugs, will be considered. It will also consider healthcare settings in which these settings are exposed to cytotoxic drugs as participants with regards to outcomes such as surface contamination and aerosol contamination. Eligible studies should report quantitative data on the prevalence of positive samples and/or the concentration of the

detected cytotoxic drugs in the positive samples. A positive sample would be defined as a sample with cytotoxic drugs above the level of detection limit of cytotoxic drugs (Chauchat et al., 2018). Studies reporting on calculated prevalence or those presenting data that would allow to calculate the prevalence or concentration of cytotoxic drugs in the collected environmental samples will be included. No restrictions on study design will be applied. It will include only articles reported in the English language.

Studies will be excluded if are not conducted in healthcare settings such as those conducted in university laboratories, drug manufacturing companies and/or veterinary facilites. Studies that do not provide quantitative information on the prevalence or the concentration of positive environmental samples of cytotoxic drug residues will be not be deemed eligible for inclusion.

2.2.1.4 Search strategy and searching sources

A comprehensive systematic search in PubMed, Web of Science (Core Collection), Scopus, Cochrane Library, CINAHL, Embase and in sources for grey literature will be conducted. The search strategy will be developed by the researcher under the guidance of an experienced librarian. PubMed and PubMed's MeSH will be used to systematically develop a comprehensive search string. All search terms will be searched in a combination of title, abstract and MeSH/Thesaurus (when available) to ensure best possible information retrieval. A filter for English language will be applied. All publication years and publication types will be included. A detailed search log with transparent and reproducible search stings, results and search variation notes for all included databases and sources for grey literature will be developed and reported. A preliminary search strategy conducted in PubMed is available in Appendix B. Hand

searching of the reference lists for studies that might been potentially missed will be conducted.

2.2.1.5 Study selection

All citations identified through the literature search will be imported into the systematic review software "Covidence" (Covidence, 2021) for deduplication and blinded screening. Two independent reviewers will screen titles and abstracts of the retrieved citations to exclude all ineligible studies against the pre-set inclusion criteria. Full texts of the eligible and potentially eligible studies will be thoroughly assessed for eligibility by at least two independent reviewers. Disagreements will be resolved through discussion and consensus after consulting a third reviewer whenever necessary. The corresponding authors of eligible articles will be contacted for clarification whenever needed. It will record all reasons for the exclusion and report the study selection process using the PRISMA flow diagram (Liberati et al., 2009).

2.2.1.6 Data extraction

For studies found eligible to be included in the systematic review, relevant data will be extracted into a predefined data extraction form, which will first be piloted using five eligible studies. Data will be extracted by at least two reviewers. Data to be extracted from each eligible study will include baseline and methodological data. It will extract information related to the authors' names, publication year, country, studied cytotoxic drugs, sample size, sampling locations, sampling year (s), analytical tool, the sensitivity of contaminant measurements [Limit of Detection (LOD) or Limit of Quantitation (LOQ)] (Connor et al., 2016), number of tested samples, number of positive samples, and mean concentration of the tested cytotoxic drugs in the tested

samples. List of variables to be extracted from eligible studies are provided in Appendix C.

2.2.1.7 Quality and risk of bias assessment

At least two reviewers will independently evaluate and assess the methodological quality of the eligible studies. If required, the authors of the studies will be contacted to request missing or additional data for explanation. Disagreements between the reviewers will be resolved by discourse. The results will be reported in narrative form and summarized in tables.

The risk of bias ROB of the included studies will be assessed using the ROB in Studies estimating Prevalence of exposure to Occupational risk factors (RoB-SPEO) tool developed by the World Health Organization (WHO) and the International Labour Organization (ILO) for studies of the prevalence of exposure to occupational risk factors (Pega et al., 2020). It will assess RoB on the levels of each individual study and the entire body of evidence overall. It will resolve any disagreements by discussion. The RoB will be assessed according to the following domains: (i) selection bias; (ii) performance bias; (iii) misclassification bias; (iv) conflict of interest; and (v) other biases. Categorization of bias will be: "low"; "probably low"; "probably high"; "high" or "not applicable".

2.2.1.8 Quality of evidence

The quality of evidence of the included studies will be assessed using the quality and strength of evidence ratings proposed by the Navigation Guide as a framework. It will decrease, or not, the quality level of the body of evidence based on the (i) RoB across studies, (ii) indirectness of the evidence, (iii) inconsistency, (iv)

imprecision, and (v) publication bias (Woodruff & Sutton, 2014; Lam et al., 2016). It will grade the evidence, using the three Navigation Guide quality of evidence ratings: “high”, “moderate” and “low” (Lam et al., 2016). Within each of the relevant reasons for downgrading, it will rate any concern per reason as “none”, “serious” or “very serious”.

2.2.2 Synthesis of evidence: meta-analysis

2.2.2.1 Pooled weighted measures

A quantitative synthesis approach will be provided to report the prevalence of cytotoxic drugs contamination in environmental samples collected from healthcare settings. To estimate the pooled prevalence, a meta-analysis will be conducted using a random-effects model to estimate the pooled prevalence of positive samples for the tested cytotoxic contamination. The *metaprop* command will be used to perform a meta-analysis of the prevalence estimates (Nyaga et al., 2014). To estimate the mean concentration of cytotoxic drugs in the tested environmental samples in healthcare settings, A meta-analysis will be conducted using a random-effects model. The *metan* command will be used to perform meta-analysis of cytotoxic drugs concentration in the tested samples. The pooled measures will be weighted using the inverse variance method (Freeman & Tukey, 1950). For each pooled estimate and its 95% Confidence Interval (CI), a forest plot will be created to show the estimated overall weighted prevalence/weighted mean concentration and its corresponding 95% CI for each study following the Cochrane guidelines (Higgins et al., 2019).

2.2.2.2 Subgroup analyses

Depending on data availability, it expects to conduct subgroup analyses stratifying by geographical regions, time periods, type of the tested cytotoxic drugs, study settings, sample locations, and quality/bias assessment classifications. Subgroup analyses will also be conducted based on study quality.

2.3 Study No. 2: Environmental assessment of cytotoxic drugs in oncology departments of UAE hospitals

2.3.1 Study area and study period

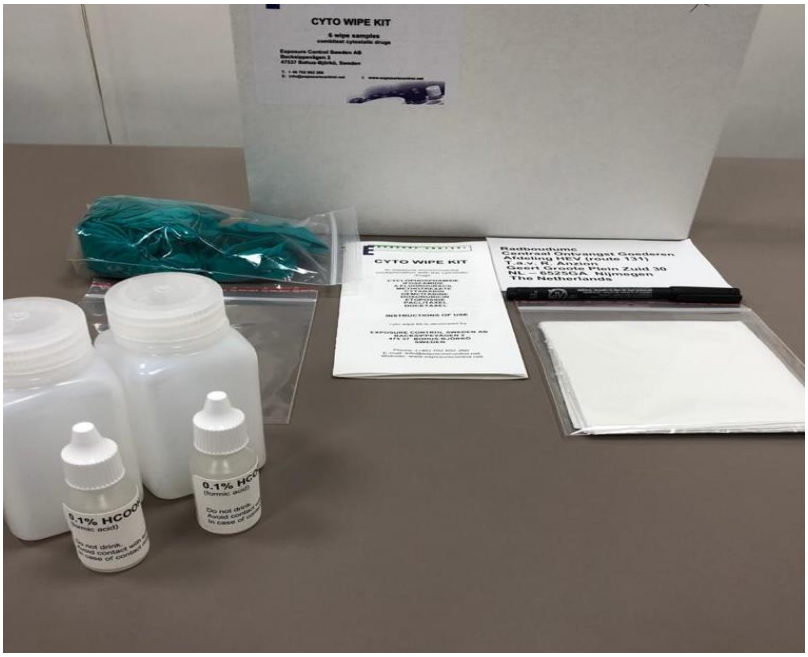
The study was conducted in two hospitals (referred to as Hospital A and B) in March 8 and 9, 2020 in the emirate of Abu Dhabi, which is the capital of the United Arab Emirates (UAE). Both hospitals have 150 and 200 beds, in hospitals A and B, respectively. The workforce of the oncology departments is 150 and 60 employees for Hospital A and B, respectively. Hospital A provides treatment to about 50 outpatient cancer patients on a daily basis, while Hospital B provides daily treatment to about 30 cancer patients. Both hospitals maintain inpatient cancer care facilities, a central pharmacy, as well as outpatient day-care facilities. Preparation of cytotoxic drugs is performed by trained pharmacists in a specifically designed unit equipped with biological safety cabinets that are externally vented. The study was conducted in cooperation with the respective management and health professionals of both hospitals.

2.3.2 Wipe sample collection

Because of the limited budget, wipe samples were taken from 40 workplace surfaces from Hospital A and 39 samples from Hospital B and tested for a total of 10 different cytotoxic drugs. The wipe samples were taken using the Cyto Wipe Kits from

Exposure Control AB (Figure 2.1) Monitoring and Consultancy in The Netherlands (Sessink, Anzion et al., 1992). The selected 10 cytotoxic drugs were determined to be the agents more frequently used in the treatment of cancer patients.

(a)



(b)

Figure 2.1: Cyto Wipe Kit was used for surface wipe sampling. (Exposure Control Sweden AB, Bohus-Björkö, Sweden). (a) Cyto Wipe Kit (b) Kit contents. This wipe kit includes the materials necessary to take 6 wipe samples, it contains: 6 x 2= 12 tissues, 6 droppers with 17 ml 0.1% HCOOH (formic acid) solution, 6 containers including labels and plastic mini bags, 6 pair of gloves, registration form, label with the address of the lab of Exposure Control Sweden AB in The Netherlands, Waterproof pen, and instruction of use.

Samples were obtained from all departments of the oncology centers (oncology pharmacy, in-patient wards, and out-patient wards). The selected sampling spots were judged to be the surfaces more potentially contaminated and, simultaneously, more frequently touched by the health professionals in the course of their daily duties. Among the several sites, a set of these were defined as common to the 2 hospitals. The selected common sites are shown in Table 2.1.

Table 2.1: Common sampling sites selected in the 2 hospital centers

Site	Oncology pharmacy	In-patient wards & Out-patient wards
1	Surface of Biological Safety Cabinet (BSC)	Nurse station
2	Chair of BSC	Computer keyboard
3	Refrigerator Handle	Floor near nurse station
4	Checking Counter/Trolley	Chemo receiving countertop/trolley
5	Floor near checking counter	Chemo pump
6	Storage bin	Waste top bin
7	IV bag prepared	Patient arm chair
8	Drug Vial Outside	Door Handle Toilet room
9	Computer Keyboard	Computer mouse
10	Telephone Handle	Patient bed
11	Chemo Transport Box/Cooler	Floor near chemo pump
12		Toilet floor-Patient room

Wipe samples were collected in March 8 and 9, 2020 by one person from both hospitals. Samples were taken during the entire working day before cleaning. Approximately similar locations were chosen in both oncology centers to allow

comparison. Collection of the wipe samples was performed in the following manner. Each predetermined sampling location was marked with colored tape and measured to determine the sample area. The actual size of the sampled areas is presented in Tables 3.1 and 3.2. A new pair of latex gloves was donned for each wipe sample. The surface wipe samples were collected by pouring the 0.1% HCOOH (formic acid) solution over the targeted sampling surface. Wipe samples were collected using a uniform sampling procedure by thoroughly wiping in multiple directions on the surfaces (Figure 2.2). Two wipe tissues were used in each sampling procedure. The tissues were then placed in the designated containers, which pre-labeled with the collection date and a coded number that identified the study site and sample location.

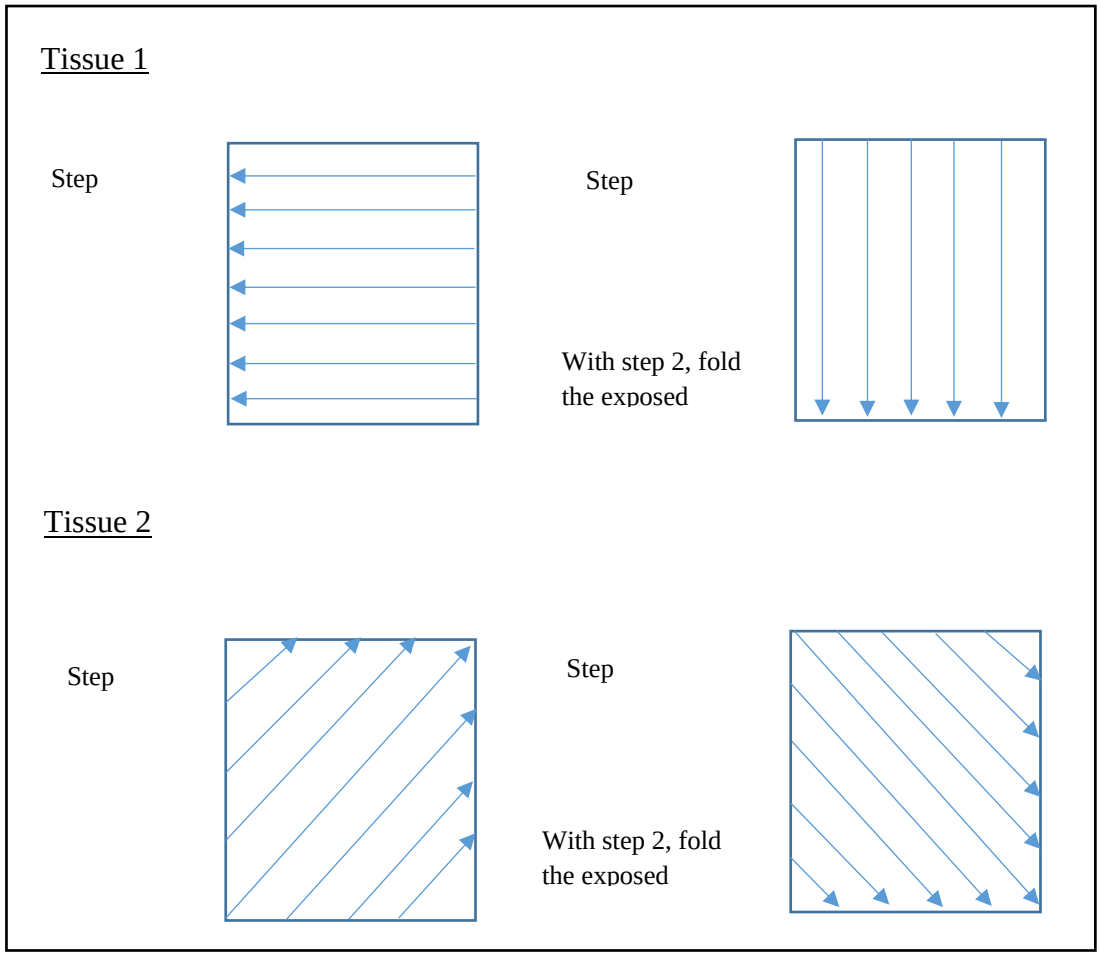


Figure 2.2: Wipe sampling schemes

2.3.3 Storage, transportation and analysis of samples

All collected samples were stored frozen at -20°C after sampling and covered with dry ice during transportation until sample preparation and analysis. All samples were sent to Exposure Control AB in the Netherlands, where analyses were performed. All samples were extracted before analysis by adding a 0.1% formic acid solution. The total extraction volume was 100 ml. Cyclophosphamide, cytarabine, docetaxel, doxorubicin, etoposide, 5-fluorouracil, gemcitabine, ifosfamide, methotrexate, and paclitaxel were analysed with Liquid Chromatography Tandem Mass Spectrometry (LC-MSMS). The detection limits for the analysis of cyclophosphamide, cytarabine, docetaxel, doxorubicin, gemcitabine, ifosfamide, and methotrexate were 0.01 ng/ml extract. For paclitaxel the detection limit was 0.2 ng/ml extract, and for etoposide and 5-fluorouracil 0.25 ng/ml extract. The contamination per square centimetre was calculated assuming a 100% recovery and wipe efficiency. Thus, all results should be considered as potential underestimates. Results were expressed in nanograms per millilitre (ng/ml) and converted to nanograms per centimetre squared (ng/cm^2). A sample was considered positive for a particular drug if the value was above the Limit of Detection (LOD) (Chauchat et al., 2018; Roland et al., 2016). Values not detected or less than the LOD were reported as ND.

2.3.4 Ethical considerations

The study was conducted in cooperation with the respective management and health professionals of both hospitals and was approved by the United Arab Emirates University Social Sciences Research Ethics Committee (ERS_2019_5982) (Appendix E) and the Abu Dhabi Health Research and Technology Committee from Abu Dhabi Department of Health (ADHRTC-10/2019-1) (Appendix F).

2.4 Study No. 3: Knowledge, attitudes and practices of oncology healthcare professionals on the handling of cytotoxic drugs

2.4.1 Study design, settings, population, and duration

A quantitative cross-sectional survey using a self-administered questionnaire was conducted to evaluate the knowledge, attitudes and practices of oncology nurses and pharmacists regarding the handling of cytotoxic drugs in three hospitals in the Emirate of Abu Dhabi. The first two were public hospitals and the third was a private hospital. The three hospitals have a combined total of 350 beds. To achieve the study aim, a self-administered questionnaire was adopted. This technique has the advantage of being easily applied to a large number of participants within a short time period, minimizing interviewer bias (WHO, 2017). The study population was all pharmacists and nurses were involved handling cytotoxic drugs during the study period and fulfilled the inclusion criteria. The actual data collection period was from May 11th to July 1st 2020. A flowchart of the hospitals selections and study participants is depicted in Figure 2.3.

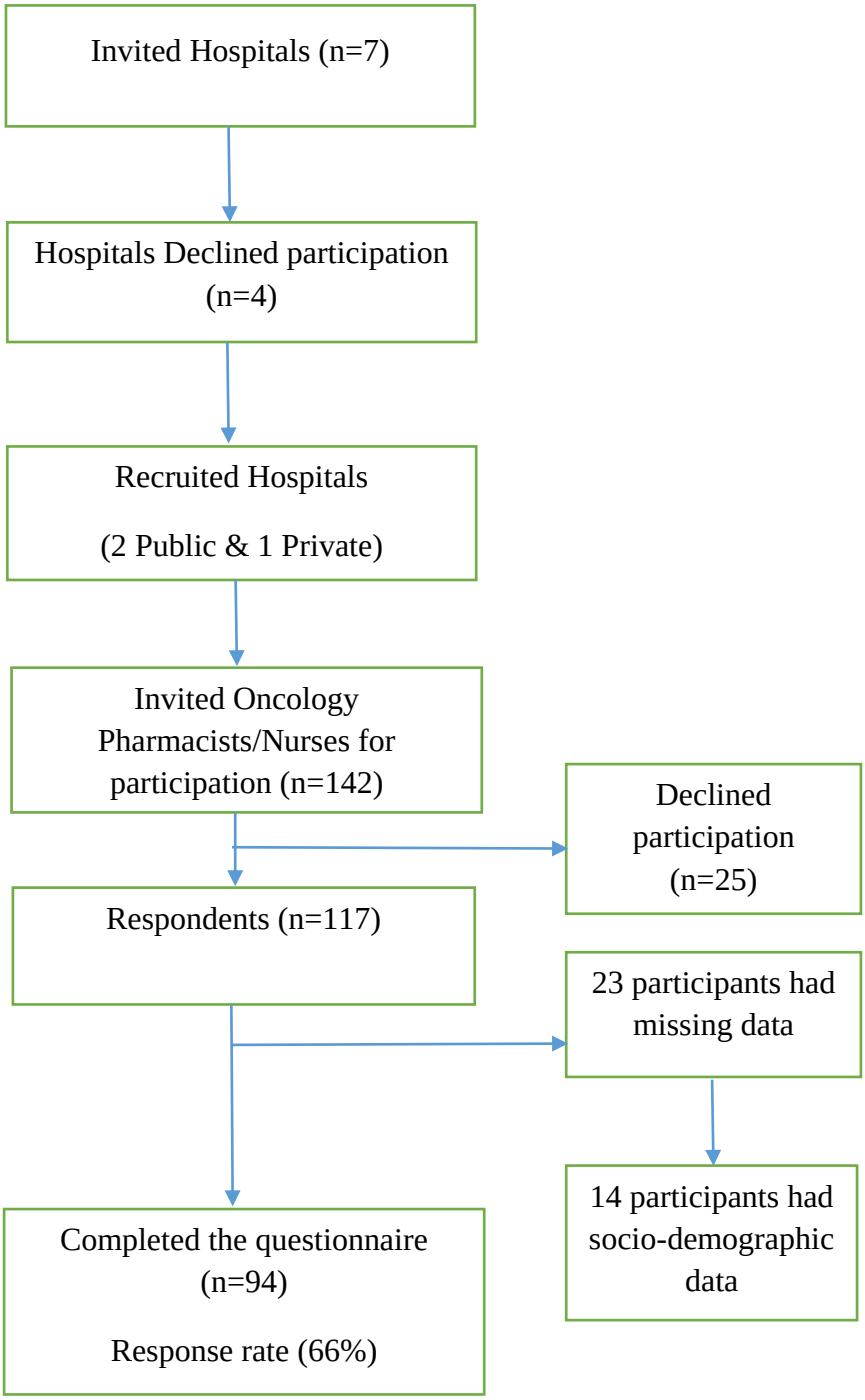


Figure 2.3: Flowchart diagram of selection of Hospitals and study participants

2.4.2 Sample size determination

The target group was all nurses and pharmacists (142 staff) working and handling cytotoxic drugs in the oncology department of sampled hospitals were eligible for inclusion.

2.4.3 Inclusion and exclusion criteria

Inclusion criteria

All pharmacists and nurses who were involved in handling cytotoxic drugs with work experience in Oncology department equal to or more than six months at the same hospital, and those who were willing to participate in the study.

Exclusion criteria

Nurses and Pharmacists who were not involved in handling of cytotoxic drugs, and those with work experience less than six months. Additionally, those were unable or not willing to take part and provide consent were excluded from the study. Physicians were excluded.

2.4.4 Sampling strategy

The study population included nurses and pharmacists with job titled registered nurse, assistant nurse, nurse practitioner, specialty nurse, pharmacists, clinical pharmacists and pharmacy technicians who hold a valid license from the Department of Health (DOH). Census sampling approach was used to recruit all eligible participants. Respondents recruitment was conducted by sending survey invitations containing general information about the survey, including its purpose, Participants' eligibility criteria, and the survey link to oncology departments heads in order to share it with all eligible participants. All nurses and pharmacists who were handling cytotoxic drugs were invited to participate in the study.

2.4.5 Data collection tool

Given the COVID-19 pandemic social distancing measures, restricted movement and lockdowns, data were collected online using SurveyMonkey platform. A previously validated questionnaire (Kyprianou et al., 2010) was used in this study to evaluate the KAP of oncology pharmacists and nurses towards the handling of cytotoxic drugs. This questionnaire was originally developed, validated and first used by Turk et al. (2004), to evaluate the knowledge, attitudes and safe behaviours of nurses' handling of cytotoxic drugs. The questionnaire (Appendix D) used in this study was conducted in English and comprised of two parts: socio-demographics characteristics, and KAP towards handling of cytotoxic drugs. Questions related to the activities pharmacists/nurses involved in and the adverse health effects due to chemotherapeutic exposure, safety challenges, management support and workers involvement in safety issues were added to the original tool. The demographic variables included age, gender, occupation, level of education, marital status, smoking status, years of work experience, years of experience in handling cytotoxic drugs, and training history. The KAP part consisted of 3 sections. These included:

- Knowledge

This section aimed at evaluating the practitioners' knowledge regarding health effects, ways of exposure to cytotoxic drugs and personal protective equipment use and consisted of 25 multiple choice questions. The questionnaire included four thematic areas namely: general knowledge, health effects of cytotoxic medications, knowledge about protection, and exposure methods. Each question was given options of "right", "wrong" and "do not know". Each correct answer received a score of four, yielding a maximum possible score of 100. The mean score was subsequently used as

a cut-off point in order to rank the level of knowledge into above average (scores above the mean (adequate knowledge)), and below average (scores below the mean (inadequate knowledge) scores.

- Attitudes

This section included 2 questions, which assessed their opinion on the management support and workers' involvement in safety issues. For attitudes questions, scores were calculated based on the respondents' answers to each statement, 0= don't know, 1=strongly disagree, 2=disagree, 3=agree, and 4=strongly agree. Total score ranged from 0 to 8, with high score indicating positive attitude.

- Practices

This section included 8 questions, which assessed the participants' practices towards handling of cytotoxic drugs using multiple-choice question, and a Likert scale. The items were related to practices (behaviour) and adherence to protective measures implemented by the pharmacists and nurses such as no smoking, eating, drinking, storing beverages and edibles or using make up at areas of drug handling, wearing PPE during handling of cytotoxic drugs, hand hygiene and disposal of cytotoxic waste. In this section, question-related to PPE use, each item was given one score and zero for 'None of the above'. The statements for options very often/always, often, sometimes, rarely, never were scored as 4, 3, 2, 1, and 0, respectively. Regarding the statement related to the disposal of cytotoxic waste, individual answer received a score of four for correct response and 0 for incorrect. Total practices score of 34. The mean score was subsequently used as a cut-off point to rank the level of practices into above

average (scores above the mean (good practice)), and below-average (scores below the mean (bad practices) scores.

2.4.6 Validity and reliability of the research questionnaire

The questionnaire was thoroughly reviewed by an expert panel. The purpose of this content validation was to ensure the questions were not ambiguous and content was appropriate. Based on panel reviews, modifications were carried out with regard to arrangement and structure of questions. Moreover, to ensure reliability (internal consistency), the survey questionnaire was retested among a randomly selected group of oncology staff (n=10) and revised based on their comments.

2.4.7 Study variables

Independent variables and dependent variables are summarized in Table 2.2.

Table 2.2: Summary of the independent and dependent variables

Variable	Variable type	How it will be measured
a. Demographic variables (oncology healthcare professionals)		
Age	Interval	26-30 years/ 31-35years/ 36-40 years/ 41-45 years/ 46-50 years/ >50 years
Gender	Binary	Male or female
Marital status	Nominal	Single/Married/Widowed
Smoking	Binary	Yes/no
Educational level	Categorical	Diploma certificate/Bachelor's degree/ Master's degree/ Doctorate's degree
Occupation	Categorical	Clinical pharmacists/ pharmacists/pharmacy technician/ registered nurse/speciality nurse/ nurse practitioner/ assistant nurse
Years of work experience (years)	Discrete	<2 years/2-5 years/ 6-10 years/ 11-15 years/ 16-20 years/ >20 years
Years of experience in handling CDs (years)	Discrete	<2 years/2-5 years/ 6-10 years/ 11-15 years/ 16-20 years/ >20 years
Working schedule	Nominal	Shifts/ regular work hours (daily)
Training	Binary	Yes/no
b. Acute side effects related to CDs exposure		
Acute side effects	Nominal	Headache/ Throat irritation/ Eye irritation/ Hair loss/ Skin irritation/ mucous membrane/ Nausea/ Vomiting/ Abdominal pain/ Dizziness

Table 2.2: Summary of the independent and dependent variables (continued)

Variable	Variable type	How it will be measured
c. Frequency of handling CDs		
Frequency of handling CDs per week	Discrete	1 day per week/ 2 day per week/3 days per week/ everyday
Number of CDs handled per day	Discrete	1 drug per day/ 2-5 drugs per day/ 6-10 drugs per day/more than 10 drugs per day
d. Attitudes of oncology healthcare professionals towards handling of CDs		
Employee involvement in Health and Safety matters	Ordinal	Don't know/ Strongly disagree/ Disagree/ Agree/ Strongly agree
Employer commitment to health and safety	Ordinal	Don't know/ Strongly disagree/ Disagree/ Agree/Strongly agree
e. Practices of oncology healthcare professionals towards handling of CDs		
Use of PPE during handling of CDs	Nominal	Gloves/Gown/Googles/Masks/Overshoes/ Head covers
Smoking at areas of drug handling	Ordinal	Never/Rarely/Sometimes/Often/Very often
Eating at areas of drug handling	Ordinal	Never/Rarely/Sometimes/Often/Very often
Drinking at areas of drug handling	Ordinal	Never/Rarely/Sometimes/Often/Very often
Storing beverages and edibles at areas of drug handling	Ordinal	Never/Rarely/Sometimes/Often/Very often
Using makeup at areas of drug handling	Ordinal	Never/Rarely/Sometimes/Often/Very often
Washing hands thoroughly after handling CDs	Ordinal	Never/Rarely/Sometimes/Often/Always
Dispose cytotoxic waste correctly	Ordinal	In a regular container/ In a special container for hospital waste/ In a special container for cytotoxic drugs/Others
f. Challenges		
Challenges	Nominal	High workload/ Lack of access to PPE/ Lack of knowledge/ PPE discomfort/ Low workload/ Others
g. Training		
Training sources	Nominal	Seminar & conferences/ Hospital administration/ Professional organization/ Scientific literature/ Internet/ Mass media/ Others
h. Knowledge of oncology healthcare professionals toward safe handling of CDs		
knowledge	Nominal	Right/Wrong/Do not know
Availability of safe handling procedure	Nominal	Yes/No/I don't know

2.4.8 Data analysis

Outcome Variable - Knowledge score: A continuous variable was created by summing the correct answers from questions 39 – 63 (Appendix D) and multiplying by 4 (25 questions each worth 4 points for a maximum of 100). A dichotomous variable of knowledge score was also created using the mean score ($\leq 74 = 0$, $>74 = 1$).

Dependent variables: All variables studied were dichotomous with values of zero and 1. Several dummy variables (0 or 1) were created for questions that had more than two answers.

Data from the Survey Monkey program were exported to Microsoft Excel directly from the online survey. Data were analyzed using SPSS (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp). In this study two approaches (descriptive and analytical) were used for data analysis.

Descriptive approach: Used to describe the frequencies and percentages for all questions (variables) in the study questionnaire (Appendix D).

Analytical approach: This was created to determine the differences in participants' responses across the dichotomous knowledge score. The Chi-Square test was used to test for association among dichotomous variables. A Fisher's Exact test of independence was calculated in cases where samples were small (expected frequency of cell size less than 5). Multivariable logistic regression analysis was performed to assess the association between knowledge score (dichotomous outcome variable) and selected correlates (independent variables). Statistical significance was set at $\alpha=0.05$.

2.4.9 Ethical considerations

Ethical approval was obtained from the United Arab Emirates University Social Sciences Research Ethics Committee (ERS_2019_5982) (Appendix E) and the Abu Dhabi Health Research and Technology Committee from the Abu Dhabi Department of Health (ADHRTC-10/2019-1) (Appendix F). Informed consent is the most essential part of research ethics. Due to Covid-19 pandemic, survey respondents consented to participate in the KAP study by completing the electronic informed consent, which embedded at the beginning of the questionnaire. The confidentiality was maintained throughout the study.

2.4.10 Operational definitions

Knowledge: is the information and the concepts that oncology healthcare professionals have regarding to handling of cytotoxic drugs.

Attitude: is the perception and internal feeling that oncology healthcare professionals possess towards handling of cytotoxic drugs, which maybe positive or negative attitude.

Practice: is the activities of oncology healthcare professionals regarding handling of cytotoxic drugs.

Chapter 3: Results

In this chapter, the main results of the three studies are presented in the following sections:

3.1 Study No. 1: Environmental assessment of cytotoxic drugs in healthcare settings: protocol for a systematic review and meta-analysis

The protocol was registered (Ref. 2020: CRD42020162780) on The International Prospective Register of Systematic Reviews (PROSPERO) and published on Systematic reviews on October 19, 2020 (Al Alawi et al., 2020).

3.2 Study No. 2: Environmental assessment of cytotoxic drugs in oncology departments of UAE Hospitals

A total of 79 samples were analyzed throughout the study. Of these, 20 samples (25%) were positive for cytotoxic drug residues. Moreover, 10 samples (13%) indicated contamination by more than one cytotoxic drug, mainly in the oncology pharmacy department in both hospitals. The levels of contamination in the positive samples ranged from 0.003 to 50 ng/cm^2. The results of the wipe sample analyses are presented in the Tables 3.1 and 3.2 for hospitals A and B, respectively.

3.2.1 Surface contamination in Hospital A

Table 3.1 presents the results from Hospital A, which showed surface contamination with cyclophosphamide, cytarabine, 5-fluorouracil, gemcitabine, and ifosfamide spread over four departments (oncology pharmacy, in-patient hematology, out-patient clinic and pediatric oncology in-patient care). However, there are large differences in the number of contaminated surfaces and the level of contamination between departments. The highest number of positive samples and the highest

contamination was observed in the oncology pharmacy, as expected. Overall, there were 15 positive samples out of 40 samples obtained showing 37.5% of contamination among the samples. The amount of contamination ranged from 0.003 to 12 ng/cm^2. A total of 40% (6/15) of the oncology pharmacy samples were positive for each of cytarabine and ifosfamide, 27% (4/15) were positive for cyclophosphamide and 20% (3/15) were positive for gemcitabine. A substantial level of contamination was found on the chair of the Biological Safety Cabinet (BSC) (cyclophosphamide 12 ng/cm^2, gemcitabine 3.24 ng/cm^2, and ifosfamide 8.53 ng/cm^2) followed by one of the BSCs (5-fluorouracil 4.78 ng/cm^2 and ifosfamide 1.01 ng/cm^2). Lower contamination was measured on the surface of the other BSC (gemcitabine 0.13 ng/cm^2 and ifosfamide 0.47 ng/cm^2), on the checking counter (ifosfamide 0.59 ng/cm^2), on the floor (cyclophosphamide 0.41 ng/cm^2) and on the refrigerator handle (ifosfamide 0.16 ng/cm^2). Contamination on the other surfaces was low or even non detectable. None of the ten cytotoxic drugs was found on any of the surfaces in the oncology in-patient department and the pediatric oncology-outpatient department.

3.2.2 Surface contamination in Hospital B

Table 3.2 delineate the results from Hospital B showing surface contamination with cyclophosphamide, cytarabine, 5-fluorouracil, ifosfamide and methotrexate in the oncology pharmacy department (Table 3.2). There was a total of five positive samples with a percentage of contamination at 13% (5/39) of the total oncology department's samples tested. The amount of contamination observed ranged from as low as 0.006 to 50 ng/cm^2. None of the ten cytotoxic drugs was detected on the surfaces in the oncology inpatient department, the inpatient hematology department, the outpatient clinic department, and in the pediatric oncology inpatient and outpatient departments.

Substantial contamination was found in the BSC (5-fluorouracil 50 ng/cm^2, ifosfamide 23 ng/cm^2, cyclophosphamide 4.83 ng/cm^2 and cytarabine 1.25 ng/cm^2) followed by the storage bin (ifosfmide 1.38 ng/cm^2). Lower contamination was observed on a prepared IV bag (cytarabine 0.51 ng/cm^2), on the chair in front of the BSC (methotrexate 0.38 ng/cm^2), and on the pharmacy storage bin (cytarabine 0.13 ng/cm^2). Contamination on the other surfaces was low or even non detectable. In 87.2% (34/39) of the wipe samples no antineoplastic were detected. No cytotoxic drugs were detected in blank samples, used for quality control.

Table 3.1: Results of a wipe-sample environmental assessment conducted on March 8, 2020. Evaluating potential contamination with Cyclophosphamide (CP), Cytarabine (CYT), Docetaxel (DOC), Doxorubicin (DOX), Etoposide (ETO), 5-Fluorouracil (5FU), Gemcitabine (GEM), Ifosphamide (IF), Methotrexate (MTX) and Paclitaxel (PAC) at Hospital A

Sample Code	Department	Description Surface	Surface Area (cm^2)	Total Volume NaOH (mL)	Contamination (ng/cm^2)									
					CP	CYT	DOC	DOX	ETO	5FU	GEM	IF	MTX	PAC
1	Oncology Pharmacy	Surface of Biological Safety Cabinet (BSC)	900	17	0.06	ND	ND	ND	ND	ND	0.13	0.47	ND	ND
2	Oncology Pharmacy	Chair of BSC	75	17	12	0.65	ND	ND	ND	ND	3.24	8.53	ND	ND
3	Oncology Pharmacy	Buffer Lock Room Handle	20	17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
4	Oncology Pharmacy	Refrigerator Handle	1035	17	0.004	ND	ND	ND	ND	ND	ND	0.16	ND	ND
5	Oncology Pharmacy	Checking Counter	900	17	ND	0.04	ND	ND	ND	ND	ND	0.59	ND	ND
6	Oncology Pharmacy	Floor	900	17	0.41	ND	ND	ND	ND	ND	ND	ND	ND	ND
7	Oncology Pharmacy	IV bag Prepared	117	17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
8	Oncology Pharmacy	Storage Bin	266	17	ND	0.06	ND	ND	ND	ND	ND	ND	ND	ND
9	Oncology Pharmacy	Drug Vial Outside	151	17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND

Table 3.1: Results of a wipe-sample environmental assessment conducted on March 8, 2020. Evaluating potential contamination with Cyclophosphamide (CP), Cytarabine (CYT), Docetaxel (DOC), Doxorubicin (DOX), Etoposide (ETO), 5-Fluorouracil (5FU), Gemcitabine (GEM), Ifosphamide (IF), Methotrexate (MTX) and Paclitaxel (PAC) at Hospital A (continued)

Sample Code	Department	Description Surface	Surface Area (cm^2)	Total Volume NaOH (mL)	Contamination (ng/cm^2)									
					CP	CYT	DOC	DOX	ETO	5FU	GEM	IF	MTX	PAC
10	Oncology Pharmacy	Computer Keyboard	736	17	ND	ND	ND	ND	ND	ND	ND	0.04	ND	ND
11	Oncology Pharmacy	Telephone Handle	125	17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
12	Oncology Pharmacy	Cooler Transport	660	17	ND	0.04	ND	ND	ND	ND	ND	ND	ND	ND
13	Oncology Pharmacy	Storage Shelves	1050	17	ND	0.003	ND	ND	ND	ND	ND	ND	ND	ND
14	Oncology Pharmacy	Employee Locker	451	17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
15	Oncology In-patient	Nurse stationary	1145	16	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
16	Oncology In-Patient	Waste Bin Top	495	17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
17	Oncology In-Patient	Floor	1232	17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
18	In-patient Hematology	Chemo Trolley	1920	17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND

Table 3.1: Results of a wipe-sample environmental assessment conducted on March 8, 2020. Evaluating potential contamination with Cyclophosphamide (CP), Cytarabine (CYT), Docetaxel (DOC), Doxorubicin (DOX), Etoposide (ETO), 5-Fluorouracil (5FU), Gemcitabine (GEM), Ifosphamide (IF), Methotrexate (MTX) and Paclitaxel (PAC) at Hospital A (continued)

Sample Code	Department	Description Surface	Surface Area (cm^2)	Total Volume NaOH (mL)	Contamination (ng/cm^2)									
					CP	CYT	DOC	DOX	ETO	5FU	GEM	IF	MTX	PAC
19	In-patient Hematology	Inside Chemo Fridge	1260	17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
20	In-patient Hematology	Floor	1350	17	ND	ND	ND	ND	ND	ND	ND	0.04	ND	ND
21	In-patient Hematology	Chemo Pump	841	17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
22	In-patient Hematology	Top Bin	495	17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
23	Out-Patient Clinic	Top of Trolley	3182	17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
24	Out-Patient Clinic	Patient Arm Chair	638	17	0.03	ND	ND	ND	ND	ND	ND	ND	ND	ND
25	Out-Patient Clinic	Door Handle	64	17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
26	Out-Patient Clinic	Toilet Floor	1365	17	0.04	ND	ND	ND	ND	ND	0.08	0.05	ND	ND
27	Out-Patient Clinic	Chemo Pump	841	17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND

Table 3.1: Results of a wipe-sample environmental assessment conducted on March 8, 2020. Evaluating potential contamination with Cyclophosphamide (CP), Cytarabine (CYT), Docetaxel (DOC), Doxorubicin (DOX), Etoposide (ETO), 5-Fluorouracil (5FU), Gemcitabine (GEM), Ifosphamide (IF), Methotrexate (MTX) and Paclitaxel (PAC) at Hospital A (continued)

Sample Code	Department	Description Surface	Surface Area (cm^2)	Total Volume NaOH (mL)	Contamination (ng/cm^2)									
					CP	CYT	DOC	DOX	ETO	5FU	GEM	IF	MTX	PAC
28	Out-Patient Clinic	Computer Mouse	55	17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
29	Out-Patient Clinic	Patient Arm Chair	624	17	0.06	ND	ND	ND	ND	ND	0.03	ND	ND	ND
30	Out-Patient Clinic	Chemo Trolley Top	3182	17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
31	Out-Patient Clinic	Chemo Waste Bin Top	868	17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
32	Pediatric Oncology	Nurses Station	1073	17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
33	Pediatric Oncology	Chemo Receiving Desk	1948	17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
34	Pediatric Oncology	Doctor Desk	1200	17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
35	Pediatric Oncology	Floor	2024	17	ND	ND	ND	ND	ND	ND	ND	0.20	ND	ND

Table 3.1: Results of a wipe-sample environmental assessment conducted on March 8, 2020. Evaluating potential contamination with Cyclophosphamide (CP), Cytarabine (CYT), Docetaxel (DOC), Doxorubicin (DOX), Etoposide (ETO), 5-Fluorouracil (5FU), Gemcitabine (GEM), Ifosphamide (IF), Methotrexate (MTX) and Paclitaxel (PAC) at Hospital A (continued)

Sample Code	Department	Description Surface	Surface Area (cm^2)	Total Volume NaOH (mL)	Contamination (ng/cm^2)									
					CP	CYT	DOC	DOX	ETO	5FU	GEM	IF	MTX	PAC
36	Pediatric Oncology-Outpatient	Top of Receiving Desk	1721	17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
37	Pediatric Oncology Outpatient	Chemo Trolley Top	209	17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
38	Pediatric Oncology-Outpatient	Patient Bed	221	17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
39	Oncology Pharmacy	Surface of Biological Safety Cabinet (BSC)	599	17	ND	0.12	ND	ND	ND	4.78	0.02	1.01	ND	ND
40	Blank Sample	-	-	17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND

ND: Not Detected: Levels of Detection for CP, CYT, DOC, DOX, GEM, IF and MIX were < 0.01 ng/mL NaOH; for ETO and 5FU were < 0.25 ng/mL NaOH, and for PAC were < 0.2 ng/mL NaOH.

Table 3.2: Results of a wipe-sample environmental assessment conducted on March 9, 2020. Evaluating potential contamination with Cyclophosphamide (CP), Cytarabine (CYT), Docetaxel (DOC), Doxorubicin (DOX), Etoposide (ETO), 5-Fluorouracil (5FU), Gemcitabine (GEM), Ifosphamide (IF), Methotrexate (MTX) and Paclitaxel (PAC) at Hospital B

Sample Code	Department	Description Surface	Surface Area (cm^2)	Total Volume NaOH (mL)	Contamination (ng/cm^2)									
					CP	CYT	DOC	DOX	ETO	5FU	GEM	IF	MTX	PAC
1	Oncology Pharmacy	Surface of Biological Safety Cabinet (BSC)	855	17	4.83	1.25	ND	ND	ND	50	ND	23	0.05	ND
2	Oncology Pharmacy	Chair of BSC	1350	17	ND	0.03	ND	ND	ND	ND	ND	ND	0.38	ND
3	Oncology Pharmacy	Supervisor Lock Room Handle	251	17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
4	Oncology Pharmacy	Refrigerator Handle	377	17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
5	Oncology Pharmacy	Checking Trolly	2044	17	ND	0.006	ND	ND	ND	ND	ND	ND	ND	ND
6	Oncology Pharmacy	Floor	1290	17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
7	Oncology Pharmacy	IV bag Prepared	286	17	ND	0.51	ND	ND	ND	ND	ND	ND	ND	ND
8	Oncology Pharmacy	Storage Bin	277	17	0.009	0.13	ND	ND	ND	ND	ND	1.38	ND	ND

Table 3.2: Results of a wipe-sample environmental assessment conducted on March 9, 2020. Evaluating potential contamination with Cyclophosphamide (CP), Cytarabine (CYT), Docetaxel (DOC), Doxorubicin (DOX), Etoposide (ETO), 5-Fluorouracil (5FU), Gemcitabine (GEM), Ifosphamide (IF), Methotrexate (MTX) and Paclitaxel (PAC) at Hospital B (continued)

Sample Code	Department	Description Surface	Surface Area (cm^2)	Total Volume NaOH (mL)	Contamination (ng/cm^2)									
					CP	CYT	DOC	DOX	ETO	5FU	GEM	IF	MTX	PAC
9	Oncology Pharmacy	Drug Vial Outside	188	17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
10	Oncology Pharmacy	Computer Keyboard	587	17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
11	Oncology Pharmacy	Telephone Handle	117	17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
12	Oncology Pharmacy	Chemo Transport Box	313	17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
13	Oncology Pharmacy	Unprepared Medication Refrigerator-Refrigerator Handle	100	17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
14	Oncology Pharmacy	Computer Mouse	72	17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
15	Oncology In-patient	Nurse stationary	1190	17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND

Table 3.2: Results of a wipe-sample environmental assessment conducted on March 9, 2020. Evaluating potential contamination with Cyclophosphamide (CP), Cytarabine (CYT), Docetaxel (DOC), Doxorubicin (DOX), Etoposide (ETO), 5-Fluorouracil (5FU), Gemcitabine (GEM), Ifosphamide (IF), Methotrexate (MTX) and Paclitaxel (PAC) at Hospital B (continued)

Sample Code	Department	Description Surface	Surface Area (cm^2)	Total Volume NaOH (mL)	Contamination (ng/cm^2)									
					CP	CYT	DOC	DOX	ETO	5FU	GEM	IF	MTX	PAC
16	Oncology In-Patient	Waste Bin Top	813	17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
17	Oncology In-Patient	Floor	1640	17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
18	In-patient Hematology	Chemo Receiving Shelves	1855	17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
19	In-patient Hematology-Nurses Station	Computer Keyboard	720	17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
20	In-patient Hematology	Floor	1716	17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
21	In-patient Hematology	Chemo Pump	841	17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
22	In-patient Hematology	Top Bin	1368	17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND

Table 3.2: Results of a wipe-sample environmental assessment conducted on March 9, 2020. Evaluating potential contamination with Cyclophosphamide (CP), Cytarabine (CYT), Docetaxel (DOC), Doxorubicin (DOX), Etoposide (ETO), 5-Fluorouracil (5FU), Gemcitabine (GEM), Ifosphamide (IF), Methotrexate (MTX) and Paclitaxel (PAC) at Hospital B (continued)

Sample Code	Department	Description Surface	Surface Area (cm^2)	Total Volume NaOH (mL)	Contamination (ng/cm^2)									
					CP	CYT	DOC	DOX	ETO	5FU	GEM	IF	MTX	PAC
23	Out-Patient Clinic	Top of Trolley	1892	17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
24	Out-Patient Clinic	Patient Arm Chair	518	17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
25	Out-Patient Clinic	Door Handle Toilet Room	230	17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
26	Out-Patient Clinic	Toilet Floor	1600	17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
27	Out-Patient Clinic	Chemo Pump	841	17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
28	Out-Patient Clinic	Computer Mouse	68	17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
29	Out-Patient Clinic	Chemo Trolley Top	1892	17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
30	Out-Patient Clinic	Chemo Waste Bin Top	813	17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND

Table 3.2: Results of a wipe-sample environmental assessment conducted on March 9, 2020. Evaluating potential contamination with Cyclophosphamide (CP), Cytarabine (CYT), Docetaxel (DOC), Doxorubicin (DOX), Etoposide (ETO), 5-Fluorouracil (5FU), Gemcitabine (GEM), Ifosphamide (IF), Methotrexate (MTX) and Paclitaxel (PAC) at Hospital B (continued)

Sample Code	Department	Description Surface	Surface Area (cm^2)	Total Volume NaOH (mL)	Contamination (ng/cm^2)									
					CP	CYT	DOC	DOX	ETO	5FU	GEM	IF	MTX	PAC
31	Pediatric Onc-Inpatinet	Nurses Station	872	17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
32	Pediatric Onc-Inpatinet	Chemo Receiving Desk	1653	17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
33	Pediatric Onc-Inpatient	Doctor Desk	989	17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
34	Pediatric Onc-Inpatient	Floor	1580	17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
35	Pediatric Onc-Outpatient	Top of Receiving Desk	1980	17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
36	Pediatric Onc-Outpatient	Chemo Trolley Top	1610	17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND

Table 3.2: Results of a wipe-sample environmental assessment conducted on March 9, 2020. Evaluating potential contamination with Cyclophosphamide (CP), Cytarabine (CYT), Docetaxel (DOC), Doxorubicin (DOX), Etoposide (ETO), 5-Fluorouracil (5FU), Gemcitabine (GEM), Ifosphamide (IF), Methotrexate (MTX) and Paclitaxel (PAC) at Hospital B (continued)

Sample Code	Department	Description Surface	Surface Area (cm^2)	Total Volume NaOH (mL)	Contamination (ng/cm^2)									
					CP	CYT	DOC	DOX	ETO	5FU	GEM	IF	MTX	PAC
37	Pediatric Onc-Outpatient	Patient Bed	200	17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
38	Pediatric Onc-Outpatient	Chemo Pump	841	17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
39	Blank Sample	-	-	17	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND

ND: Not Detected: Levels of Detection for CP, CYT, DOC, DOX, GEM, IF and MIX were < 0.01 ng/mL NaOH; for ETO and 5FU were < 0.25 ng/mL NaOH, and for PAC were < 0.2 ng/mL NaOH.

3.3 Study No. 3: KAP of oncology healthcare professionals on the handling of cytotoxic drugs

3.3.1 Demographic characteristics of study participants

Of 142 nurses and pharmacists working in the oncology departments who were invited to participate in this study, 117 participants started the survey but only 94 participants completed the survey questionnaires (response rate 66%). Majority of the study participants were female (80.0%). More than a third (32.0%) were between the ages of 31 to 35 years while 89 (79.0%) were married. Most of the oncology healthcare professionals (94.0%) were nurses and only 7 (6.0%) were pharmacists. Regarding educational qualifications, ninety-seven participants (86.0%) held a bachelor's degree. Employment duration of the participants varied. A total of 13 had two to five years of work experience (12.0%), nearly a third of the participants (28.0%, 31) had six to ten years of work experience, 22 had eleven to fifteen years of work experiences (20.0%), 18 had sixteen to twenty years of work experience (17.0%), and 24 had more than twenty years of work experience (22.0%). Exposure duration of the participants to cytotoxic drugs also varied. More than third of the participants (32.0%, 35) had two to five years of experience in handling cytotoxic drugs, 26 had six to ten years (24.0%), 17 had sixteen to twenty years (15.6%), 14 had eleven to fifteen years (13.0%), and 6 had more than twenty years of experience in handling CDs (5.5%). Interestingly, most of the participants (92.6%) were non-smokers. About 71% of the participants worked in the cyclic work shifts. All the participants (100%, 98) had received training on the safe handling of cytotoxic drugs during the past year (Table 3.3).

Table 3.3: Demographic characteristics of the study participants

Characteristics	Classification	n	Percentage (%)
Age group (Years) (n=113)	26-30	18	16
	31-35	36	32
	36-40	10	8.8
	41-45	19	16.8
	46-50	18	16
	>50	12	10.6
Gender (n=113)	Male	23	20
	Female	90	80
Marital status (n=113)	Single	23	20
	Married	89	79
	Widowed	1	0.8
Smoking (n=108)	Yes	8	7.4
	No	100	92.6
Education level (n=113)	Diploma certificate	5	4.4
	Bachelor's degree	97	86
	Master's degree	10	8.8
	Doctorate's degree	1	0.8
Occupation (n=113)	Clinical Pharmacist	3	2.6
	Pharmacist	3	2.6
	Pharmacy Technician	1	0.8
	Registered Nurse	94	83
	Specialty Nurse	9	8
	Nurse Practitioner	2	1.7
	Assistant Nurse	1	0.8
Years of work experience (Years) (n=109)	<2 years	1	1
	2-5 years	13	12
	6-10 years	31	28
	11-15 years	22	20
	16-20 years	18	17
	>20 years	24	22
Years of experience in handling cytotoxic drugs (n=109)	<2 years	11	10
	2-5 years	35	32
	6-10 years	26	24
	11-15 years	14	13
	16-20 years	17	15.6
	>20 years	6	5.5
Working schedule (n=109)	shifts	77	71
	Regular work hours (daily)	32	29
Received training on safe handling of cytotoxic drugs (in the past year) (n=98)	Yes	98	100

3.3.2 Acute side effects experienced by the oncology healthcare professionals who are handling cytotoxic drugs

Figure 3.1 shows 10 acute side effects related to cytotoxic exposure that the participants have reported. Headache (45.8%) was the most common acute side effect reported by the oncology healthcare professionals, followed by throat irritation (20.2%), and eye irritation (12.8%). Other reported acute side effects by the respondents were hair loss and skin irritation with 11.7 % for each of them. The least reported symptoms were abdominal pain and dizziness each accounted by 1 (1.1%).

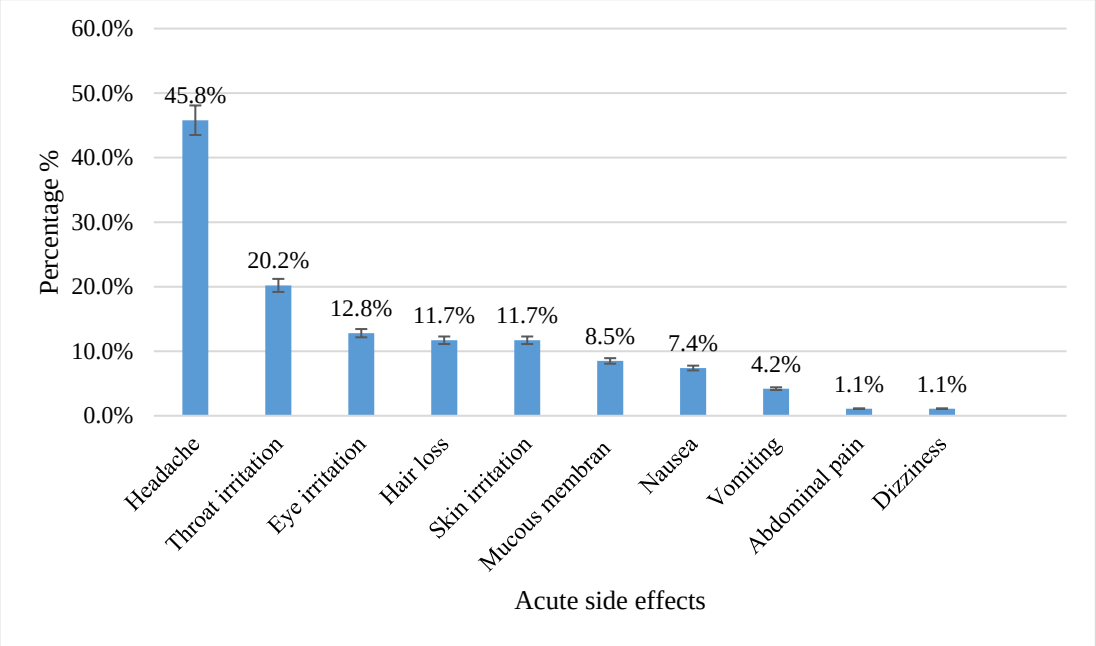


Figure 3.1: Percentage of oncology healthcare professionals reporting acute side effects while handling cytotoxic drugs

3.3.3 Frequency of handling cytotoxic drugs

The frequency of handling of CDs is presented in Table 3.4. Less than half of the participants handled cytotoxic drugs every day, indicating their continuous exposure to these drugs. More than sixty percent (62.8%) of the participants handled

from two to five medications schemes per day. These results are implying exposure of oncology healthcare professionals with different types of drugs.

Table 3.4: Frequency of handling cytotoxic drugs

Frequency	n (%)
How often do you handle cytotoxic drugs? (n=94)	
1 day per week	5 (5.3)
2 days per week	8 (8.5)
3 days per week	15 (16.0)
4 days per week	22 (23.4)
Everyday	44 (46.8)
How many cytotoxic drugs do you handle each day? (n=94)	
1 drug per day	16 (17.0)
2-5 drugs per day	59 (62.8)
6-10 drugs per day	7 (7.44)
More than 10 drugs per day	12 (12.8)

3.3.4 Attitudes of oncology healthcare professionals towards handling of cytotoxic drugs

Table 3.5 summarizes oncology healthcare professionals' attitude with respect to employee involvement in safety and Health matters (e.g. reporting incidents, safety meetings, risk assessment) and employer commitment to Health and Safety in relation to hazardous materials. Overall, the results showed that a high percentage of the respondents had a positive attitude toward handling of cytotoxic drugs. Nearly all of oncology healthcare professionals (99.0%) reported positive attitude regarding their involvement in safety and health matters related to handling of cytotoxic drugs. Majority of oncology healthcare professionals (91.5%) reported positive attitude about their employer commitment to health and safety in relation to hazardous materials.

Whereas (8.5%) of the study group reported negative attitude regarding their employer commitment to health and safety concerning handling of cytotoxic drugs.

Table 3.5: Attitudes of oncology healthcare professionals towards handling of cytotoxic drugs (n=94)

Attitude	Positive attitude n (%)	Negative attitude n (%)
Employee involvement in safety and Health matters (e.g., reporting incidents, safety meetings, risk assessment)	93 (99.0)	1 (1.0)
Employer commitment to Health and Safety in relation to hazardous materials	86 (91.5)	8 (8.5)

3.3.5 Practices of oncology healthcare professionals towards handling of cytotoxic drugs

Table 3.6 summarizes oncology healthcare professionals' practice with respect to compliance with Personal Protective Equipment (PPE) use and other safety measures, disposal of cytotoxic drugs waste, hand hygiene. Overall, the results showed that a high percentage of the respondents had good practices toward handling of cytotoxic drugs. Nearly all respondents reported high adherence levels to the use of PPE such as gloves, protective gown, and mask (98.14%), (97.22%,) and (96.29%) respectively while handling cytotoxic drugs. However, only (46.29%) and (52.77%) of the respondents reported adhering to over shoes and head covers, respectively, whereas (1.85%) of the study group reported not wearing personal protective equipment while handling these drugs.

Concerning compliance with cytotoxic drugs' safety measures and cytotoxic drugs management, almost all oncology healthcare workers who handle cytotoxic drugs stated that they never smoke (100%), eat (99.0%), drink (98.0%), store

beverages and edibles (100%), or using makeup (99.03%) at the workplace. It is also interesting that the majority (92.15%) of the respondents claimed that they are always washing their hands thoroughly after handling cytotoxic drugs. In comparison (6.90%) of the study group reported inconsistent compliance with hand hygiene and (1%) of the respondents ever wash their hands after working with CDs. Disposal of CDs waste was also evaluated. Only 3.0 % of the respondents did not dispose of related wastes properly.

Table 3.6: Practices of oncology healthcare professionals towards handling of cytotoxic drugs

Practice		n (%)
Use of PPE during handling of CDs (108)	Gloves	106 (98.14)
	Gown	105 (97.22)
	Googles	91 (84.25)
	Mask	104 (96.29)
	Overshoes	50 (46.29)
	Head covers	57 (52.77)
	None	2 (1.85)
Smoking at areas of drug handling (n=104)	Never	104 (100)
	Rarely	
	Sometimes	
	Often	
	Very often	
Eating at areas of drug handling (n=104)	Never	103 (99.0)
	Rarely	
	Sometimes	1 (1.0)
	Often	
	Very often	
Drinking at areas of drugs handling (n=104)	Never	102 (98.0)
	Rarely	
	Sometimes	1 (1.0)
	Often	
	Very often	1 (1.0)
Storing beverages and edibles in a refrigerator or at areas of drug handling (n=104)	Never	104 (100)
	Rarely	
	Sometimes	
	Often	
	Very often	
Using makeup at areas of drug handling (n=104)	Never	103 (99.03)
	Rarely	
	Sometimes	
	often	1 (1.0)
	Very often	
Washing hands thoroughly after handling cytotoxic drugs (n=102)	Never	1 (1.0)
	Rarely	
	Sometimes	2 (2.0)
	Often	5 (4.90)
	Always	94 (92.15)
Dispose cytotoxic waste correctly (n=102)	In a regular container	
	In a special container for hospital waste	2 (2.0)
	In a special container for cytotoxic drugs	99 (97.0)
	Other	1 (1.0)

3.3.6 Challenges in safe handling of cytotoxic drugs

The oncology pharmacists and nurses reported a range of challenges towards the safe handling of cytotoxic drugs. Fifty-nine (62.8%) participants considered high workload as a major challenge in the safe handling of cytotoxic drugs, while 44 (46.8%) reported lack of access to PPE. The lack of knowledge about the safe handling of cytotoxic drugs and PPE discomfort were also reported as challenges by 21.3% and 16.0% of participants, respectively. Other participants (6.4%) stated there are no challenges towards the safe handling of cytotoxic drugs. Figure 3.2 below indicates the various challenges faced by oncology healthcare professionals towards the safe handling of cytotoxic drugs.

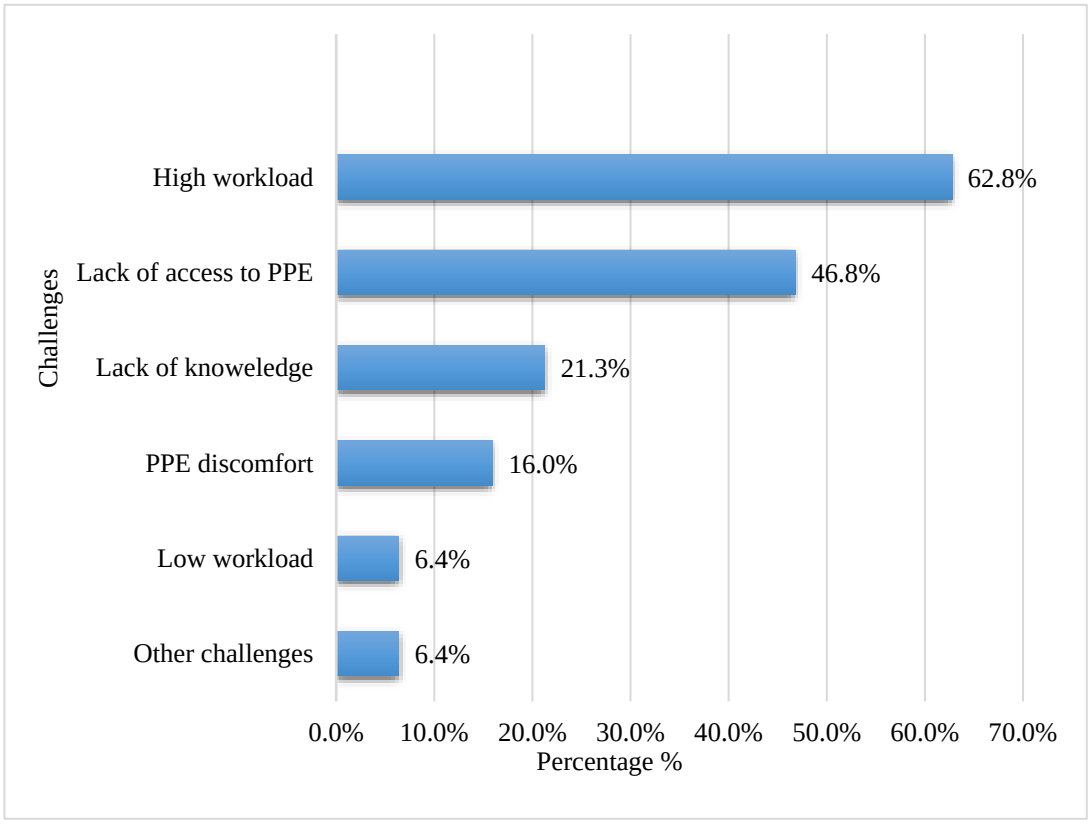


Figure 3.2: Challenges reported by oncology healthcare professionals towards the safe handling of cytotoxic drugs

3.3.7 Training on safe handling of cytotoxic drugs

Figure 3.3 below represents the various training sources reported by oncology healthcare professionals. All the participants reported that they had received training on the safe handling of cytotoxic drugs during the past year and 84% of them received training from different sources. The majority (82%) of the participants reported seminars and conferences as the main source of information, followed by hospital administration (63.8%), professional organizations (52.1%), scientific literature (52.1%) and internet (42.6%). About 8.5% of the participants reported receiving information from other sources, which include supervisors and colleagues. However, only 7.4% of oncology healthcare professionals obtain information from mass media.

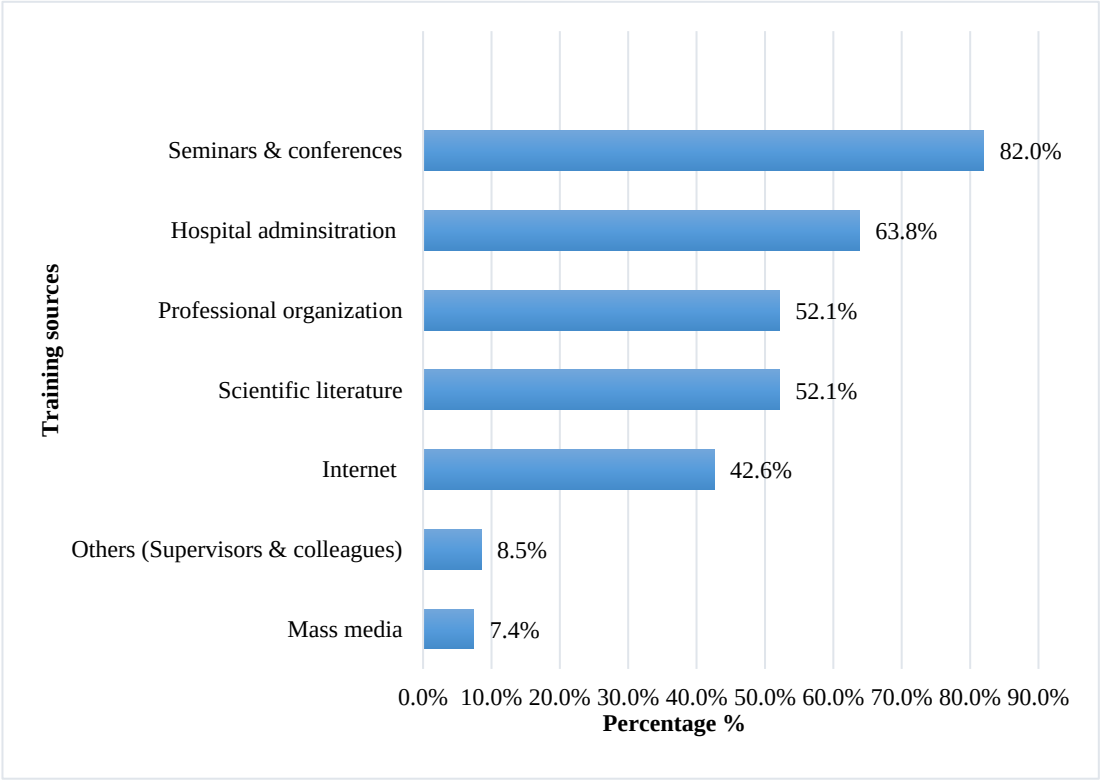


Figure 3.3: Training sources of the oncology healthcare professionals about the safe handling of cytotoxic drugs

3.3.8 The level of knowledge among oncology healthcare professionals on cytotoxic agents handling

Regarding the level of knowledge, out of a maximum score of 100, the mean score of the participants' knowledge on cytotoxic agents handling was 74.04 (SD 10.50, range 48–96). More than half of the study group (53.20%, 50 participants) was above the groups' mean score (Table 3.7).

Table 3.7: The mean score of the participants' knowledge on cytotoxic drugs handling

Knowledge score (n=94)	N (%)	Mean ± SD
Adequate knowledge (>74)	50 (53.20)	74.04 ±10.50
Inadequate knowledge (≤74)	44 (46.80)	

3.3.9 Knowledge of oncology healthcare professionals towards handling of cytotoxic drugs

Oncology healthcare workers' knowledge about cytotoxic drugs is shown in Table 3.8. All oncology healthcare workers (100%) knew that 5-fluorouracil is a cytotoxic agent and CDs can cause damage to nucleic acids of healthy cells. Overall, most of them had a correct response to questions concerning the potential hazards associated with handling of cytotoxic medications; however, only (11.7%) of the participants knew about the symptoms related to exposure to CDs.

Table 3.8: Responses to knowledge toward Safe handling of cytotoxic drugs

Question	Right N (%)	Wrong N (%)	Do not know N (%)
5-Fluorouracil is a drug used as a cytotoxic agent	94 (100)		
Some cytotoxic drugs can be used for organ transplant patients.	68 (72.3)	8 (8.5)	18 (19.1)
Cytotoxic drugs can cause damage to the RNA or DNA of healthy cells, as seen in cancer cells.	94 (100)		
It has not been verified that 5-Fluorouracil, 6-Mercaptopurine, Methotrexate which are cytotoxic drugs from the group of antimetabolites, have carcinogenic action.	46 (49)	43 (46)	5 (5.3)
Cytotoxic drugs have genotoxic effects.	85 (90.4)	4 (4.2)	5 (5.3)
Cytotoxic drugs have carcinogenic effects.	91 (96.8)	2 (2.1)	1 (1)
Some cytotoxic drugs have teratogenic effects.	91 (96.8)	1(1)	2 (2.1)
Cytotoxic drugs have toxic effects on the liver.	93 (99)		1 (1)
The only symptoms observed on those who handle cytotoxic drugs is hair loss, weakness and allergies.	11 (11.7)	73 (77.6)	10 (10.6)
Exposure to cytotoxic drugs can cause spontaneous abortions.	71 (75.5)	16 (17)	7 (7.4)
All cytotoxic drugs, while being handled with a syringe, do not react with air because their molecular mass is large.	24 (25.5)	51 (54.2)	19 (20.2)
In places of preparation of cytotoxic drugs, the application of cosmetics is strictly prohibited.	77 (82)	4 (4.25)	13 (13.8)
Cytotoxic drugs reach the blood by only penetrating through the skin.	18 (19.1)	73 (77.6)	3 (3.2)
The two most important ways of contamination with cytotoxic drugs is inhalation and ingestion.	78 (83)	16 (17)	
Clothes contaminated with urine and linens of patients who have received cytotoxic drugs may probably cause a problem of exposure to cytotoxic drugs.	93 (99)	1 (1)	
Vertical chambers of laminar flow (cabinets) which are used for the preparation of cytotoxic drugs must be cleaned once every week.	31 (33)	32 (34)	31 (33)
Those who use cytotoxic drugs must wear special chemotherapy gloves made from latex or nitrile.	85 (90.4)	8 (8.6)	1 (1)
Those who use cytotoxic drugs must not wear gloves with powder.	62 (66)	20 (21.2)	12 (12.8)
To avoid the potential exposure of employees with cytotoxic drugs through inhalation, surgical masks must be used.	27 (29)	67 (71)	
Gloves used for the preparation of cytotoxic drugs must be replaced every one to two hours.	43 (45.8)	39 (41.5)	12 (12.8)
During the preparation of cytotoxic drugs, appropriate ventilation system must be used.	88 (94)	1 (1)	5 (5)
The cleaning of the biological safety chamber (cabinet) must be done with a germicide.	52 (55.3)	13 (13.8)	29 (31)
All waste that is contaminated with cytotoxic drugs must be assessed and handled in the same way like all the other medical waste of a hospital.	22 (23.4)	72 (76.6)	
The part of the skin that comes in direct contact with cytotoxic drugs must be washed directly with water and soap.	90 (95.8)	3 (3.20)	1 (1)
For the preparation of cytotoxic drugs it is better to use needles with a small lumen.	28 (29.8)	40 (42.6)	26 (27.6)

3.3.10 Factors associated with knowledge score

Chi-square and Fisher's exact test analyses were used to compare oncology healthcare professionals with knowledge score ≤74 and those with knowledge score >74 in relation to the HCWs' characteristics including age, gender, education level, smoking, working duration/years, handling of cytotoxic drugs by duration/years, and number of drugs handled per day. Finding demonstrated that smoking status was significantly associated with knowledge score as 54.4% of oncology healthcare professionals with high knowledge score (adequate knowledge >74) of handling CDs are more likely to not-smoke compared to oncology healthcare workers with low knowledge score (inadequate knowledge ≤74). However, age, gender, education level, working duration/years, handling cytotoxic drugs duration/years, and number of drugs handled per day were not associated with knowledge score towards handling of cytotoxic drugs. Table 3.9 details the above results.

Table 3.9: Factors associated with knowledge score

Variables	N (94)	Knowledge score ≤74 N (%)	Knowledge score >74 N (%)	P Value
Age (years)				
≤40	53	24 (45.2)	29 (54.7)	0.568
>40	41	21 (51.2)	20 (48.8)	
Gender				
Male	19	8 (42.1)	11 (57.9)	0.573
Female	75	37 (49.3)	38 (50.7)	
Education Level				
Diploma or Bachelor	84	41 (48.8)	43 (51.2)	0.598
Master or Doctoral	10	4 (40.0)	6 (60.0)	
Do you smoke?				
Yes	4	4 (1.0)	0	0.033*
No	90	41 (45.6)	49 (54.4)	
How many years of working?				
≤10 years	42	18 (42.8)	24 (57.1)	0.382
>10 years	52	27 (52.0)	25 (48.0)	
How many years have you been handling CDs?				
≤10 years	60	29 (48.3)	31 (51.7)	.905
>10 years	34	16 (47.0)	18 (53.0)	
How many CDs do you handle each day?				
≤5 CDs	79	37 (46.8)	42 (53.2)	0.644
>5 CDs	15	8 (53.3)	7 (46.7)	

*Statistically significant result at $p<0.05$

3.3.11 Regression analysis

Table 3.10 represents the regression analysis for knowledge score as dependent variable and age, gender, education level, years of handling CDs, smoking status, number of drugs and years at work as independent variables. There was no significant relationship between the knowledge score of cytotoxic drug handling and independent variables studied.

Table 3.10: Regression analysis for knowledge score as dependent variable and age, gender, education level, years of handling CDs, smoking status, number of drugs and years at work as independent variables

Variables	Regression Coefficient (B)	P-value
Knowledge score (Constant)	74.991	0.000
Age group	1.208	0.745
Gender	0.517	0.863
Education Level	-1.185	0.753
Years of handling CDs	3.889	0.268
Smoking status	-10.487	0.074*
Number of drugs	0.773	0.805
Years at work	-4.586	0.199

*Borderline significant at $\alpha=0.05$

Chapter 4: Discussion

4.1 Introduction

This dissertation reports findings from three studies designed and carried out in Abu Dhabi Emirate to: 1) develop a protocol for systematic review and meta-analysis on the environmental assessment of cytotoxic drugs in the healthcare settings; 2) evaluate the environmental cytotoxics contamination; and 3) survey the KAP of healthcare professionals towards handling of cytotoxic drugs in the workplace. The systematic review protocol was developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol-2015 (PRISMA-P) guidelines (Moher et al., 2015). The second study evaluated workplace contamination with 10 cytotoxic drugs by collecting 79 surface wipe samples from preparation and administration of two Abu Dhabi oncology centers. The third study used an on-line questionnaire to assess the KAP of handling cytotoxic drugs among 113 Abu Dhabi healthcare professionals. The stimulus for this research arose from the investigator's work with occupational health and safety in Abu Dhabi Department of Health, a strongly held belief of the importance of measuring cytotoxic drugs residues in healthcare settings and the need to raise awareness among oncology healthcare professionals to reduce the risk of exposure to these agents.

4.2 Study No. 1: Environmental assessment of cytotoxic drugs in healthcare settings: protocol for a systematic review and meta-analysis

The extensive use of cytotoxic drugs in the treatment of cancer patients has led to occupational hazards associated with exposure of healthcare professionals to such drugs. Exposure to cytotoxic drugs lead to different adverse health effects such as spontaneous abortion, infertility, premature labor, and developmental and behavioral

abnormalities. Systematically compiling and summarizing primary studies as well as providing pooled evidence on the burden of cytotoxic drugs in healthcare settings is still lacking in the literature. This protocol reduces the possibility of duplication, minimises possible biases and allows peer-review using the proposed methods to conduct a high-quality systematic review and meta-analysis. The systematic review to be produced following this protocol, as far as it is known, is the first systematic review and meta-analysis to provide systematic evidence on the levels of environmental contamination of the healthcare settings with cytotoxic drugs. The results of the systematic review will be published in a peer-reviewed journal and will be publicly available. The findings will also be disseminated electronically and in printed versions.

4.3 Study No. 2: Environmental assessment of cytotoxic drugs in oncology departments of UAE Hospitals

The results in general show contamination with six cytotoxic drugs in the oncology pharmacy departments of both hospitals combined. The other departments related to drug administration show no contamination on surfaces or small numbers of contaminated surfaces with very low contamination levels. Four drugs were not detected at all (doxorubicin, docetaxel, etoposide, and paclitaxel). Differences can be explained by different volumes of each of the drugs prepared and administered, and differences in working and cleaning procedures. Notably, the contamination in both oncology pharmacy departments is spread in and around the BSCs and is very high on some surfaces.

In general, the results of this study compared to many other international reports of environmental assessment of cytotoxic drugs, continue to reveal widespread surface contamination in either preparation and/or administration areas of oncology

hospital units (Dugheri et al., 2018; Bussières et al., 2012; Kiffmeyer et al., 2013; Sessink et al., 2015; Janes et al., 2015; Böhlandt & Schierl, 2016; Sottani et al., 2017; Koller et al., 2018; Poupeau et al., 2018; Vyas et al., 2014; Viegas et al., 2018; Soteriades et al., 2020; Palamini et al., 2020; Hilliquin & Bussières, 2020).

Overall, the proportion of positive samples 25% (20/79) is much lower than what has been reported in previous monitoring studies (Garcíaa et al., 2018; Stover & Achutan, 2011; Connor et al., 2010; Chu et al., 2012). For example, Garcíaa et al. (2018) analyzed 204 samples from ten Spanish hospitals and showed 49% of positive samples for cyclophosphamide, 23% for ifosfamide and 10% for 5-fluorouracile in pharmacy areas. Stover and Achutan (2011) reported 20% of CP positive samples in patient care areas, and Connor et al. (2010) reported 43% of CP positive samples and 24% of IF positive samples in pharmacy and patient care areas combined. In the current study, the proportion of positive samples are 14% for each of cytarabine and ifosfamide, 11% for cyclophosphamide, 6% of gemcitabine, and 2.5% for each of 5-fluorouracil and methotrexate in preparation and administration areas collectively.

An interesting finding that detectable contamination is more frequent in Hospital A but the contamination levels, where detectable, are higher in Hospital B. Differences can be explained by a defect in the working procedures and cleaning procedures in Hospital A and the spill of drugs in Hospital B.

It is also interesting that four drugs were not detected at all (doxorubicin, docetaxel, etoposide, and paclitaxel). This can be explained by different volumes of each of the drugs prepared and administered, differences in cleaning procedures, and maybe these drugs were not prepared or administered in the sampling day. A recent study by Simon et al. (2020) examined the efficiency of four solutions in removing 23

cytotoxic drugs from contaminated surfaces. In that study, Docetaxel and Paclitaxel were removed efficiently (100%) with 10^{-2} M Sodium dodecyl sulfate/Isopropanol 8:20, and Etoposide removed with 0.5% Sodium hypochlorite, while Doxorubicin was removed efficiently with both decontamination solutions (Simon et al., 2020). Another study by Cox et al. (2017) reported that the decontaminating product (Hazardous drug clean) was effective in removing surface contamination with Docetaxel and Paclitaxel (Cox et al., 2017).

The results show high levels of contamination in both oncology pharmacy departments. These results are supported by Hon and colleagues (2011) and Headmer and others (2008) that concluded that dermal exposure is common among oncology pharmacists (Hon et al., 2011, Headmer et al., 2008). High levels of contamination are mainly found inside and around the BSCs used for drug preparation. The highest amount was noticed for 5-fluorouracil (4.78 ng/cm^2, 50 ng/cm^2) and ifosfamide (1.01 ng/cm^2, 23 ng/cm^2) in hospitals A and B, respectively. These results are not surprising, given that the BSC is used to dilute and prepare all cytotoxic drugs delivered for treatment. During preparation, spills inside the BSCs may occur resulting in contamination of the BSCs, the gloves of the technicians, and prepared IV bags, as observed in this study. Several other studies have consistently shown contamination of such surfaces (Korczowska et al., 2020; Soteriades et al., 2020). In general, results show that the BSC, the floors, the chair of the BSCs, the handles of the refrigerators, as well as prepared IV bag, storage bins, and checking counters/trolleys were often contaminated with CYT, CP, and IF. This confirms that contamination was often spread throughout the pharmacy. In a 2016 literature review, Lancharro and his team reported that the presence of contamination by cytotoxic drugs was confirmed in many hospitals across all five continents. In all evaluated cases, contamination was found in

the biological safety cabinet, on the floor in front of the cabinet, in different tables where the drugs are temporarily placed and in other places of the hospital pharmacy (Lancharro et al., 2016). Drug vials contaminated on the outside may also contribute to the spread of contamination to other hospital departments (Power et al., 2014; Nygren et al., 2002; Favier et al., 2003; Mason et al., 2003). In this study, vials were not found to be contaminated but the number of samples (one vial per hospital) was probably insufficient to conclude that there was no vial contamination. Similar findings were reported by Crauste-Manciet et al. (2005). Contamination on the gloves can easily be transferred to all surfaces that are touched such as the chairs of the BSCs, the handles, counters and the storage bins as observed in this study. In order to limit cross-contamination, glove changes could be recommended between preparations when a different cytotoxic agent is used (Mason et al., 2003; Fleury-Souverain et al., 2014).

Regarding Hospital A, surfaces contaminated with one or more cytotoxic drugs were found in both preparation and administration areas, although contamination was significantly higher in the preparation area. In the administration area, low contamination (except floor sample in patient room pediatric oncology in-patient with contamination level 0.20ng/cm^2) was found in the treatment chair armrest and floors in the patient room and patient toilet. Floors were previously reported as heavily contaminated (Korczowska et al., 2020). Contamination on floors in preparation and administration areas are in general caused by spill during activities including patient care followed by ineffective cleaning. More cleaning will remove the remaining contamination on the floors and the other surfaces. Cleaning of floors is known to be very difficult, but contamination will reduce in the course of time after frequent cleaning.

At present, no exposure limits have been established for cytotoxic drugs in general. Therefore, the contamination of armrest can be a serious risk given the high number of healthcare workers, patients and accompanying family members potentially exposed to this contamination. Chauchat et al. (2019) have also reported contaminated armrest (81.7% of samples positive for at least one cytotoxic drugs). This contamination may result from insufficient cleaning methods between patients. This type of surface is also probably difficult to clean because of its cushioned surface.

4.3.1 Strengths and limitations

To this knowledge, this is the first study of environmental assessment of cytotoxic drug contamination in United Arab Emirates hospitals and provides results from both preparation and administration areas of oncology units. Environmental assessment of the oncology pharmacy and drug administration areas provide a baseline level of potential contamination that health professionals are exposed to on a daily basis. To limit technical bias and to ensure a consistent sampling method across both hospitals, all wipe samples were collected by one researcher based on the supplied manual explaining the correct sampling technique. This study was conducted in two facilities with a relatively small sample, which limits the generalizability of findings. As much as possible, sampling was performed over a working day, to generate values that were representative of a working day and also representative of the potential professional exposure to these drugs among healthcare workers. However, all sampling at each facility was collected on a single day, and different results might have been obtained from different workloads. Many different analytical techniques are available, so caution should be exercised while comparing these results with the results

of other studies. The limits of detection were comparable to those used by other investigators.

4.4 Study No. 3: KAP of oncology healthcare professionals on the handling of cytotoxic drugs

To this knowledge, this study is the first in the UAE to assess oncology healthcare professionals' KAP towards handling cytotoxic drugs. The study concurrently evaluated the level of healthcare professionals' knowledge about cytotoxic medications, their attitudes, and their handling practices as reported by oncology healthcare professionals to assess whether these conform with the international safety guidelines and local standards concerning hazardous materials. Moreover, the study investigated the type of adverse health outcomes associated with exposure to cytotoxic drugs and the challenges of safe handling of cytotoxic agents. Most of the participants in this study were aware of the potential hazards associated with handling cytotoxic medications. The mean score of the participants' knowledge was 74.04 out of 100. The majority of the participants reported high adherence levels to the use of personal protective equipment such as gloves, protective gown, and mask (98.14%, 97.22%, and 96.29%), respectively, while handling these agents. All the participants (100%) had received training on the safe handling of cytotoxic drugs during the past year. Headache (45.8%) was the most common side effect reported by oncology healthcare professionals. Furthermore, more than half of the participants (62.8%) considered high workload as a major challenge in the safe handling of cytotoxic drugs.

The mean score of the nurses' and pharmacists' knowledge was 74.04 out of 100. This is higher compared to findings of studies conducted in Nepal and Turkey

(61.32 ±17.12 out of 100) and Malaysia (73.40 ±8.88 SD out of 100) (Chaudhary & Karn., 2012; Turk et al., 2004; Keat et al., 2013). The potential reason for the difference might be the variation in the target population, policies, and interventions.

Training healthcare workers on the safe handling of cytotoxic drugs is vital in increasing their knowledge and use of safety measures at the workplace (Keat et al., 2013). All the participants in this study received training on the safe handling of cytotoxic drugs during the past year. This finding is consistent with previous studies (Kalenge et al., 2018; Koulounti et al., 2019) and it could be due to the Healthcare Professional Requirements (PQR) in UAE, which mandate the healthcare professionals to gain minimum annual requirements of Continuing Professional Development (CPD) to renew their professional license (PQR, 2017). Finding from other research, which involved oncology nurses, were inconsistent with the current study regarding cytotoxic drugs handling training (Kyprianou et al., 2010). The researcher reported that only 33% of the respondents had received a specialized training on how to safely handle cytotoxic drugs in the workplace. Furthermore, the result of the current study is significantly different from other study conducted in Turkey by Kosgeroglu et al. (2006). In that study, only 7.4% of nurses had received in-service training about chemotherapeutics.

The adherence of healthcare workers with the international guidelines of using PPE was previously reported to be limited in other countries such as Jordan (Al-Azzam et al., 2015), Egypt (Mohamed & Sharaf, 2019), and Turkey (Baykal et al., 2009). Using PPE was found to minimize the occupational exposure to cytotoxic therapies (Connor, 2006; Crauste-Manciet et al., 2005). Current results show nearly all respondents reported high adherence levels to the use of personal protective equipment

such as gloves, protective gown, and mask (98.14%, 97.22%, and 96.29%), respectively. In contrast, the use of overshoes (46.29%) and headcovers (52.77%) was relatively lower. In line with these results, previous studies from Greece (Constantinidis et al., 2011), Cyprus (Kyprianou et al., 2010), and Turkey (Baykal et al., 2009) reported high use levels of gloves and protective gowns. Another survey among oncology healthcare workers in the US demonstrated high use of protective chemotherapy gloves (85%) and low use percentages for overshoes (3%) and headcovers (4%) (Boiano et al., 2014). According to the results, the use of glove, gown and masks were very high. However, an effective PPE risk assessment (e.g., type of PPE, fitting, and maintenance) may also need to be addressed in future studies.

Another important finding is that most oncology healthcare professionals, was found to have positive attitudes and practices towards the management of chemotherapy, 100% of the sample did not smoke, 99.0% did not eat, and 98.0% did not drink in the designated cytotoxic drugs handling areas, similar 100% stated that they never store beverages and edibles in the designated areas. Similar results were noted in other studies conducted in Cyprus (Koulounti et al., 2019). Conversely, Chaudhary and Karn (2012) reported that more than 62% of the nurses in their study had developed one or more dangerous behaviours in the preparation area of cytotoxic drugs (Chaudhary & Karn, 2012). It is also interesting that the majority (92.15%) of the respondents claimed that they are always washing their hands thoroughly after handling cytotoxic drugs. The result is consistent with that of a study conducted by Boiano et al. (2014), which examined the practices level regarding the cytotoxic drugs safe handling guidelines by oncology healthcare workers. The study reported high adherence rate (92.0%) to hand washing. Opposite findings were reported by Esmail

et al. (2016) who revealed that 59.30% oncology nurses were not washing hands thoroughly after any contact with chemotherapy.

Regarding the challenges of safe handling cytotoxic drugs, more than sixty percent (63.0%) of the oncology healthcare professional reported that their heavy workload was a major challenge of PPE use. Compared to the results of a previous study (Sarita et al., 2019), less than one-third of nurses perceived the main challenge of PPE use is high workload (Sarita et al., 2019). In contrast, a study by He et al. (2017) claimed that higher workloads were significantly associated with higher scores on the PPE use scale. While a study by Callahan et al. (2016), examined the hazardous drug safe-handling practices of oncology nurses working on inpatient units at the National Institutes of Health Clinical Center (NIH CC) in Maryland, USA. In that study, nurses exhibited more hazardous drug precaution use when assigned fewer patients. Prior research had revealed that the likelihood of cytotoxic drug exposure decreased when nurses reported favourable working conditions and lower workloads (Friese et al., 2012). Another research has found that higher workloads are significantly associated with more drug spills (OR 1.03, 95% CI 1.01 to 1.06) (He et al., 2017).

In this study, nearly half (47%) of the oncology pharmacists and nurses worked daily with CDs, indicating the continuous exposure of oncology personnel with CDs. Considering both the daily exposure of oncology workers and the number of medications prepared (more than 10 drugs) and administrated (from 2 to 5 drugs), pharmacists and nurses may be at increased risk of exposure to CDs. In a study of pharmacists' exposure to cytotoxic drugs in Canada, despite the existence of control measures, workplace contamination with these drugs was detected, and 4 of 8 urine samples were positive for cyclophosphamide (Ramphal et al., 2015). Since various

kinds of CDs are available in oncology departments, pharmacists and nurses may be expose to a variety of them. More than sixty percent (62.8%) of the oncology healthcare workers of this study handled two to five medications per day. In a study in Iranian hospitals (Orujlu et al., 2016), 63% of nurses worked with four and more than four medications each day. Thus, safety measures should be practiced by all oncology healthcare workers during the handling of CDs and the environmental assessment program should be considered to identify the contaminated work areas.

The study also examined all symptoms reported in the scientific literature as possible adverse health outcomes associated with the exposure to cytotoxic drugs (Ivanova & Avota, 2016; Shahrasbi et al., 2014). The most prominent symptom in the present as well as in previous studies was headache (El Hosseini et al., 2019; Ivanova & Avota, 2016; Kyprianou et al., 2010; Turk et al., 2004); however, this is a prevalent symptom that may not be specifically connected to the exposure to cytotoxic agents. High workload, which was present in the current study as a major challenge in the safe handling of cytotoxic drugs, can also cause this symptom (Vaernes et al., 1993; Tsai & Liu, 2012; Medisauskaite & Kamau, 2017). On the other hand, symptoms such as dizziness, which was reported by 1.1% of the participants, is far less common than the percentage of dizziness reported in previous studies (Kyprianou et al., 2010; Turk et al., 2004; Unsar et al., 2016). More research is needed to examine the health effects of long-term occupational exposure to cytotoxic drugs.

This study revealed that smoking status was significantly associated with knowledge score of handling CDs, oncology healthcare professionals with high knowledge scores of handling CDs were more likely to not-smoke than oncology healthcare professionals with inadequate knowledge score. This reason might be that

knowledgeable Health care professionals are more responsible for themselves. A study conducted in Egypt, reported that nearly all socio-demographic data did not significantly affect a change of knowledge and performance (Bolbol et al., 2016). Another study conducted by Kyprianou et al. (2010), reported that no significant differences between the level of knowledge and age, gender or adherence to protective practices (use of gloves and protective equipment overall) (Kyprianou et al., 2010).

4.4.1 Strengths and limitations

The study's strength is that this is the first study done in UAE to assess the KAP of oncology healthcare professionals regarding handling of cytotoxic drugs. Valid questionnaire used in other studies was adapted for this study, and thus the measurement errors were substantially reduced.

This study had several limitations that must be acknowledged. Although the response rate was acceptable (66%), further studies with larger sample sizes including more public and private hospitals are needed to understand better the level of knowledge, attitude and practices of healthcare professionals about the safe handling of cytotoxic drugs in the Emirate of Abu Dhabi and the other emirates of UAE. In addition, the generalizability of the results to other emirates might not be possible since the health service delivery and regulatory bodies are different from Abu Dhabi emirate to other emirates. It is not known whether similar results will be obtained in other emirates. This could demonstrate a valuable contribution for possible future research too. Lastly contamination of data is likely to have affected the results of the study, as the participants were not observed while completing the tool and could have consulted information resources to respond to the questions.

Chapter 5: Conclusion

This research project included three studies. The first study developed a protocol on environmental assessment of cytotoxic drugs in healthcare settings. The protocol was developed in accordance in the Preferred Reporting Items for Systematic review and Meta-Analyses Protocol-2015 (PRISMA-P) guidelines. The second study evaluated workplace contamination with 10 cytotoxic drugs by collecting 79 surface wipe samples from preparation and administration areas of two Abu Dhabi Oncology centers. The wipe samples were taken using the Cyto Wipe kits from Exposure Control AB. This is the first study in the Middle East and North Africa (MENA) region, and in UAE in particular, that evaluated the potential environmental contamination with ten widely used cytotoxic drugs in preparation and administration areas.

These results show that the overall percentage of sample contamination at both oncology departments were relatively low compared to other studies around the world. Also, the detected contamination levels with cytotoxic drugs were low except of the workspace inside and around the biological safety cabinets. Employee education as well as review and evaluate the drug preparation procedures and handling of cytotoxic drugs in the pharmacy along with careful examination of cleaning procedures are warranted to reduce the potential contamination, with particular attention of areas in and around the biological safety cabinets. The application of regular environmental assessments helps to monitor the effectiveness of newly adopted and enhanced health and safety control measures.

The third study was a cross-sectional survey using an online self-administrated questionnaire to assess oncology pharmacists and nurses' KAP regarding the handling of cytotoxic drugs. In this study, 113 oncology healthcare professionals participated in

the survey (23 Male and 90 Female). Most of them were aware of the potential hazards associated with handling cytotoxic medications. The mean score of the participants' knowledge was 74.04 out of 100. The majority of the participants reported high adherence levels to the use of personal protective equipment such as gloves, protective gown, and mask (98.14%, 97.22%, and 96.29%), respectively, while handling these agents. All the participants (100%) had received training on the safe handling of cytotoxic drugs during the past year.

Interestingly, the KAP study is also the first in the UAE to assess oncology healthcare professionals' KAP towards handling cytotoxic drugs. The findings may be used to develop programs about cytotoxic drugs handling that will help to minimize the risk of these agents. Such initiatives will contribute to raise both knowledge and practices of healthcare workers regarding the handling of cytotoxic drugs.

This research offers the following implications for management, and future research.

5.1 Managerial implications

This study recommends that the Hazardous Materials Management Standard-AD Department of Health be revised to consider the surface wipe sampling programme. Introduction of this requirement in the standard could reduce the risk of occupational exposure to these drugs.

The resultant recommendations should help decision-making at the highest level within and among local government departments, health authorities, and health facilities.

5.2 Research implications

The developed systematic review and meta-analysis protocol provides a framework to systematically review the published literature and quantify the level of environmental contamination of healthcare settings with cytotoxic drugs. The review to be carried out will be the first to fill an evidence gap on the environmental contamination of healthcare settings with cytotoxic drugs. Therefore, it is planned to follow up on the protocol and complete the systematic review and meta-analysis. The findings of this review will help understand the risk of occupational exposure of healthcare workers to cytotoxic drugs and facilitate the identification of priority areas for specific interventions.

For future research also, the combination of environmental monitoring along with biological monitoring is needed. Combining both approaches will give deep insight into the actual exposure of healthcare professionals to cytotoxic drugs.

The most commonly reported barriers to PPE use were increased workload, lack of access to personal protective equipment, and lack of knowledge on the importance of PPE use. Therefore, future research should focus on the barriers identified in this study and to address effective strategies to overcome them.

Although this research examined oncology healthcare professionals' practices by self-administrated approach, future studies should explore the translate of knowledge into the practice such as observational studies to evaluate the compliance with PPE use.

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List of Publications

Al Alawi, L., Soteriades, E. S., Paulo, M. S., Östlundh, L., Grivna, M., Al Maskari, F., & Al-Rifai, R. H. (2020). Environmental assessment of cytotoxic drugs in healthcare settings: protocol for a systematic review and meta-analysis. Systematic Reviews, 9(1). DOI: https://doi.org/10.1186/s13643-020-01494-4.

Appendices

Appendix A: PRISMA checklist

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol) (Al Alawi et al., 2020).

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to Participants, Interventions, Comparisons, Outcomes, and Study Design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	

Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	

Appendix B: Search specifications

Pre-search in PubMed, 2020-08-20

Search specifications: All terms are searched in the fields for “Title” and “Abstract” and in “MeSH” when available. No filters or limitations applied

Result: 983 references

Search string
(("Hospitals"[Mesh] OR "Oncology Nursing"[Mesh] OR "Oncology Service, Hospital"[Mesh] OR "Medical Oncology"[Mesh] "Adult Day Care Centers"[Mesh] OR "Health Facilities"[Mesh] OR "cancer care facilities" [Title/Abstract] OR "cancer care facility"[Title/Abstract] OR "outpatient clinic" [Title/Abstract] OR "outpatient clinics" [Title/Abstract] OR "healthcare environment"[Title/Abstract] OR "work environment"[Title/Abstract] OR "workplace environment"[Title/Abstract] OR hospital[Title/Abstract] OR hospitals[Title/Abstract] OR "oncology"[Title/Abstract] OR "day care centres"[Title/Abstract] OR "day care centers"[Title/Abstract] OR "day care centre"[Title/Abstract] OR "day care center"[Title/Abstract] OR "medical centres"[Title/Abstract] OR "medical centers"[Title/Abstract] OR "pharmacy"[Title/Abstract] OR "pharmacies"[Title/Abstract] OR "patient care area"[Title/Abstract] OR "patient care areas"[Title/Abstract] OR "inpatient ward"[Title/Abstract] OR "outpatient ward"[Title/Abstract] OR "preparation room"[Title/Abstract] OR "administration room"[Title/Abstract] OR "healthcare facilities"[Title/Abstract] OR "health facility"[Title/Abstract] OR "medical facility"[Title/Abstract] OR "medical facilities"[Title/Abstract] OR "Health Personnel"[Mesh] OR "health care professionals"[Title/Abstract] OR "health personnel"[Title/Abstract] OR "health care providers"[Title/Abstract] OR "health care provider"[Title/Abstract] OR "healthcare providers"[Title/Abstract] OR "healthcare workers"[Title/Abstract] OR "healthcare worker"[Title/Abstract] OR "healthcare professionals"[Title/Abstract] OR "health care professional"[Title/Abstract] OR "healthcare professional"[Title/Abstract] OR "healthcare personnel"[Title/Abstract] OR "health care personnel"[Title/Abstract] OR "health care workers"[Title/Abstract] OR "medical worker"[Title/Abstract] OR "healthcare staff"[Title/Abstract] OR "health care staff"[Title/Abstract] OR "pharmacists"[Title/Abstract] OR "pharmacy technicians"[Title/Abstract] OR "nurses"[Title/Abstract] OR "nurse"[Title/Abstract] OR "drug-handlers"[Title/Abstract] OR physician*[Title/Abstract] OR doctor*[Title/Abstract] OR "physician assistants" [Title/Abstract] OR "physicians'

assistants" OR "physician assistant" [Title/Abstract] OR "physicians' assistant" OR "doctor's assistants" OR "doctor assistants" OR "doctor's assistant" OR "doctor assistant" OR "physicians' extenders" OR "physicians extenders" OR "physicians' extender" OR "physicians extender" OR clinician*[Title/Abstract] OR "healthcare technicians"[Title/Abstract] OR "healthcare technician"[Title/Abstract] OR "medical technicians"[Title/Abstract] OR "medical technician"[Title/Abstract]) AND ("Equipment Contamination"[Mesh] OR "equipment contamination"[Title/Abstract] OR "environmental assessment"[Title/Abstract] OR "environmental assessments"[Title/Abstract] OR "surface contamination"[Title/Abstract] OR "surface contaminations"[Title/Abstract] OR "exposure assessment"[Title/Abstract] OR "exposure assessments"[Title/Abstract] OR "personal protective equipment"[Title/Abstract] OR "biological safety cabinet"[Title/Abstract] OR "BSC"[Title/Abstract] OR "closed system devices"[Title/Abstract] OR "closed-system transfer device"[Title/Abstract] OR "closed-system drug transfer device"[Title/Abstract] OR "drug transfer device"[Title/Abstract] OR "robotic system"[Title/Abstract] OR "robotic systems"[Title/Abstract] OR "compounding aseptic containment isolator"[Title/Abstract] OR "environmental sampling"[Title/Abstract] OR "environmental monitoring"[Title/Abstract] OR "environmental contamination"[Title/Abstract] OR "workplace contamination"[Title/Abstract] OR "contamination levels"[Title/Abstract] OR "contamination level"[Title/Abstract] OR "wipe samples"[Title/Abstract] OR "wipe sampling"[Title/Abstract] OR "environmental exposure"[Title/Abstract] OR "workplace exposure"[Title/Abstract] OR "workers exposure"[Title/Abstract] OR "control measures"[Title/Abstract] OR "occupational risk"[Title/Abstract] OR "occupational risks"[Title/Abstract] OR "occupational hazards"[Title/Abstract] OR "occupational hazard"[Title/Abstract] OR "occupational exposure"[Title/Abstract] OR "Occupational Exposure"[Mesh] OR "occupational exposures"[Title/Abstract] OR "occupational medicine"[Title/Abstract] OR "Occupational Medicine"[Mesh] OR "employee health"[Title/Abstract] OR "Personal Protective Equipment"[Mesh] OR "personal protective equipment"[Title/Abstract] OR "personal protective equipments"[Title/Abstract] OR "PPE" [Title/Abstract])) AND ("antitumor drugs"[Title/Abstract] OR "antitumor drug"[Title/Abstract] OR "antitumor agent"[Title/Abstract] OR "antitumor agents"[Title/Abstract] OR "cytotoxic drug"[Title/Abstract] OR "cytotoxic drugs"[Title/Abstract] OR "cytotoxic agent"[Title/Abstract] OR "cytotoxic agents"[Title/Abstract] OR "cytostatic drugs"[Title/Abstract] OR "cytostatic drug"[Title/Abstract] OR "cytostatic agent"[Title/Abstract] OR "cytostatic agents"[Title/Abstract] OR "Cytostatic Agents"[Mesh] OR "antineoplastic drugs"[Title/Abstract] OR "antineoplastic drug"[Title/Abstract] OR "antineoplastic agent"[Title/Abstract] OR "antineoplastic agents"[Title/Abstract] OR "Antineoplastic Agents"[Mesh] OR "hazardous drugs"[Title/Abstract] OR "hazardous drug"[Title/Abstract] OR "anticancer drugs"[Title/Abstract] OR "anticancer drug"[Title/Abstract] OR "anticancer

agent"[Title/Abstract] OR "anticancer agents"[Title/Abstract] OR "chemotherapy drugs"[Title/Abstract] OR "chemotherapy drug"[Title/Abstract] OR "chemotherapy agent"[Title/Abstract] OR "chemotherapy agents"[Title/Abstract] OR "chemotherapeutic drugs"[Title/Abstract] OR "chemotherapeutic drug"[Title/Abstract] OR "chemotherapeutic agent"[Title/Abstract] OR "chemotherapeutic agents"[Title/Abstract] OR "cancer drugs"[Title/Abstract] OR "cancer drug"[Title/Abstract] OR "anti-carcinogenic"[Title/Abstract] OR "anticarcinogenic drug"[Title/Abstract] OR "anticarcinogenic drugs"[Title/Abstract] OR "anticarcinogenic agent"[Title/Abstract] OR "anticarcinogenic agents"[Title/Abstract] OR "Anticarcinogenic Agents"[Mesh] OR docetaxel[Title/Abstract] OR paclitaxel[Title/Abstract] OR etoposide[Title/Abstract] OR gemcitabine[Title/Abstract] OR cytarabine[Title/Abstract] OR doxorubicin[Title/Abstract] OR methotrexate[Title/Abstract] OR "5-fluorouracil"[Title/Abstract] OR ifosfamide[Title/Abstract] OR cyclophosphamide[Title/Abstract] OR "Docetaxel"[Mesh] OR "Paclitaxel"[Mesh] OR "Etoposide"[Mesh] OR "Cytarabine"[Mesh] OR "Doxorubicin"[Mesh] OR "Methotrexate"[Mesh] OR "Ifosfamide"[Mesh] OR "Cyclophosphamide"[Mesh] OR "hazardous agent"[Title/Abstract] OR "hazardous agents"[Title/Abstract] OR "chemotherapies"[Title/Abstract] OR "anti-tumor"[Title/Abstract] OR "category-D"[Title/Abstract] OR "category-X"[Title/Abstract] OR "oncology drugs"[Title/Abstract])

Appendix C: List of string and numerical variables

String and numerical variables to be extracted from eligible studies

Variable Name	Variable Type	Variable Label	Values
Record	Numeric	Study record number	Numeric
Author	String	First author's name, initials, et al	String
Pub_year	Numeric	Publication year	Numeric
Journal	String	Journal where the study published	String
Country	String	Country where the study was executed	String
City	String	City where the study was executed	String
Study_des	Numeric	Study design	1 Cross-sectional
			2 Prospective cohort
			3 Retrospective cohort
			4 Case-control
			5 Unclear
Yrstart	Date (MM/DD/YYYY)	Year data collection started	Numeric
Yrend	Date (MM/DD/YYYY)	Year data collection ended	Numeric
Duration	Numeric	Data collection duration in years	Numeric
Location	Numeric	Location from where the environmental sample were collected	1 Pharmacy
			2 Store
			3 Inpatient ward
			4 Laboratory
			5 Outpatient clinic
			6 ……
			4 ……
			5……
			6 ……
			7 ……
Sampling_strategy	Numeric	Subjects sampling strategy	1 Convenience
			2 Systematic
			3 Consecutive

			4 Random sampling 5 Multistage probability sampling 6 Unclear
Cyto_drug	Numeric	Tested cytotoxic drugs	Name of the tested cytotoxic drug
Anal_tool	String	Analytical tool [High-performance Liquid Chromatography-Tandem Mass Spectroscopy (LC-MS/MS) or Inductively Coupled Plasma Mass Spectrometry (ICP-Ms)]	1 LC-MS/MS 2 ICP-Ms
Sensitivity	Numeric	Sensitivity of contaminant measurements	1 LOD 2 LOQ
Sample	Numeric	Tested sample size	Numeric
Positive	Numeric	Number of the positive sample	Numeric
Mean_Con	Numeric	Mean concentration of the tested cytotoxic drug	Numeric
Stdev	Numeric	Standard deviation of the mean concentration of cytotoxic drugs in the tested sample	Numeric
Unit	String	Unite of the measured mean concentration (e.g. nanogram)	String

LC-MS/MS: High-Performance Liquid Chromatography-tandem Mass Spectroscopy

ICP-Ms: Inductively Coupled Plasma-Mass Spectrometry

LOD: Limit of Detection

LOQ: Limit of Quantitation

Appendix D: KAP study instruments

Questionnaire on Cytotoxic Drugs

You are invited to take part in a study to evaluate the knowledge, attitudes and practices of Abu Dhabi healthcare professionals on the hazards associated with occupational exposure to cytotoxic drugs. This study will be conducted by Dr. Elpidoforos S. Soteriades and Ms. Laila Al Alawi from the Institute of Public Health, College of Medicine and Health Sciences, Al Ain.

Kindly take a few minutes to answer the questions in the survey below, keeping in mind that all responses will remain confidential and you will not be identified in any way.

Participating in this study is voluntary and you are free to withdraw from the study at any time.

If you have any further information, questions or any ethical concerns, please feel free to contact Dr. Elpidoforos S. Soteriades at esoteria@uaeu.ac.ae or Ms. Laila Al Alawi at 200070202@uaeu.ac.ae

1. Please indicate your willingness to participate in this survey:

- ☐ I ACCEPT to participate in this survey
- ☐ I do NOT ACCEPT to participate in this survey

2. What is your age in years?

a. ☐ 20 - 25
b. ☐ 26 - 30
c. ☐ 31 - 35
d. ☐ 36 - 40
e. ☐ 41- 45
f. ☐ 46 - 50
g. ☐ 50+

3. What is the highest degree or level of education you have completed?

a. ☐ Diploma
b. ☐ Bachelor Degree
c. ☐ Master Degree
d. ☐ Doctoral Degree

4. What is your current occupation?

a. ☐ Clinical Pharmacist
b. ☐ Pharmacist
c. ☐ Pharmacy Technician
d. ☐ Registered Nurse
e. ☐ Assistant Nurse
f. ☐ Nurse Practitioner
g. ☐ Specialty Nurse

5. What is your marital status?

a. ☐ Married

b. ☐ Single

c. ☐ Divorced

d. ☐ Widowed

6. What is your gender?

a. ☐ Male

b. ☐ Female

7. Have you ever had pregnancy complications?

a. ☐ Yes

b. ☐ No

8. What kind of pregnancy complications did you face?

a. ☐ Congenital anomalies

b. ☐ Miscarriage

c. ☐ Premature birth

d. ☐ Stillbirth

e. ☐ Other (please specify):
……

9. How many years have you been working?

a. ☐ Less than 2 years

b. ☐ 2 – 5 years

c. ☐ 6 – 10 years

d. ☐ 11 – 15 years

e. ☐ 16 – 20 years

f. ☐ Over 20 years

10. Which of the following corresponds to your working schedule?

a. ☐ Shifts

b. ☐ Regular work hours (daily)

11. How many years have you been preparing/administrating cytotoxic drugs?

a. ☐ Less than 2 years

b. ☐ 2 – 5 years

c. ☐ 6 – 10 years

d. ☐ 11 – 15 years

e. ☐ 16 – 20 years

f. ☐ Over 20 years

12. Where do you usually prepare cytotoxic drugs?

a. ☐ On the drug preparation bench

b. ☐ In the nurses' room

c. ☐ In a biological safety cabinet

d. ☐ In an incubator

e. ☐ Other (please specify):
……

13. Do you know if there is a ventilation (negative pressure) in the place of preparation of cytotoxic drugs?

a. ☐ Yes, there is ventilation

b. ☐ No, there is no ventilation

c. ☐ I don't know

14. Which of the following do you use during the preparation of cytotoxic drugs? (please check all that apply)

a. ☐ Gloves

b. ☐ Gown

c. ☐ Goggles

d. ☐ Mask

e. ☐ Overshoes

f. ☐ Head covers

g. ☐ None of the above

15. Do you smoke?

a. ☐ Yes

b. ☐ No

16. For how long have you been smoking?

a. ☐ Less than 1 year

b. ☐ 1 – 5 years

c. ☐ 6 – 10 years

d. ☐ 11 – 15 years

e. ☐ Over 15 years

17. Do you ever smoke in a place of preparation of cytotoxic drugs?

a. ☐ Never

b. ☐ Rarely

c. ☐ Sometimes

d. ☐ Often

e. ☐ Very often

18. Do you ever eat in a place of preparation of cytotoxic drugs?

a. ☐ Never
b. ☐ Rarely
c. ☐ Sometimes
d. ☐ Often
e. ☐ Very often

19. Do you ever drink in a place of preparation of cytotoxic drugs?

a. ☐ Never
b. ☐ Rarely
c. ☐ Sometimes
d. ☐ Often
e. ☐ Very often

20. Do you ever store beverages and edibles in a refrigerator or a place of preparation of cytotoxic drugs?

a. ☐ Never
b. ☐ Rarely
c. ☐ Sometimes
d. ☐ Often
e. ☐ Very often

21. Do you ever use makeup in a place of preparation of cytotoxic drugs?

a. ☐ Never
b. ☐ Rarely
c. ☐ Sometimes
d. ☐ Often
e. ☐ Very often

22. How often do you handle cytotoxic drugs?

a. ☐ 1 day per week

b. ☐ 2 days per week

c. ☐ 3 days per week

d. ☐ 4 days per week

e. ☐ Everyday

23. How many cytotoxic drugs do you prepare each day?

a. ☐ 1 drug per day

b. ☐ 2 – 5 drugs per day

c. ☐ 6 – 10 drugs per day

d. ☐ More than 10 drugs per day

24. How many cytotoxic drugs do you administer (deliver) in one day?

a. ☐ 1 drug per day

b. ☐ 2 – 5 drugs per day

c. ☐ 6 – 10 drugs per day

d. ☐ More than 10 drugs per day

25. Do you change linens of beds used by patients who receive cytotoxic drugs?

a. ☐ Yes

b. ☐ No

26. Do you change the urine collection cups and the collection of nasogastric tubes used by patients who receive cytotoxic drugs?

a. ☐ Yes

b. ☐ No

27. Do you change the IV line and/or cannula used by patients who receive cytotoxic drugs?

a. ☐ Yes

b. ☐ No

28. If you perform the above (changing linens, nasogastric tubes etc.), please report the personal protection equipment that you use (check all that apply):

a. ☐ Gown

b. ☐ Goggles

c. ☐ Mask

d. ☐ Gloves

e. ☐ Overshoes

f. ☐ Head covers

g. ☐ None of the above

29. Do you wash your hands every time after handling cytotoxic drugs?

a. ☐ Never

b. ☐ Rarely

c. ☐ Sometimes

d. ☐ Often

e. ☐ Always

30. Where do you put the waste from cytotoxic drugs or from objects/materials which have been contaminated by cytotoxic drugs?

a. ☐ In a regular container
b. ☐ In a special container for hospital waste
c. ☐ In a special container for cytotoxic drugs
d. ☐ Other (please specify):

……

31. Have you had any of the following symptoms while you were at work in the last 6 months?

a. ☐ Nausea

b. ☐ Vomiting

c. ☐ Dizziness

d. ☐ Skin irritation

e. ☐ Mucous membrane irritation

f. ☐ Throat irritation

g. ☐ Eye irritation

h. ☐ Abdominal pain

i. ☐ Headache

j. ☐ Hair loss

32. Out of the symptoms that you have reported in the previous question, which they were triggered by exposure to cytotoxic drugs?

a. ☐ Nausea

b. ☐ Vomiting

c. ☐ Dizziness

d. ☐ Skin irritation

e. ☐ Mucous membrane irritation

f. ☐ Throat irritation

g. ☐ Eye irritation

h. ☐ Abdominal pain

i. ☐ Headache

j. ☐ Hair loss

33. Have you had any training on how to handle cytotoxic drugs in the past year?

a. ☐ Yes

b. ☐ No

34. From where do you receive information regarding the risks associated with your job? (please check all that apply)

a. ☐ Mass media

b. ☐ Hospital administration

c. ☐ Internet

d. ☐ Seminars and conferences

e. ☐ Professional organizations

f. ☐ Scientific literature

g. ☐ Other (please specify):

……

35. Which challenges would prevent you from handling cytotoxic drugs safely?

(please check all that apply)

a. ☐ Low workload

b. ☐ High workload

c. ☐ Availability of Personal Protective Equipment (PPE)

d. ☐ Lack of knowledge

e. ☐ Comfort in using of PPE

f. ☐ Other (please specify):

……

36. Is there a safe handling policy/procedure for cytotoxic drugs at your facility?

a. ☐ Yes

b. ☐ No

c. ☐ I don’t know

37. In my department, employees are encouraged to become involved in workplace health and safety matters (e.g. reporting incidents, safety meetings, risk assessment)

a. ☐ Don't know

b. ☐ Strongly Disagree

c. ☐ Disagree

d. ☐ Agree

e. ☐ Strongly Agree

38. The protection of workers from exposure to hazardous agents is a high priority in my department

a. ☐ Don't know

b. ☐ Strongly Disagree

c. ☐ Disagree

d. ☐ Agree

e. ☐ Strongly Agree

The next few questions will assess your knowledge about the ways of contamination with, methods of protection from and potential effects of cytotoxic drugs. Please answer the following questions as best as you can.

Table 1: Examples on Cytotoxic Drugs. Please check the correct answer				
		Right	Wrong	I do not know
39	5-Fluorouracil is a drug used as a cytotoxic agent			
40	Some cytotoxic drugs can be used for organ transplant patients.			
41	Cytotoxic drugs can cause damage to the RNA or DNA of healthy cells, as seen in cancer cells.			
42	It has not been verified that 5-Fluorouracil, 6-Mercaptopurine, Methotrexate which are cytotoxic drugs from the group of antimetabolites, have carcinogenic action.			
43	Cytotoxic drugs have genotoxic effects.			
44	Cytotoxic drugs have carcinogenic effects.			
45	Some cytotoxic drugs have teratogenic effects.			
46	Cytotoxic drugs have toxic effects on the liver.			
47	The only symptoms observed on those who handle cytotoxic drugs is hair loss, weakness and allergies.			
48	Exposure to cytotoxic drugs can cause spontaneous abortions.			
49	All cytotoxic drugs, while being handled with a syringe, do not react with air because their molecular mass is large.			
50	In places of preparation of cytotoxic drugs, the application of cosmetics is strictly prohibited.			
51	Cytotoxic drugs reach the blood by only penetrating through the skin.			
52	The two most important ways of contamination with cytotoxic drugs is inhalation and ingestion.			
53	Clothes contaminated with urine and linens of patients who have received cytotoxic drugs may probably cause a problem of exposure to cytotoxic drugs.			

54	Vertical chambers of laminar flow (cabinets) which are used for the preparation of cytotoxic drugs must be cleaned once every week.			
55	Those who use cytotoxic drugs must wear special chemotherapy gloves made from latex or nitrile.			
56	Those who use cytotoxic drugs must not wear gloves with powder.			
57	To avoid the potential exposure of employees with cytotoxic drugs through inhalation, surgical masks must be used.			
58	Gloves used for the preparation of cytotoxic drugs must be replaced every one to two hours.			
59	During the preparation of cytotoxic drugs, appropriate ventilation system must be used.			
60	The cleaning of the biological safety chamber (cabinet) must be done with a germicide.			
61	All waste that is contaminated with cytotoxic drugs must be assessed and handled in the same way like all the other medical waste of a hospital.			
62	The part of the skin that comes in direct contact with cytotoxic drugs must be washed directly with water and soap.			
63	For the preparation of cytotoxic drugs it is better to use needles with a small lumen.			

Thank you for Completing this Survey

Appendix E: UAEU ethical approval

UAEU

Letter of Ethics Approval for Dr. Elpidoforos Soteriades Research Application ERS_2019_5982

جامعة الإمارات العربية المتحدة
United Arab Emirates University

This is to certify that the Research Application ERS_2019_5982 by Dr. Elpidoforos Soteriades for the project on "Exposure and Handling Practices of Healthcare Professionals for Cytotoxic Drugs in the Workplace Environment," has been approved by the UAEU sub-committee for research ethics in social sciences.

Sincerely, WMcDonald

Associate Professor William McDonald
Chair of UAEU Research Ethics Sub-Committee for Social Sciences
United Arab Emirates University
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Appendix F: AD-DOH ethical approval

عام التسامح
YEAR OF TOLERANCE

دائرة الصحة
DEPARTMENT OF HEALTH

Ref: ADHRTC-10/2019-1
Date: 14/11/2019

Abu Dhabi Health Research and Technology Committee
Approval Letter

Research proposal "**Exposure and Handling Practices of Healthcare Professionals for Cytotoxic Drugs in the Workplace Environment**"

Dear Laila,

Thanks for submitting all required documents to support the review process of above-mentioned study to Abu Dhabi Health Research and Technology Committee.
The request has been carefully reviewed by the committee and we are pleased to inform you that the committee, after deliberation, has granted you ethical approval for the research proposal submitted.

Please note that this approval is considered as an official approval and it overrides the local committee's approval; however, you need to report to the local Research Ethics Committee in the desired institutions mentioned in the study protocol in order for us to receive the following:

1. Local REC feedback in case of anything that might warrant the review of the ethical approval given
2. Any proposed changes to the research protocol/the conduct of research
3. Any information that might affect the safety of the Human Subjects
4. Annual report to Medical Research Department about the progress of the study
5. Pre-publication request

ADHRTC wishes you all the best in your research endeavors.

Abu Dhabi Health Research and Technology Committee Chair (ADHRTC),
Department of Health,
Abu Dhabi-UAE.