Cytostatic-drugs handling in hospitals:
Impact study of the contamination at occupational environments

João Oliveira da Silva

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Universidade do Minho
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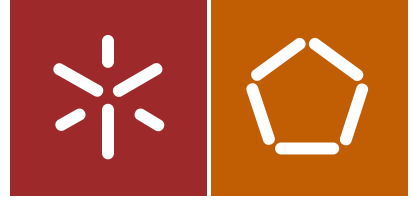

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Cytostatic-drugs handling in hospitals: Impact study of the contamination at occupational environments

Thesis of the Doctoral Program in Industrial and Systems Engineering

Work carried out under the supervision of
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Dr. Rudolf Schierl (U. Munique)
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September, 2018

STATEMENT OF INTEGRITY

I hereby declare having conducted my thesis with integrity. I confirm that I have not used plagiarism or any form of falsification of results in the process of the thesis elaboration.

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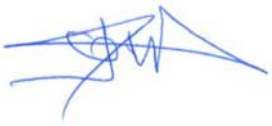
Signature: 

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ABSTRACT

Cytostatics are antineoplastic drugs capable of inhibiting the growth of tumour cells, used mainly in the treatment of cancer, and are of vital importance in the health treatment of patients suffering from neoplastic diseases. These drugs are prepared in hospital pharmacies and administered in medical oncology Day-care hospitals, both by pharmacy and nursing professionals, in occupational context. These professionals may be exposed to chemical risk, which constitutes a threat to safety in work environments. The main objective of this research is to assess the level of environmental contamination and to study the links between the exposure and the possible effects associated with it. Also, the exposure effects felt by pharmacy and nursing professionals that handle and/or administer these drugs in their daily tasks were evaluated. To study the impact on the work environment, twenty-four sites, from 3 hospital centers (A, B and C), were chosen and fifty-six samples collected from each of the selected drugs, i.e., platinum (Pt) drugs (cis/carbo/oxaliplatin) and 5-fluorouracil (5-FU). The used sampling technique was the "*wipe sampling*", which consists of cleaning a specific area surface with a previously moistened paper filter (hydrogen chloride (HCl) for Pt and methanol (MeOH) for 5-FU. The most significant contamination was found in the laminar flow hood, with samples reaching 179.3 pg/cm^2 (5-FU, hospital B) and 100.0 pg/cm^2 (Pt, hospital C). It was also found high contamination levels in the bathroom floor, namely 1228 pg/cm^2 (5FU, hospital A) and 750.0 pg/cm^2 (Pt, hospital B). To study the potential exposure effects, a questionnaire survey technique was used. The questions aimed at a better characterization of nursing professionals that handle and administer cytostatics, their characterization as well as their workplace characteristics. The sample considered in this study included 154 health professionals, 98 of which work in hospital pharmacies and in medical oncology Day-care hospitals, the exposure group, and 56 from vascular surgery, with the latter being the control group. From the obtained results it is possible to see that professionals reported that the site where the greatest number of spills occurred was in the patient's chair and in the laminar flow hood. The most reported cause of these spillages was a poorly closed wrap. This may be related to the intention of its future use. The exposure effects were more visible in the exposed group, and the one most mentioned by health professionals was headache. This study confirmed that there are important contamination issues at the analyzed workplaces. Therefore, in order to reduce contamination, a set of measures have been implemented to minimize exposure and associated effects.

Keywords: Cytostatics, exposure effects, occupational exposure, handling and surface

RESUMO

Os citostáticos são fármacos antineoplásicos capazes de inibir o desenvolvimento de células tumorais. São usados essencialmente no tratamento do cancro e têm uma importância vital no tratamento da saúde de pacientes que sofrem de doenças neoplásicas. Estes fármacos são preparados nas farmácias hospitalares e administrados nos hospitais de Dia de medicina oncológica, por profissionais de farmácia e de enfermagem respetivamente. Estes profissionais podem estar expostos ao risco químico, o qual constitui uma ameaça à segurança em ambientes laborais. O objetivo principal desta pesquisa é avaliar o nível de contaminação ambiental e estudar a relação entre exposição e os possíveis efeitos a ela associados. Também foram avaliados os efeitos colaterais sentidos pelos profissionais que nas suas tarefas diárias manipulam/administram estes fármacos. Para estudar o impacto no local de trabalho foram selecionados 24 locais de três centros hospitalares (A, B e C) e foram recolhidas, 56 amostras de cada um dos dois fármacos selecionados, platina (Pt) e 5-fluorouracil (5-FU). A técnica de amostragem utilizada foi "wipe sampling", que consiste na limpeza de uma área de superfície específica com um filtro de papel previamente humedecido co cloreto de hidrogénio (HCl) para Pt e metanol (MeOH) para 5-FU. A contaminação mais significativa foi detetada na câmara de fluxo laminar, com amostras atingindo 179.3 pg/cm2 (5-FU, hospital B) e 100.0pg/cm2 (Pt, hospital C). Também foram detetados elevados níveis de contaminação no piso da casa de banho, sendo 1228 pg/cm2 (5-FU, hospital A) e 750.0 pg/cm2 (Pt, hospital B). No estudo dos potenciais efeitos colaterais, foi utilizada a técnica do inquérito por questionário. As questões consideradas visaram uma melhor caraterização dos profissionais de saúde que manipulam/administram citostáticos, bem como das suas condições laborais. A amostra deste estudo foi constituída por 154 profissionais de saúde, sendo que 98 deles, o grupo exposto, trabalham nas farmácias hospitalares e nos hospitais de Dia de medicina oncológica, e 56, o grupo de controlo, desempenham funções em cirurgia vascular. Nos resultados do inquérito os profissionais reportaram que o local onde ocorreu o maior número de derramamentos foi na cadeira do paciente e na câmara de fluxo laminar. A causa mais referida para esta ocorrência foi o facto do invólucro do recipiente estar mal fechado. Isso pode estar relacionado com a intenção do seu uso futuro. O efeito colateral mais reportado no grupo exposto foi a cefaleia. Este estudo confirmou a existência de níveis elevados de contaminação em vários locais de trabalho. Assim, para reduzir a contaminação, foi implementado um conjunto de medidas para diminuir a exposição e os efeitos associados.

Palavras-chave: Citostáticos, efeitos colaterais, exposição ocupacional, manipulação e superfície

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ABBREVIATIONS, INITIALS AND ACRONYMS LIST

CSTD - Closed system transfer device

DNA - Deoxyribonucleic acid

5-FU - 5-Fluorouracil

LFH - Laminar Flow Hood

LOD - Limit of Detection

HCl - Hydrogen Chloride

HEPA - High Efficiency Particulate Air Filter

HPLC - High Performance Liquid Chromatography

MeOH - Methanol

PPE - Personal Protective Equipment

Pt - Platinum

RNA - Ribonucleic acid

SPSS - Statistic Package for the Social Science

TGV1 and **TGV2** - "threshold guidance values"

VLE - limit value exposure

χ^2 - Chi-Square

PART I - INTRODUCTION AND OBJECTIVES

CHAPTER 1 - INTRODUCTION

In general, working environment conditions are a constant concern of European and national authorities in the field of occupational health and safety. It is necessary to ensure that workplaces and workers in different sectors of activity carry out their tasks in good safety and hygiene conditions, as set out in Directive 2014/27 / EU of the European Parliament and of the Council, of 26 February, 2014, and transposed into national law by Decree-Law No. 88/2015 of 28 May, 2015.

Different business activities, in the development of their transformation processes, confine, in themselves, a set of hazards that can put their collaborators' health at risk. Different workplaces can have different risks. However, risks can also be common regardless of the sector of activity. Thus, we can find workers exposed to various risk factors, such as physical (noise, vibration, radiation, etc.), chemical (gases, aerosols, dust, cytostatics, etc.), biological (viruses, fungi, and bacteria), ergonomic (e.g. postures and physical effort) and psychosocial (stress, violence, harassment, etc.).

In hospitals, the working environment has a very similar framework towards risks as described above, although the chemical and biological risks are more specific of the health sector. As an example, health care professionals may be exposed to physical risk factors when in contact with or close to radiation equipment, of biological risk due to viruses and bacteria present in these environments, of chemical risk, when handling or administering anesthetic gases, cytostatics, or other drugs with potential for damage, but also of ergonomic risks, such as bad designed workplaces, and also psychosocial risks, such as harassment.

Among the listed risks, chemicals contamination stand out because they may cause health problems in professionals who are in contact with dangerous chemical substances, and some of these are the cause of neoplastic diseases.

Patients with cancer disease are treated in specific hospitals or in hospitals with oncology units. These patients, who typically stay in hospitals or in Day-care hospitals, are treated with cytostatic drugs, which are antineoplastic, i.e., they have the ability to eliminate cancer cells even though they have esposure effects (Kaijser, 1990). Cytostatics are prepared in hospital pharmacies by pharmacists and/or pharmacy technicians under aseptic conditions and, supposedly, in strict compliance with specific procedures, including the use of adequate protective equipment. These drugs are then administrated in Day-care hospitals by nurses, who should also use adequate personal protective equipment. These health professionals, even when complying with all cleaning and safety procedures

and using personal protective equipment, are exposed to chemical risk during the preparation and administration of cytostatics (Brouwers et al., 2007).

Several studies have been carried out in different countries and, in general, contamination has been detected in several locations, among them laminar flow hoods, floors, shelves, packing tables, infusion pumps, etc. (Schmaus, Schierl, & Funck, 2002; Schierl et al., 2009; Kopp, Schierl, & Nowak, 2013; Janes, Tanguay, Caron, & Bussières, 2015).

Environmental contamination by cytostatics in Portuguese pharmacies and Day-care hospitals has been insufficiently researched, with the exception of the works developed by Silva (2011) and Viegas, Pádua, Veiga, Carolino, & Gomes, (2014). In these studies, contamination was detected in hospital pharmacies, namely in laminar flow chambers, on shelves, trays and the floor near laminar flow chambers. Also, in Day-care hospitals, contamination was detected in infusion pumps, armchairs, and the bathroom floors. These levels of contamination can be harmful to human health. It is therefore relevant to gain more detailed knowledge of environmental conditions and the possible exposure of health professionals in hospital centers.

The aim of this study is based on the existence of a previous work in this field (Silva, 2011), which, although of a exploratory nature, allowed to raise the interest in developing the knowledge about cytostatics handling in Portugal, as well as the working procedures, the factors that contribute to environmental contamination, and played a role in reducing and/or eliminating contamination. Likewise, it intends to make health professionals reflect and think about their practices, procedures, and occupational exposure to cytostatics.

The knowledge of “hot spots“ and sources of surface contamination within the hospital environment as well as the detection of the potential impacts of the working procedures on the contamination levels contributes to develop adequate hygiene strategies and prevention measures in order to reduce occupational exposure to cytostatics.

This thesis is divided into three different parts, in order to facilitate its structure: a preliminary part, which corresponds to the introduction and to the definition of the objectives and the topic under research; a second part, for the literature review; and a third one, for the development of the study in its different components.

The first part is divided into two chapters: the first one refers to the introduction, and the second one deals with the definition of the objectives and the research itself.

The second part consists of two chapters. The first deals with the importance of cytostatics, their definition, state-of-the-art, applications and preparation. The second refers to occupational exposure to cytostatics. In this chapter, emphasis is given to the cytostatics phases of exposure, effects of exposure, means of prevention and risk assessment and control.

The third part of this thesis, as mentioned above, covers the study itself and consists of 3 chapters. The first chapter of this part corresponds to chapter 5, introducing the methodology, and is organized in ten subchapters, which refer to the general aspects of the study. The first is the literature review, the second refers to the selection of hospital units, the third shows the observation and recording routines, the fourth shows the development of the questionnaire, the fifth sub-chapter presents the sampling technique and its practical application, the sixth shows the sample setup, the seventh shows the sample locations, the eight compares the methodology used by the 2010 and the 2015 studies in hospital center B, the ninth examines the laboratory analysis techniques applied to the samples and the tenth refers to the statistical analysis. The results and their interpretation are shown in chapter 6. In order to make their analysis easier, this chapter was also divided into seven sub-chapters, the first of which shows the results of the questionnaire and the exposure effects under study, the second refers to the results of the environmental monitoring, the third to the impact of the working procedures on contamination, the fourth to the results comparison between the 2010 and 2015 studies in hospital center B, the fifth to the results discussion, the sixth to the list of recommended procedures for handling and administration practices of cytostatics, and the seventh refers to the study limitations. Finally, chapter 7 presents the conclusions and future perspectives.

CHAPTER 2 - AIMS AND RESEARCH QUESTIONS

Considering the health of the hospital units' staff, especially those who handle/administer cytostatics in hospital pharmacies and in ambulatory care, respectively, and due to the risks that they are exposed to, the following aims were defined for this study:

Main aim:

- To assess the impact caused by the occupational exposure to platinum-drugs (e. g. cisplatin, Pt) and 5-fluorouracil (5-FU) in two aspects, in the measurement of environmental contamination at the workplace and in the verification of the existence of self-reported symptoms among the exposed workers;

Specific aims:

- To quantify the concentrations of the referred products on the workstations in an hospital environment;

- To observe and record the work methods and practices of handling/administration of cytostatics in order to establish possible relations between these and the results obtained in laboratory analysis;

- To elaborate and apply a questionnaire to the workers on the existence of self-reported symptoms potentially associated to the occupational exposure;

- To determine the existence of accidental exposure to cytostatics and to characterize the unsafe act that leads to that occurrence;

- To proceed to the analysis of the environmental results obtained for the cytostatics under study;

- To relate eventual differences in the working methods/procedures used by health professionals;

- To analyse the relation between the contamination levels/contaminated surfaces during the working tasks and the self-reported symptoms potentially associated to it;

- Compare the results of a study previously performed in 2010 with those of the current study;

- To verify if there is a contamination variation over the period (before, middle, end task) of handling, considering different moments of exposure assessment;

- To create a procedures checklist of actual practices in the handling/administration;

- To propose intervention measures for the reduction of the exposure.

Taking into account the mentioned aims and the need of a clear evidence of the original and scientific character of the current proposal, the research questions that will guide the present research are the following:

- Is the exposure to Pt and 5-FU higher for health professionals that handle/administer cytostatics in hospitals, in comparison with the rest of health professionals?

- Are there self-reported symptoms by health professionals occupationally exposed to cytostatics?

- Are there any different procedures to handle/administer cytostatics?

- Is there an accidental exposure to cytostatics? Which are the unsafe act*s that lead to its occurrence?*

- Which are the factors that most influence the exposure results? Are these human or technological?

PART II - LITERATURE REVIEW

CHAPTER 3 - THE IMPORTANCE OF CYTOSTATICS

3.1 - Definitions

Cytostatics are a heterogeneous group of chemical substances capable of inhibiting the growth and/or the vital process of tumor cells, with tolerable toxicity on normal cells, that interfere with the DNA or with the DNA synthesis of the tumor cells (Sessink & Bos, 1999). Cytostatics are antineoplastic drugs that have certain characteristics that cause toxic effects in patients and, a risk possibly, for the health professionals that prepare them in hospital pharmacies, in pharmacists and pharmacy technicians, and in the nurses who administer them (Brouwers et al., 2007).

These drugs are classified as carcinogenic, mutagenic and teratogenic to humans by the International Agency for Research on Cancer (IARC) (Sessink & Bos, 1999). Teratogenic drugs are able to inhibit the development of tumors by eliminating actively growing cells, but may also interfere with cell division and fetal cell formation (Shirangi, Bower, Holman, Preen, & Bruce, 2014). This agency grouped 10 antineoplastic drugs in group 1 as carcinogenic to humans, and another 10 drugs in group 2A, as probably carcinogenic to humans (Sottani, Porro, Comelli, Imbriani, & Minoia, 2010).

3.2 - Cytostatics as a occupational risk factor

Cytostatics are powerful drugs used in the treatment of patients suffering from cancer. However, they represent a professional risk for health workers (pharmacists, pharmacy technicians and nurses), who are also exposed to these drugs (Humer & Balen, 2001).

This interest in researching the toxic effects of cytostatic drugs on workers increased in the 1980's, after Falk (1979) and (Sorsa, Hämeilä, & Järviluoma, (2006) expressed concern about the potential risks on these professionals, due to the greater mutagenicity observed in urine samples from nurses of the oncology unit, compared to hospital office workers at large (Sorsa, 2006). This interest occured because, according to Hon, Barzan, & Astrakianakis (2014), in Europe since a 2004, the number of publications on the exposure of health workers to cytostatics, is higher than in North America.

According to IARC, Suspiro & Prista (2012) (International Agency for Research on Cancer), Suspiro (2012), antineoplastic drugs are classified according to their carcinogenicity by the following groups: group 1 comprises 7 cytotoxic drugs that are considered carcinogenic to man (Busulfan, Clorambucil, Cyclophosphamide, Etoposide, Melphalan, MOPP and Treosulfan containing regimens); group 2A

shows 4 cytotoxic drugs which are considered to be carcinogenic to humans (Adriamycin (doxorubicin), Azacitidine, Cisplatin and Teniposide); and group 2B, with 7 cytotoxic drugs considered to be possibly carcinogenic to man (Amsacrine, Bleomycin, Dacarbazine, Daunomycin, Merfalan, Mitomycin C and Mitoxantrone) (Suspiro & Prista 2012).

Pharmaceutical health professionals, pharmacy technicians and nurses, who carry out their activities in hospitals, laboratories, pharmaceutical companies and in other places (e.g. in veterinary clinics) where cytostatics are handled, are exposed to chemical risks that are harmful to their health (Kiffmeyer et al., 2013). This health professionals' concern has been increasing due to emerging factors related to the increasing of new oncological cases, therefore we can estimate an increase of the workload of these professionals. Overload, combined with lack of staff and budgetary constraints that aim at cost reduction by hospital management, may cause an increase in risk exposure and the consequent development of exposure effects on the workers' health in these organizations (Sottani, Porro, Imbriani, & Minoia, 2012).

The handling of these drugs continues to be a health professionals' concern, because even applying and strictly complying with certain safety and health rules, the potential danger to their health is still a reality (Schmaus et al., 2002). Pharmacists and nurses who manipulate cytostatics, following the procedures and implementing measures to improve their practice, get a significant reduction of this contamination in their workplaces. (Acampora et al., 2005). Healthcare workers, who work with or near cytostatics may feel acute effects, (skin rashes, headache, infertility, abortion, birth defects), and long term effects (CMR) of cytostatics on their health (NIOSH, 2004). But it is also possible to find other effects, such as headache, vertigo, dizziness, hair loss, hyperpigmentation of the skin and vomiting, observed in workers who prepare and administer cytostatics, without extractor and personal protection equipment (Kaijser, 1990). Despite knowing all these effects, there are still nurses and other healthcare professionals who do not applied safe handling guidelines for cytostatics in their daily activity, putting themselves at risk of exposure (Boiano, Steege, & Sweeney, 2014; Boiano, Steege, & Sweeney, 2015). In patient care, the most neglected equipment are gloves and gowns, showing that there is a general feeling about risk exposure as being unusual and inconsequential (Boiano et al., 2014). According to Boiano et al. (2014), this feeling induces the idea that it is not justified to adopt measures of protection.

Chemical risks are an important risk factor in the development of professional diseases and a threat to safety in many work environments. These substances enter the body through the cutaneous, respiratory and digestive tracts (Kromhout et al., 2000). Hospital workers who prepare and administer

treatments may be exposed to cytostatic agents by inhalation of aerosols, droplets and dust from products or by direct contact with the skin, which is considered the main way of exposure. Contaminated surfaces and equipment are areas of direct contact that enable skin exposure to cytostatic drugs (Sessink & Bos, 1999; Kromhout et al., 2000; Fransman, Vermeulen, & Kromhout, 2005; Fransman et al., 2007; Schierl et al., 2009; Maeda et al., 2010) and indirect contact through body fluids and excretions of patients under treatment, as a significant amount of cytostatics was detected in beddings (Fransman, Vermeulen, & Kromhout, 2004). Faced with this contamination, Fransman et al. (2007) suggested that beddings should be separately transported and pre-washed.

Most of the studies carried out and published are focused on the environmental assessment of hospital pharmacies, mainly on the surfaces, where contamination has been detected (Mason et al., 2005; Maria Hedmer, Tinnerberg, Axmon, & Jönsson, 2008; Schierl et al., 2009; Touzin, Bussières, Langlois, & Lefebvre, 2009; Sottani et al., 2010; Odraska et al., 2014) and in the cancer wing (Fransman et al., 2004; Fransman et al., 2005; Connor et al., 2010). However, the number of studies carried out under Day-care hospital (ambulatory) is limited (Fransman et al., 2007; Sugiura et al., 2011). More recently, Kopp, et al. (2013) carried out a study in a Day-care hospital, which involved several drugs from various workplaces in hospitals. In this study, general contamination was detected on work surfaces, and the most detected drugs were 5-FU, Pt and its complexes of carboplatin, cisplatin and oxaliplatin (Kopp et al., 2013). In Day-care hospitals, patients are considered a source of contamination and perhaps this contamination of the surfaces in the hospital with antineoplastic drugs cannot be avoided, even with careful handling and the use of protective devices (Kopp et al., 2013).

There is also the possibility of contamination from accidental spillage. Accidental spillages can occur even if all handling regulations are complied with, therefore they cannot be completely avoided (Sorsa & Anderson, 1996; Sottani et al., 2012). A particular case of a nurse who usually administers treatments to patients with neoplasia has been reported by Sottani et al. (2012). This accidental spillage was described in a survey after this event. The concentrations of cytostatics detected in the forearm of the exposed nurse were high, compared with those of other workplaces, due to the severe exposure, as well as the results detected in the area of the patient where the accident occurred (Sottani et al., 2012). Skin absorption is the most susceptible way of contamination on unprotected collaborators in case of spillage. In case of accidental exposure, the cytogenetic surveillance of the exposed workers is recommended (Kopjar et al., 2009).

Despite repeated guidelines and recommendations on cytostatics manipulation, significant contamination continues to be detected on the glove surface of the nurses (Rioufol et al., 2014). Health workers who prepare and administer antineoplastic drugs without collective protection and individual protection may experience acute exposure effects (Kaijser, 1990). These professionals, when they are not wearing personal protective equipment, are likely to come into contact with contaminated surfaces, (Clark & Sessink, 2013). Health professionals may also be exposed to the exposure reactions of cytostatics, similar to those in patients treated with these drugs (Sugiura et al., 2011).

However, surface contamination may not only be caused by spillages during the preparation and administration of chemotherapy drugs. Another reason for the spread of contamination is due to using wrong storage procedures, where uncontaminated objects are placed close to contaminated ones. Likewise, vials with cytostatic drugs, coming from factories, present contamination at the moment they arrive at the hospital pharmacy, which may spread the contamination into the workplaces and increase the health professionals' exposure (Nygren, Gustavsson, Ström, Eriksson, et al., 2002; Mason, Morton, Garfitt, Iqbal, & Jones, 2003; M. Hedmer, Georgiadi, Rämme Bremberg, Jönsson, & Eksborg, 2005; Touzin, Bussières, Langlois, Lefebvre, & Gallant, 2008; Bobin-Dubigeon et al., 2013; Hon, Teschke, Chu, Demers, & Venners, 2013).

Detailed cleaning and working procedures may not be enough to prevent the contamination of workplaces, due to inadequate compliance with these procedures by the health professionals involved in these tasks (Brouwers et al., 2007; Chu, Hon, Danyluk, Chua, & Astrakianakis, 2012). The cleaning procedures for the different cytostatics are assessed in order to maximize the removal of all the drugs. Cleaning stainless steel surfaces with 80% percent ethanol, to remove Pt, demonstrated not to be effective. However, when water was used, Pt recovery was higher, although it was not possible to remove it completely from the stainless steel surface (Brouwers et al., 2007). The workbenches and shipping carton should be cleaned daily with sodium hypochlorite, as well as the laminar flow hood, at its different sites, but this one more frequently (Acampora et al., 2005). According to Berruyer, Tanguay, Caron, Lefebvre, & Bussières, (2015) a reduction in contamination on the surface of the vials was verified after the implementation of the cleaning procedure on these, when they arrive and after removal from the packaging. According to the studies conducted by Brouwers et al. (2007) and Schierl et al. (2009) in hospital pharmacies, Pt contamination was detected on the warehouse shelves.

The monitoring results encourage nurses to reconsider their own practices when working with cytostatic drugs (Humer & Balen, 2001). Meanwhile, several environmental and surface monitoring

studies were carried out in hospital facilities through the sampling cleaning technique. Even though protocols and operational procedures are strictly applied, it has been found that there is widespread contamination in the workplace (Turci, Sottani, Spagnoli, & Minoia, 2003; Mason et al., 2005; Brouwers et al., 2007).

To evaluate nurses, physicians and pharmacists' exposure to cytostatics in the work environment, the sampling technique used was "*wipe sampling*" (Schierl et al., 2009) and "*personal pads*" (Sottani et al., 2012). Cytogenetic parameters that allow to carry out simultaneous evaluation can also be useful for monitoring people exposed to risk. Several biomonitoring studies on pharmacy staff and nurses involved in the preparation or administrationhave revealed the presence of these agents in their urine (Ensslin, Pethran, Schierl, & Fruhmann, 1994; Ensslin et al., 1997; Turci et al., 2002; Schreiber et al., 2003; Fransman et al., 2007) and in their blood (Nygren & Lundgren, 1997). Thus, cytogenetic surveillance was discussed as an indicator, enabling an earlier detection of dangerous exposure (Kopjar et al., 2009). In the biomonitoring of healthcare workers exposed to antineoplastic drugs, several cytogenetic studies have been carried out in the following areas: chromosomal aberrations, germ cells exchange, micronuclei, immune toxicological biomarkers, etc. (Kopjar et al., 2009).

To develop a surface environmental monitoring, the commonly used technique is "*wipe sampling*", used to evaluate a drug, disregarding the rest. However, to study the risk of simultaneous exposure, Sabatini, Barbieri, Tosi, & Violante (2005) used a new method of high spectrometric liquid chromatography (HPLC/ESI-MS/MS) to evaluate 3 drugs simultaneously. Nussbaumer et al. (2012) and Pretty et al. (2012) used analytical methods in the liquid chromatography and the mass spectrometry technique (LC-MS / MS) to simultaneously evaluate 10 and 5 drugs, respectively, thus determining the contamination of surfaces and the health workers' professional exposure to a set of cytostatics. Bobin-Dubigeon et al. (2013) used the HPLC system and applied the new LC-MS analysis method to simultaneously assess 3 drugs. This system was applied in the cleaning of the surfaces of the bottles of drugs used in hospital pharmacies. This method enables a better response towards time detection and analysis of detection quantification, compared to the previous methods, and allows to evaluate the contamination on the surfaces in hospital pharmacies, in order to evaluate the health risks (Bobin-Dubigeon et al., 2013).

In turn, Jeronimo, Colombo, Astrakianakis, & Hon (2015) applied the same liquid chromatography and mass spectrometry techniques (LC-MS/MS) to analyze 6 drugs that are widely applied (5-FU, paclitaxel, cyclophosphamide, vincristine, oxaliplatin and methotrexate), even though oxaliplatin had

never been evaluated in previous studies. This method, besides being appropriate to simultaneously evaluate several drugs, allows a fast (few minutes) quantification of the exposure of the drugs. Therefore, this is a very suitable process for evaluating drugs in hospitals and health centers. It can also be applied to accurately determine the contamination of surfaces, with levels equal to or less than those recommended recently in the proposal of United States Pharmacopoeia (Jeronimo et al., 2015). Like the previous methods, it also allows to determine the contamination of the surface and the occupational exposure of health workers to various antineoplastic drugs.

Even if surface contamination is at a low level, it is essential to keep collaborators aware so that occupational exposure remains as low as desirable (Merger, Tanguay, Langlois, Lefebvre, & Bussières, 2014; Berruyer et al., 2015). Berruyer et al. (2015) proposed that an annual prevention program be considered. This program should include the monitoring of surface contamination, since it seems to be an instrument of great importance for the promotion of good working practices and contributes to the reduction of occupational exposure of health professionals to cytostatic drugs (Odraska et al., 2014). In addition to the above program, employers should provide proper training about the risk, because it is important to ensure that they and their health workers are aware of the risks and the precautionary measures to minimize exposure to antineoplastic drugs (Boiano et al., 2014). They should also ensure that workers receive training regularly, that safe handling procedures comply with current national guidelines, that they support their implementation and the availability of personal protective equipment to employees and that they know how to use it. They should also provide medical surveillance, exposure monitoring, and other administrative controls (Boiano et al., 2015). The Québec Regulatory Authority, Canada, has created a new rule (OPQ 2012), that came into effect in 2013, which includes the preparation of cytostatics, with the objective of requiring the annual certification of pharmacy technicians, thus contributing to the improvement of safety procedures and the reduction of contamination risks (Merger et al., 2014). Another measure to be implemented is a periodic environmental monitoring, as a way to educate employees of health units' in the interpretation of results and their respective corrective measures (Merger et al., 2014).

3.3 - Applications

Cytostatics are antineoplastic drugs with a wide application in the treatment of neoplastic diseases in several organs. Among these, Pt with its coordination complexes (carboplatin, cisplatin and oxaliplatin) and 5-FU are the most used in the treatment of the most varied types of malignant tumors (Turci et al. 2003; Brouwers et al., 2007).

Pt and its compounds play an important role in the treatment of various types of cancerous tumors (Brouwers et al., 2007). The interaction of these complexes with DNA promotes their activity as anticancer agents. The efficacy of carboplatin treatment, compared to cisplatin, seems to be equivalent. However, the former shows lower overall toxicity (Turci et al., 2003). All Pt complexes are mutagenic *in vitro*, teratogenic and carcinogenic in animals. Still, cisplatin is considered to be probably carcinogenic to humans, classified as belonging to group 2A (IARC) and is used in the treatment of a variety of solid tumors (breast, prostate, etc.) (Turci et al., 2003).

5-FU is an antimetabolite widely used in the treatment of neoplastic diseases (Turci et al., 2003). To achieve its effect, it needs to be converted to the nucleotide level, thereby competing with the pyrimidine. The conversion of 5-FU into nucleotides implies the necessity of involving several enzymes in the pyrimidine metabolism, being integrated in different fractions (Turci et al., 2003).

5-FU is a drug administered in the treatment of breast, lung and digestive tract cancer (Turci et al., 2003).

3.4 - Preparation

Pharmacists, nurses and support staff, who work with cytostatics, should have specific training and knowledge about the preparation and administration of antineoplastic drugs (Turci, Sottani, Ronchi, & Minoia, 2002), in particular those who work in hospital pharmacies where the number of preparations is high (Odraska et al., 2014).

The preparation of cytostatics occurs in centralized hospital pharmacies. Inside these, there is a room, called preparation room or clean room. The clean room is a room with environmental control defined in terms of particle contamination, designed and used to reduce the introduction, creation and retention of contaminants inside, which contains one or more vertical laminar air flow hoods. This room must be in an asepsis and negative pressure condition.

The professionals outside the preparation room dress in cloth, surgery unit type, footwear (clogs) and gloves. However, when they go inside the preparation room, they move into the transition zone, where they proceed to disinfection by washing their hands and arms up to the elbows. Then, they dry their hands and arms thoroughly in the sterilized air dryer, scrub them with alcohol at 70% percent or other disinfectant and let them dry. Finally, they put on a sterile plastic gown for their body protection, a

scrub hair protection, a mask, the shoes' protection and a second pair of gloves. This personal protective equipment is required to safely perform the preparation tasks (Silva, 2011).

The preparation is carried out in a class II vertical laminar flow hood (LFH), type B2 (Turci et al., 2003) (NIOSH, 2004). Also in the clean room, are the HEPA filters (High Efficiency Particulate Air Filter) to filter very small particles during the preparation, and their efficiency is of about 99.9% (Turci et al., 2003).

After preparation, the pharmacists take the drugs outside the room on a tray through the transfer. These drugs may be packaged inside the preparation room, into a plastic bag and glued with thermal gluing (figure 1). They can also be received outside the room, where they will be packaged in a plastic bag and glued through thermal gluing or other gluing system. Subsequently, the drugs are placed in the transport bag, or another properly arranged bag, to be sent to the Day-care hospital, to be administered to the patients.

Figure 1 - Packing table inside preparation room.

The preparation room and all equipment are cleaned at the end of a working period. Some hospitals perform the cleaning once, at the end of the day. However, others do this twice daily, i.e., in the late morning and late afternoon. In general, cleaning is carried out with water and detergent followed by 70% alcohol (Yoshida et al., 2009). The vertical laminar flow hood is cleaned once a week with sodium hypochlorite. This general cleaning procedure is used in the hospitals under study. This cleaner is effective in decontamination. However, due to surface corrosion, it is not suitable for a laminar flow hood and routine insulation cleaning (Lamerie et al., 2013; Anastasi et al., 2014).

CHAPTER 4 - OCCUPATIONAL EXPOSURE TO CYTOSTATICS

The occupational exposure to cytostatics arises mainly when health professionals are performing their professional activity. Among these, hospital pharmacies professionals, responsible for the preparation of the drugs, and nursing professionals responsible for administering the treatment of cytostatics, are highlighted. However, in addition to these, other professionals connected to the cytostatic circuit (storage, preparation, drugs transport, administration, waste transport and treatment), such as the operational assistants, are also exposed to cytostatics, although in residual quantities (Hon, Teschke, Chua, Venners, & Nakashima, 2011).

4.1 - Exposure phases

The exposure of health care professionals started gathering attention in the late 1970s, Falk 1979, work was cited by Turci, Sottani, Schierl, & Minoia (2006), and the first reported effects derived from contact with cytostatics were exclusively of the acute type, as a consequence of contact in the main forms, i.e., dermic and/or inhalation, and in cases of accidents or manipulation errors (Sorsa & Anderson, 1996).

Occupational exposure occurs in the different phases of the cytostatic circuit. The first stage takes place in manufacturers in pharmaceutical companies, in storage, where employees carry out packaging handling and are therefore exposed to cytostatic drugs through the contact with containers and bottles that may contain outside contamination from the factory (Nygren, Gustavsson, Ström, & Friberg, 2002; (Mason et al., 2003; Hedmer et al., 2005; Touzin et al., 2008).

The second phase takes place in the hospital pharmacy, where pharmacists and pharmacy technicians manipulate cytostatics in the preparation of antineoplastic drugs for the treatment of patients with neoplasia, being professionally exposed to cytostatics. The centralized preparation of cytostatics implies the presence of two technicians inside the preparation room, where one prepares and the other assists and they may or may not switch roles (Schreiber et al., 2003). In the study of Schreiber et al. (2003) it is shown that there is no difference in relation to internal exposure between the technician that assists compared to the technician that prepares the cytostatics. Exposure results from the direct manipulation of cytostatic drugs or from contact with contaminated surfaces and equipment (Sessink & Bos, 1999), contaminated containers and flasks from the factory (Nygren, Gustavsson, Ström, & Friberg, 2002). The preparation of the cytostatics is processed in the vertical

laminar flow hood under aseptic conditions. However, several studies have demonstrated the existence of contamination on surfaces outside the laminar flow hood and even at sites farther away from the laminar flow hood, as a result of either the spread of aerosol vapors of the drug (Connor et al., 2016) or the transfer through hands, feet and contaminated objects (Brouwers et al., 2007; Schierl et al., 2009; Connor et al., 2010; Silva, 2011). Health professionals involved in the preparation of cytostatics may be occupationally exposed by the inhalation of aerosols, drug and powder drops. Unplanned intake is also possible in case of accidental events (Turci et al., 2006).

The transport of cytostatics is included in the third phase, which is carried out by nursing assistants, whose task is to transport the drugs from the hospital pharmacy to the medical oncology Day-care hospital. They are exposed due to contact with the transport bag, or due to the spillage that may occur due to breakage of vials (Connor & McDiarmid, 2006).

The fourth phase takes place at the medical oncology Day-care hospital, where the subjects exposed are usually the nurses, since they administer the treatment to the patients who suffer from neoplastic disease and are treated with cytostatic drugs. This exposure results from the direct manipulation of cytostatic drugs, or from contact with contaminated surfaces and equipment (Sessink & Bos, 1999). Among these, the most noteworthy are the infusion pumps, armchairs and waste bins (Kopp, Schierl, et al., 2013), as well as the beddings (Fransman et al., 2007). In addition, these professionals may also be in contact with secretions and excretions eliminated by patients after treatment, thus becoming a probable additional cause of contamination (Sessink & Bos, 1999). During administration, nurses may be at risk of occupational exposure to cytostatics, due to the inhalation of aerosols, for example paclitaxel, drops of the drugs and contaminated dust, such as cyclophosphamide (Turci et al., 2006).

The amount of professional exposure on nurses, estimated from the environmental monitoring, cannot in fact exceed 0.2mg/year (ambient air 0.5μg/m3; 2h/day; 5 days/week; 40 weeks/year), not allowing the cumulative total dose over 20 years to exceed 4mg, which is 0.1% of the usual therapeutic dose (4g) (Sorsa & Anderson, 1996).

Nursing assistants carry out the transportation of the waste from the treatment and, even though they are not in direct contact with the cytostatics, they are also occupationally exposed due to contact (Turci et al., 2006; Connor& McDiarmid, 2006).

During the different phases, occupational exposure may occur due to direct contact with the antineoplastic drugs, but also with work surfaces, floors, work equipment, clothing, beddings of patients

under treatment and containers that have been used in the excretions, due to the existence of widespread contamination (Mason et al., 2005; Brouwers et al., 2007; Fransman et al., 2007). Accidental spillages may also occur mainly on the preparation and administration stages, even if all handling regulations have been adopted, as they cannot be completely avoided (Sorsa & Anderson, 1996) (Sottani et al., 2012).

4.2 - Exposure effects

Cytostatics exposure, besides the exposure effects already analyzed in the survey with health professionals, presents other effects that can also cause changes in life and health of this professional. According to DeMeo et al. (1995) and Connor & McDiarmid, (2006), these drugs are carcinogenic, teratogenic, genotoxic, or toxic for development, toxic for reproduction and, at low doses, toxic to organs.

Health professionals who handle or administer cytostatics may suffer from infertility, miscarriage, offspring with birth defects, and possibly from leukemia or other types of cancer (NIOSH, 2004).

Acute toxic effects such as skin, eyes and mucous membranes irritation, alopecia, nausea, vomiting, among others, usually occur in patients receiving cytostatic treatments (Sessink & Bos, 1999). In addition to these effects, several organs and tissues, such as bone marrow, the liver, bladder and lung, may be exposed to more severe toxicities (Sessink & Bos, 1999). However, no acute toxic effects have been observed in pharmacists and pharmacy technicians that prepare drugs for patients' treatment and in the nurses who administer them, except in case of accidental spillage, when these professionals may be exposed to large quantities of cytostatics (Sessink & Bos, 1999).

Cytostatics present toxicity to female and male germ cells, verified in several animal studies. Thus, in animals, alkylating agents that interfere with female germ cells have been related to spontaneous abortion. Yet, alkylating agents that interfere with male germ cells are mutagenic at all stages of maturation. Platinum derivatives are also associated with lethal changes, causing the early death of the embryo (Suspiro & Prista, 2012). Connor & McDiarmid (2006) reported that in several studies, female nurses exposed to cytostatics have reported toxic effects on their reproductive health. Likewise, according to Lawson et al. (2012), an increase in the number of spontaneous abortions and malformations has been reported by the nurses' group, resulting from the occupational exposure to cytostatics, as well as an association between manipulation and menstrual dysfunction (Sessink & Bos, 1999).

The exposure effects due to manipulation of cytostatic drugs by pregnant women may also include an increased risk of congenital malformations (Shirangi et al., 2014). This risk is higher in women with unplanned pregnancies, compared to those with planned pregnancies (Shirangi et al., 2014). Planning implies an early removal of professionals from cytostatics manipulation and administration tasks.

Thus, other cytostatics effects have been described in the literature, such as: menstrual disorders, abortions, bronchial asthma, cough, musculoskeletal problems, ulcers or gastritis, allergies, nasal mucosa irritation, tearing, eye irritation and dry eyes (Constantinidis et. al., 2011). Exposure effects on reproduction have been described (NIOSH, 2004), such as congenital malformations, low birth weight, longer time to conception, infertility, birth defects, fetal loss and miscarriage (Hemminki, Kyyrönen, & Lindbohm, 1985; Sorsa & Anderson, 1996; Fucic, Jazbec, Mijic, Šešo-Šimic, & Tomek, 1998; Fransman et al., 2007; Lawson et al., 2012; Shirangi et al., 2014). Occupational exposure effects in health professionals handling cytostatics can also include DNA damage, chromosomal aberrations, and germ cells exchange of sperm chromatids (Yoshida et al., 2006; Sasaki, Dakeishi, Hoshi, Ishii, & Murata, 2008). An investigation conducted by Tompa et al. (2006) found that an exposed group showed a significant increase in thyroid complaints due to pathological changes in the thyroid gland.

Chromosomal aberrations, although transient and without repercussion on offspring, can be induced by Pt derivatives (Suspiro & Prista, 2012). In their study, Moretti et al. (2015) found a higher frequency of chromosomal aberrations (CA) and micronuclei (MN) in the exposed group, when compared to the control group.

However, the lymphocytes of nurses who handle cytostatic drugs show a higher exchange of chromatid siblings (SCE) and more chromosomal anomalies than nurses unexposed to cytostatics (Stucker, Hirsch, Doloy, Bastie-Sigeac, & Hemon, 1986).

Regarding DNA, an increase in the extent of DNA damage of health professionals exposed to cytostatics was reported (Yoshida, Kosaka, Tomioka, & Kumagai, 2006; Villarini et al., 2012).

4.3 - Means of prevention and control

The existence of environmental contamination in the workplace shows the presence of a potential source of exposure (Connor, Zock, & Snow, 2016). As a means of reducing exposure, it is essential that preventive measures are taken. Thus, all health professionals exposed to cytostatics should be informed regarding the drugs they handle at the hospital pharmacy, or administer in Day-care hospitals, and

should receive training before starting cytostatic manipulation or administration. While performing their tasks they should also receive specific training on cytostatics. They also have to show knowledge of the manual and the instructions included in it, thus contributing to prevention.

According to NIOSH, prevention is based on compliance with the guidelines on cytostatic manipulation, among which we present: the preparation of these drugs must take place inside the laminar flow hood, preventing dangerous drugs from being released into the working environment; use of high efficiency air filters (HEPA filter) in removing air particles to the outside; after the preparation has finished, the laminar flow hood must remain on; in the preparation, use 2 pairs of gloves, 1 normal, another made of latex, and change gloves every 30 minutes or when they tear or puncture. Quickly place them in the chemotherapy trash container. According to NIOSH, in hospital pharmacies and Day-care hospitals, the risks should be assessed and the entire process of preparation and administration of cytostatic drugs checked to identify the sites where they can be released into the working environment, as well as considering the possible contamination of the containers' outer surface (NIOSH, 2004). The access to preparation areas should also be limited to those who are involved in the drug preparation process (NIOSH, 2004). The tasks of preparation and administration of cytostatic drugs should be coordinated with the aim of more effectively controlling the exposure of health professionals (NIOSH, 2004). According to NIOSH (2004), the personal protective equipment used in hospital pharmacies is different from that in medical oncology Day-care hospitals. Par example the type of gloves is different, i.e. in the pharmacy the professionals wear 2 pairs of gloves, being a rubber pair, while in Day hospital, the nurses wear only a pair of gloves. Prevention is performed through the use of personal protective equipment defined for each workplace.

The preparation of cytostatic drugs should be carried out in the hospital pharmacy, more precisely in the safe cabinet, by pharmacists and pharmacy technicians, under conditions of hygiene, safety and with appropriate equipment, as well as with personal protective equipment, but according to Yoshida et al. (2008) this only happens in about half of the hospitals.

The preparation room is in asepsis conditions (absence of germs, infectious or pathogenic bacteria), through measures that prevent the entry of these agents. The aspiration is adequate and the pressure is positive. Before entering this room, health professionals enter a transition zone for washing their hands and arms and putting the appropriate personal protective equipment on. The access to this area is restricted to people who are involved in the drug preparation process (NIOSH, 2004).

A vertical laminar air flow hood (LFH), class II, type B2, should be used. The exhaust and air flow in this equipment should be adequate and HEPA (High Efficiency Particulate Air Filter) filters, with a nominal efficiency of the order of 99.97%, should be used. These filters, due to their high efficiency, are normally used in "clean" rooms (NIOSH, 2004). These laminar air flow hoods have been strongly recommended in the preparation of cytostatics (NIOSH, 2004). However, doubts have been raised about the safety of laminar flow hoods. Therefore, the use of closed devices and disposable syringes has been recommended as they prevent spills inside the laminar flow hood (Turci et al., 2006).

The use of the closed system in the preparation and administration of antineoplastic agents may eliminate several of the possible sources of contamination during handling. This technique allows less experienced professionals to apply it after a brief training action, without leaks (Nygren, Gustavsson, Ström, Eriksson, et al., 2002; Wick, Slawson, Jorgenson, & Tyler, 2003; Tans & Willems, 2004; Yoshida, Kosaka, Nishida, & Kumagai, 2008). With the PhaSeal closed system transfer device (CSTD), the laminar flow hood contamination has been significantly reduced and the risk of leakage is radically eliminated when the preparation system version is used. Thus, this system increases the protection of the professionals that prepare cytotoxic drugs (Connor, Anderson, Sessink, & Spivey, 2002; Favier et al., 2012).

This system CSTD is a device that significantly reduces contamination on work surfaces in hospital pharmacies and its use is encouraged in the preparation (Connor et al., 2002; Yoshida et al., 2009; Siderov, Kirsa, & McLauchlan, 2010; Sessink, Connor, Jorgenson, & Tyler, 2011; Favier et al., 2012; Vyas, Yiannakis, Turner, & Sewell, 2013; Sessink, Trahan, & Coyne, 2013). The use CSTD, of a device may also reduce the exposure of health workers to cytotoxic agents in the preparation and administration, and reduces the risk of spillages and the appearance of aerosols (Yoshida et al., 2009; Siderov et al., 2010; Sessink et al., 2011; Clark & Sessink, 2013; Berruyer et al., 2015; Vyas, Turner, Clark, & Sewell, 2016; Simon et al., 2016). In addition to these advantages, the closed system device also offers other, including the elimination of needle lesions and the elimination of the exposure risk on nurses that have to administrate cytostatics (Vyas et al., 2016). However, even using the closed system transfer device (CSTD), contamination remains a possibility (Sessink et al., 2011) (Simon et al., 2016).

Technological evolution enabled the preparation of cytostatics with the use of robots, which allow lower levels of contamination compared to manual preparation, and offer greater safety for manipulation technicians and greater precision in the preparation of doses of antineoplastic drugs (Seger et al., 2012; Palma & Bufarini, 2012; Sessink et al., 2014; Schierl et al., 2016). However, Seger

et al., (2012) and Sessink et al., (2014), suggest a cost/benefit analysis of the use of this equipment. Palma & Bufarini, (2012) and Schierl et al., (2016) verified a significant reduction of the contamination outside the robot, when the preparation is done with the "APOTECAchemo" robot. This is considered a third generation robot, limiting the technical staff to the tasks of loading the products inherent to the preparation, and discharging the drugs to be sent to administration. Besides significantly reducing the contamination, it allows a significant time reduction in the preparation of the drugs and controls the internal pressure of the bottles in the process, so that there is no pressure difference, thus avoiding drug spillage (Palma & Bufarini, 2012).

Gloves are personal protective equipment that are used in the preparation and administration of cytostatics. On preparation of cytostatics, 2 pairs of disposable protective gloves should be used, at the same time covering the sleeves of the gown (Fransman et al., 2004). Considering that gloves are the first protection against contact with cytostatic drugs, it is fundamental to know their resistance towards permeability (Wallemacq et al., 2006). Gloves are made of different materials and their resistance to permeability is different according to factors such as the duration of exposure, glove thickness, drug liposolubility and its molecular weight (Wallemacq et al., 2006). After a glove permeability test with 13 types of 4 different materials and 13 cytostatics, it was concluded that neoprene gloves, natural rubber latex gloves (NRL), and nitrile gloves showed higher resistance to permeability (Wallemacq et al., 2006). Fransman et al., (2004) and Mason et al., (2005) have detected contamination in the external surface of the gloves. Fransman et al., (2004) found that the protection of gloves ranged according to the different tasks evaluated. So, for a task with an average time of approximately 2 hours, the average level of protection was higher (98,5%) in the preparation of cyclophosphamide, using 2 pairs of latex surgical gloves. The gloves used in the preparation were more contaminated than on other tasks associated with cytostatics (Fransman et al., 2004).

To minimize the risks of occupational exposure, several guidelines were given for the handling of antineoplastic agents, as well as safety recommendations (NIOSH, 2004). The measures proposed by NIOSH for risk control for professionals handling / administering cytostatics in an occupational context vary according to the specific nature of the task.

Health professionals involved in the preparation of cytostatics wear a cloth suit, surgery unit type, and appropriate footwear (clog). However, when they go into the clean room, they use the following personal protective equipment: footwear protection, gown, scrub hair protection, goggles, mask and double gloves. When they leave the preparation room, they remove the protective equipment and place them in

a container (NIOSH, 2004). However, the preparation entails the fulfilment of the following procedures (NIOSH, 2004):

- Gloves should be changed every 30 minutes except in case of spillage, when it should be done immediately;

- After preparation, the exterior of the mixture should be cleaned for administration and the system should be filled up with non-drug-containing liquid;

- The transport of the drugs should be in closed containers to minimize the risk of bottle breakage;

- Written emergency procedures must exist on the location in case of accidental spillage. Training on spillage should also be given to all personnel involved in the preparation and administration, according to the written procedures and policies.

Health professionals involved in the administration treatments to patients in Day-care hospitals follow a strict set of rules:

- The administration of these drugs also requires the use of the following personal protective equipment: gown, goggles, mask, gloves and scrub hair protection. These should be removed after handling and placed in the appropriate container (NIOSH, 2004);

- A way of reducing exposure to cytostatics is to administer the drug through a closed system, eliminating some of the possible sources of contamination (Nygren, Gustavsson, Ström, Eriksson, et al., 2002);

- The mixture should be directly connected and, after the administration has finished, the entire system should be removed and placed in the appropriate container (NIOSH, 2004);

- During administration, written emergency procedures should also exist on the location in case of accidental spillage (NIOSH, 2004);

- Cleaning procedures are common to preparation and administration. Cleaning should be periodic and carried out with suitable products for all surfaces and for potentially contaminated equipment (NIOSH, 2004);

Potentially contaminated clothing is treated separately. Cleaning procedures should be recorded and monitored. Contaminated material should be disposed separately from other waste and stored in properly sealed containers (NIOSH, 2004).

Considering the protective measures implemented, it is still pertinent to check if there is occupational exposure in the manipulation and administration of cytostatics. Therefore, exposure monitoring is required. This may include environmental monitoring to measure environmental exposure, or biological monitoring to measure absorption (Sessink & Bos, 1999; Turci et al., 2003; Acampora et al., 2005; Hedmer et al., 2008; Mader, Kokalj, Kratochvil, Pilger, & Rüdiger, 2009; Kopp, Crauste-Manciet, et al., 2013). Environmental monitoring allows the identification of sites in hospital pharmacies and in Day-care hospitals that may be contaminated by cytostatics and, consequently, where health professionals may have been exposed.

4.4 - Risk management

Hospital workers are concerned about the potential health risks to the professionals who prepare and administer cytostatic drugs, as well as the potential exposure and its subsequent effects (Acampora et al., 2005). Contamination in hospital pharmacies by cytostatic drugs is considered a potential health risk, which should be monitored (Brouwers et al., 2007).

In hospital pharmacies and Day-care hospitals, where cytostatics are handled, risks are even more complex due to the quantity of drugs prepared and administered, increasing the potential exposure of health professionals, and making the risk management task more difficult. A strong collaborative spirit should exist among hospital personnel, and safety and health professionals with experience in different areas of knowledge, such as industrial hygiene, toxicology and analytical chemistry, should be integrated (Sorsa et al., 2006).

As long as exposure assessments continue to exist that indicate that the risks detected are not fully controlled, it will be necessary to reflect on codes of good practices, responsibility in the task, carelessness, reduced work space, or less careful co-workers, to improve the results of the following assessments. Considering the importance of these rules and their possible non-compliance, a greater number of professionals who prepare and administer cytostatics may be put at risk of exposure, since the trend verified is an increase in the number of patients requiring treatment (Sorsa et al., 2006).

According to Sorsa et al. (2006), the effective management of risks requires attention to several aspects, including:

- Improve handling practices;
- Use standard analytical methods to enable comparison of studies;
- Quantitative risk assessment of new cytostatic drugs and multiple exposures;
- Introduce improvements in the psychosocial environment, in the workplace;
- Prevent neglect due to a false illusion of constant safety;
- Use of closed system "insulators" and robots for drugs preparation;
- Prevention in the transport of cytostatic drugs;
- Accidental spillages cleaning procedures;
- Prevent the transfer of contaminated drugs vials from companies.

Considering that, until now, no exposure limit values (VLE) have been defined for cytostatic, except for a recommended value proposal (Schierl et al., 2009), it makes it even more complex to manage the risk associated to the corresponding exposure.

To improve quantitative risk assessment, studies should be performed in professionals occupationally exposed to cytostatic drugs. The reproductive health of these professionals should be an integral part of the studies. These health professionals should receive ongoing training, and new professionals should be receive follow-up training in order to maintain the motivation for good practice and appropriate occupational safety measures (Sorsa et al., 2006). A better risk communication is needed to ensure that employers and health professionals are fully aware of the risks they are exposed to and the preventive measures to reduce exposure to cytostatic drugs (Boiano et al., 2014). The purpose of risk assessment and its management is to prevent health risks to health professionals exposed to cytostatics. This requires periodic statistical data collection through environmental and biological monitoring (Acampora et al., 2005). Sample collection is carried out at sites likely to be contaminated, at hospital pharmacies, and at medical oncology Day-care hospitals (Brouwers et al., 2007). Environmental and biological monitoring allows results that characterize the risk (Sottani et al., 2012).

PART III - WORK DEVELOPED

CHAPTER 5 - METHODOLOGY

The development of this research implied a set of previous actions for its accomplishment. First, a literature review based on the PRISMA methodology was carried out, followed by the criteria that assisted the selection of the hospital units to be studied. After the selection of these, observations, routine records, the development of the questionnaire, the sampling technique and its application were also performed and are described in this chapter.

5.1 - Literature review

The literature review was carried out in 4 databases in order to find as many records as possible. The databases used for the research were Pubmed, Scopus, Web of Science and ScienceDirect, because they contain the most information on the subject. The methodology followed was PRISMA, which is based on the definition of criteria to be applied in the sorting and eligibility of articles (Moher, Liberati, Tetzlaff, Altman, & Grp, 2009) and is represented in figure 2.

The review started with the keyword "Antineoplastic", with 1,631,349 articles being found, and then with the keywords combination "Antineoplastic AND drugs", resulting in 608,006 articles found, followed by the keywords "Antineoplastic AND drugs AND exposure", with 62,156 articles being registered. The keywords "Antineoplastic AND drugs AND exposure AND handling", resulted in 3,274 articles. By including the terms “surface” AND "contamination", the resulting number was 789 articles. Finally, the complete search string was "Antineoplastic AND drugs AND exposure AND handling AND surface contamination AND sampling", with 426 articles. This procedure continued with the elimination of 68 "duplicate articles" and a final amount of 358 articles was reached.

Then, the eligibility criterion was applied, eliminating all non-relevant articles, posters and abstracts, 254, in total, resulting in 104 relevant articles. The relevance of these articles is based on the fact that their content includes an approach to the manipulation of cytostatics and occupational exposure of health professionals, namely nurses and pharmacists, in the hospital context.

Finally, 10 papers were removed as they were not written either in Portuguese or English.

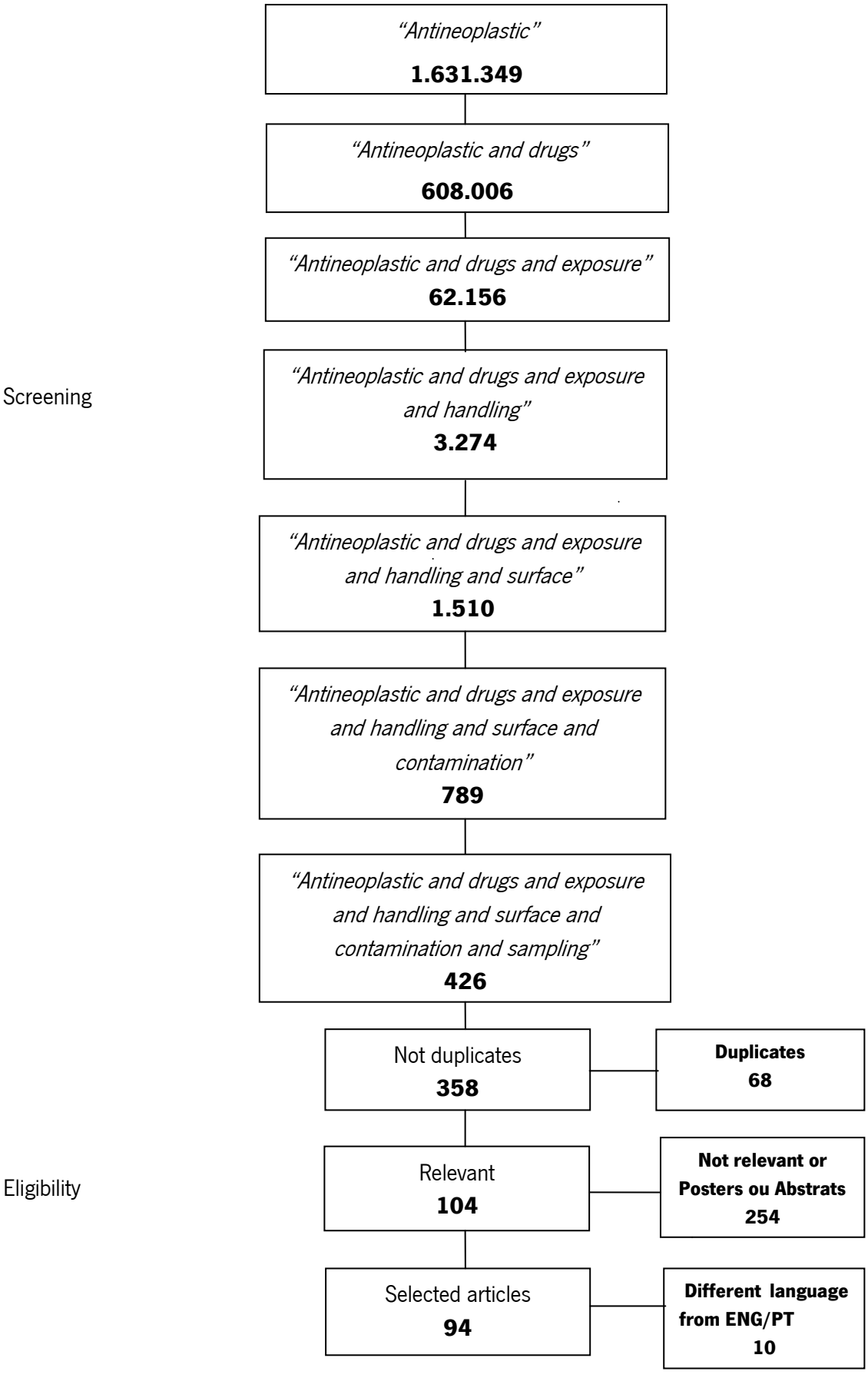

Figure 2 - Procedure adopted for literature review.

5.2 - Selection of hospital units

Considering the existence of about 50 hospital units in the country whose mission is to treat neoplastic diseases, written contacts were established with convenient sample of hospital units, in order to verify their availability to carry out this investigation in their facilities.

Thus, to carry out the selection of hospital units, it was necessary to define specific criteria. The criteria adopted for the selection of hospital units were: the number of patients and the quick positive answer, since there was limited time availability for the two-drug evaluation by the partner laboratory.

After the entire process was analyzed by the Ethics Committee of the hospitals, the responses from the respective Board of Directors arrived. Thus, one hospital rejected the proposal, another did not respond and another accepted the proposal, but too late. After receiving authorization from three hospitals, their identity was protected by changing their names to A, B and C. The health units were designated by hospital center A, hospital center B and hospital center C, respectively, the first, second and third hospitals that responded affirmatively. The process of contacting managers was initiated to schedule meetings with collaborators.

These meetings were held with service providers and collaborators, i.e., hospital pharmacies, Day-care hospitals and vascular surgery (control group). During these meetings, a presentation of the research project was made and the involvement of all the collaborators was requested. The project was disclosed to the collaborators by the heads of the services, through a message sent to the respective institutional email addresses.

5.3 - Observation and recording of routines

The project was followed by three sessions of observation and recording of the procedures and practices through the verification checklist of the procedures (Appendix 1) and the consultation of the manual procedures, in the three hospital centers, in the hospital pharmacies and in the medical oncology Day-care hospitals. The first session was devoted to observations of the equipment used and the procedures for the preparation and administration of cytostatics. The second session aimed at continuing the observation and recording procedures and practices for the different tasks. The third session intended to conclude the work started in the two previous sessions. The questionnaires were given to those present during the visit, as well as to the managers, so that they could be later given to the absent collaborators.

Hospitals A and B had a fourth observation session, which was carried out with the presence of two of the supervisors, Dr. Rudolf Schierl and Professor Nélson Costa, to check the work areas *in situ*, to analyze them and participate in the selection of sampling sites in the hospital pharmacies and in the medical oncology Day-care hospitals. The selection of these sampling sites were based on the fact that, according to Brouwers et al. (2007), they are more susceptible to high chemical contamination, for example laminar flow hood, reception table, transfer, infusion pump, armchair.

Subsequently, a meeting was held with the heads of each site/service, with the aim of scheduling the date for the collection of samples. This task was completed during 3 months.

5.4 - Questionnaire development

The questionnaire was developed and used considering that it is an elementary and auxiliary approach to data research (Amorim, 1995). The questionnaire was designed to allow the data collection about the exposure effects due to exposure to cytostatics by pharmacists, preparation technicians and nurses.

A questionnaire is a non-documental technique of non-participant observation that allows the collection of appropriate and important information, allowing to find answers to the goals defined for this study.

The questionnaire is a research technique that contains a quantitative approach, allowing to transform the information provided by the respondents through their answers into numbers.

5.4.1 - Questionnaire description

The questionnaire consisted of 4 pages, being the first the cover page for informed consent, and the other 3 included 18 multiple choice questions. These aimed at evaluating the maximum information in the most objective way possible. Some questions are sociodemographic and others refer to information, regarding routines, performance and self-reported symptoms (Appendix 2). In the construction of the survey, the published literature and the pertinence of the questions were taken into account in order to obtain relevant information regarding the queries and aims of the study, and in order to obtain information that correspond to the reality.

The sample was characterized at the sociodemographic level by the following elements: gender, place of service, qualifications, age, descendants, length of service in the health sector, time of service in the

manipulation/administration task, perception of the risk, use of individual protective equipment, separation of waste practices and frequency of training actions.

The factors considered relevance for the questionnaire are:

- Sociodemographic elements such as age, gender, qualifications, etc;

- Elements related to performance, with relevance to the factors that can promote errors and cause spillage;

- Individual engagement, such as reading information on cytostatics, and presentation of proposals for improving practices;

- Self-reported effects due to handling cytostatics such as: nausea and vomiting, alopecia (hair loss), headache, dizziness, vertigo and cutaneous hyperpigmentation.

The sample is composed by a population of 154 health professionals who work in hospital pharmacies, medical oncology Day-care hospital, and at the vascular surgery service of hospital centers A, B and C.

The questionnaire was applied to two groups: the first, those that manipulate and administer cytostatics, the exposed group, consisting of 98 professionals (pharmacists, pharmacy technicians, nurses and nursing assistants), who perform their tasks in the hospital pharmacy, in oncology and drug transport, respectively. The second, the control group, consisting of 56 nurses, who are not exposed to cytostatics and develop their activity at the vascular surgery service in each of the three hospitals.

5.4.2 - Exposed/control group

This research is based on health professionals who perform their tasks in different workplaces and, in the current case, the differentiating element between the two groups (exposed/control group) consists in the exposure (or not) to cytostatics.

In one hand, we have the exposed group, which is composed of professionals that develop their activity in hospital pharmacies (pharmacists, preparation technicians and auxiliaries), and those who develop the activity in the medical oncology Day-care hospital, (nurses and auxiliaries). All of them manipulate / administer cytostatics.

On the other hand, we have the control group that consists of nurses who perform their activity in the vascular surgery service. This service was chosen because it is the only group not exposed in one of the hospitals, so the same group was replicated in the other hospitals. In this service, no cytostatics are prepared or administered.

5.5 - The sampling technique

The sampling technique used during this study is called "*wipe sampling*" technique, and was developed and applied by Schmaus et al., (2002) and Schierl et al., (2009), in a study developed for analyzing the exposure to 5-FU and Pt. These drugs are sampled by methanol (MeOH) and by hydrogen chloride (HCl), respectively.

The "*wipe sampling*" technique (Schmaus et al., 2002; Schierl et al., 2009) consists in cleaning a defined area, usually of 20 by 20 cm, with 3 paper filters, blue ribbon®, 90 mm (Schmaus et al., 2002). The researcher uses each filter to clean in a different direction, so the surface area is cleaned in three different directions (Schierl et al., 2009). Before cleaning the area, it is necessary to moisten the filters with only 6 drops of the fixative applied to avoid excessive moist. The fixative is a chemical substance that has properties that enable to capture other chemical substances from a surface, attaching it to the filter, which later allows its separation in laboratory.

This technique was applied to verify the presence of 5-FU and Pt, in hospital pharmacies and in medical oncology Day-care hospitals, in the hospitals identified above, using as fixatives methanol (MeOH) and hydrogen chloride (HCl), which structural formulas are presented in figure 3.

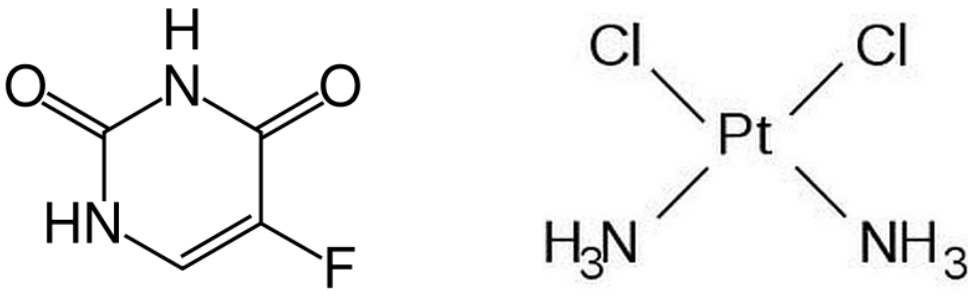

Figure 3 - Structural formula of 5-FU and Pt.

These procedures are repeated to search each of the drugs, with the exception of the fixative which is different, i.e., methanol (MeOH) for 5-FU and hydrogen chloride (HCl) for Pt. These procedures start at

the workplace for one of the drugs, with the 3 filters. Then, at the end, the filters are placed in the bottle and the gloves are changed. The research technique contemplates the following procedures:

1 - Clear the selected surface area, usually a square of 20 cm^2, although different areas can be considered, with 3 filters. Each filter cleans the surface area in a different direction and finishes with a movement in a perpendicular direction, as demonstrated in figure 4;

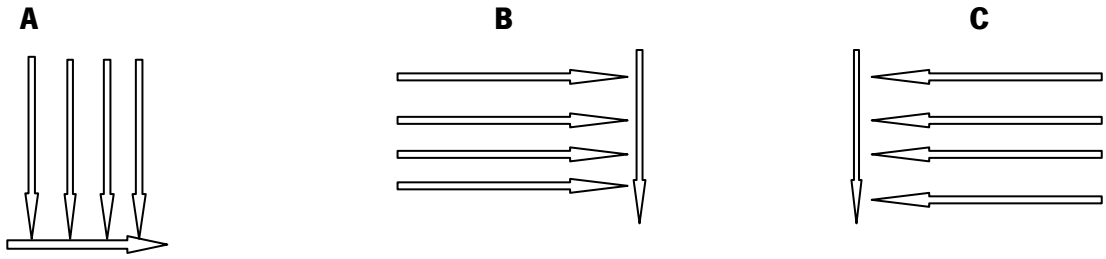

Figure 4 - Surface cleaning scheme (ABC).

2 - The filters are held by the soft ends with the thumb and middle finger so that it can be strongly pressed into the surface area to be cleaned;

3 - Apply 6 drops of methanol (MeOH) for wiping 5-FU or 6 hydrogen chloride drops (0.1% HCl) for taking wipe samples analysed for Pt. The solvents should be slowly applied on the filter surface, (figure 5). These filters are moist but not too wet for sampling;

Figure 5 - Fixative application (MeOH) and (HCl) to the paper filter (reproduced from Schierl, 2009).

4 - Clean the surface area with a good deal of pressure (figure 6), but according to Scheme A, (figure 4), at the beginning, from a point farther away, to another closer to the operator. Finally, wipe from left to right;

5 - The sampled filter is placed in the container with the number corresponding to the location;

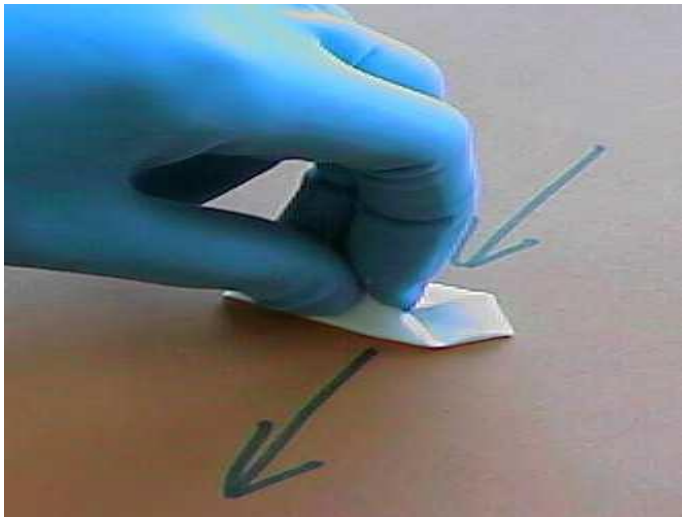

Figure 6 - Exemplification of how to hold the filter in order to clean the surface (reproduced from Schierl, 2009).

6 - The procedures are repeated for the other two filters in the same way, but with different cleaning directions (scheme B and C, figure 4. The 3 sampled filters from the same spot are placed together in the numbered container;

7 - The filters container must be closed tightly;

8 - Finally, collect the blank sample. This task consists in moistening the three filters, one after another, with the fixative (MeOH) and placing them in the appropriate container, without wiping any surface. Repeat this procedure for the fixative (HCl). The blank sample is used to evaluate the quality of the sample collection process.

The bottles with solvents must be returned to the laboratory along with the samples.

5.6 - Sample setup

In order to detect contamination by Pt and 5-FU on the surface areas, it was necessary to prepare all needed equipment (filters, fixative, lists, ruler, pen, etc.). The first samples from the pharmacies were taken at 7.30 am before the professionals started their preparation tasks.

Wipe samples were taken during the work shift, except for the first sample in the laminar flow hood, which was collected before the start of the task. During the sample collection, only two pharmacists/pharmacy technicians, who prepare the treatments in the laminar flow hood, were inside the clean room, although several pharmacists were inside the Day-care hospital oncologic pharmacy. The samples were collected at mid-morning, except for the first one in the laminar flow hood that was collected before the start of the task, and the last one in the laminar flow hood hat was collected at the

end of the task, before cleaning. In the medical oncology Day-care hospital, there are several nurses who administer treatments to patients. In this location, the samples were collected during the afternoon, after treatment applications.

Only the materials needed to collect samples inside the clean room were taken into the room (pharmacy) and the rest were left outside to avoid possible contamination and to be used at the collection sites at the hospital pharmacy and medical oncology Day-care hospital, where cytostatic treatments are administered.

Samples were collected at each site using the technique described in 5.5 all the procedures listed in the previous paragraphs. With the exception of a sampling surface area that may vary by location (e.g. armchair), the surface area to be cleaned corresponds to 3 subareas (right arm, left arm and floor adjacent to the high chair) each 1 of the 3 filters cleans a subarea.

The collection was done by location, not by product, in order to cause less constraint to the pharmacists who perform this task in the workplace. The option was first to fix the 5-FU and then the Pt, and this procedure required the exchange of gloves to avoid contamination from the previous product. This measure was repeated at several sample collection sites.

After the samples were collected, they were properly closed and packed together with the unused HCl and MeOH and sent to the “Institute for Occupational and Environmental Medicine” of the University of Munich, in order to be analyzed and to quantify the existing levels of contamination.

Finally, it should be emphasized that the use of this technique requires good logistical planning, since the time between the collection and the entry into the laboratory cannot exceed 48 hours.

5.7 - Sample locations

The "*wipe sampling*" technique was applied in this project for the 3 hospitals (A, B and C) chosen for this purpose and the sampling sites were defined in agreement with the supervisors and the person in charge for risk management (or his representative) at the hospital centers. Among the several sites, a set of these were defined as common to the 3 hospitals. These selected common sites are shown in table 1.

The criterion used for the selection of the sites was the susceptibility of these sites, i.e., the fact that they present high potential of chemical contamination, with the pharmacists, pharmacy technicians and

nurses being exposed to chemical risk (Brouwers et al., 2007). The previous observations of the work routines helped in the choice of the sampling sites. The sites chosen are characterized in the following points.

Table 1 - Sampling sites selected common to 3 hospital centers.

Site	Hospital Pharmacy	Medical Oncology Day-care Hospital
1	Laminar flow hood (LFH), including the gutter.	Reception table.
2	Floor near laminar flow chamber.	Transport cart.
3	Transfer.	Waste bin.
4	Three plate trays.	Infusion pump.
5	Reception table.	Floor near infusion pump.
6	Packaging table.	Armchair.
7	Transport bag.	Bathroom floor.
8	Waste bin.	
9	Carbo/cisplatin and 5-FU shelves.	
10	Computer area.	
11	Floor near computers.	

5.7.1 - Hospital pharmacies

The preparation room/clean room is located inside the pharmacy in hospitals A and B. In hospital C, it is located near the Day-care hospital. The clean room must be in a condition of asepsis and negative pressure. It may have more than one laminar flow hood, support table, and waste bins inside. The equipment required for the procedures is:

- The laminar flow hood figure 7 - (a), is the equipment where several drugs are handled inside and several cytostatic treatments are prepared to be administered to the patients, where spillages, splashes and evaporation in the form of aerosols may occur. In the laminar flow hood, 3 samples were collected at 3 different times: the first moment before the beginning of the activity period, the second moment at the middle of the activity period and the third at the end of the activity period. The activity period is defined as the since the beginning of the working time of the laminar flow hood until it is cleaned at the end of the day. If it is cleaned at the end of the morning, it corresponds to half a period of activity. However, sometimes, at the end of the morning, it may correspond to the activity period. Cleaning at the end of the day is

the activity period. These samples are collected to observe the contamination evolution in the laminar flow hood during the preparation of cytostatics;

- The transfer figure 7 - (b), is a system that allows the transfer of drugs to and from the clean room. It has two airtight glass doors, one on the side of the clean room and another on the side of the hospital pharmacy, thus to be opened, one of the doors must be closed. Being a place where drugs are moved, it may be exposed to some drug spillages;

- The plate trays figure 7 - (c), are containers used to place the drugs on and allow their transfer into the clean room. After the treatment preparation, the same plate trays are used to transfer them to the hospital pharmacy. As a transport means, they may be exposed to liquid splash and spillages;

Figure 7 - (a) Laminar Flow Hood, (b) Transfer, (c) Tray.

- The floor next to the laminar flow hood is a location near the chamber were the drug is moved over to the bottle support table. If for some reason, the professional did not detect fluid in the walls of the bottle, some precipitation may occur on the floor;

- The reception table is used to place the trays that come from the clean room, with the preparations already completed and ready to be packed. Since they are taken from inside the clean room, they may be contaminated;

- The packaging table is used to package the treatments per patient. The treatments are placed on the table and later inside the plastic package, properly closed;

- Transport bags are used to carry the treatments from the hospital pharmacy to the medical oncology Day-care hospital, where the treatments are administered. Spillages may occur during the transportation, regardless of how it is done;

- The waste bins (figure 8) are used to place all the personal protective equipment used by the pharmacists/preparation technicians, inside the clean room, which are located in the transition room between the hospital pharmacy and the clean room;

Figure 8 - Waste bins.

- Carboplatin/cisplatin/fluorouracil shelves (figure 9) are sites where small amounts of these drugs are stored for daily use. Due to the high frequency of contact without exchange of gloves and the possible contamination of the bottles there may be the possibility of contamination;

Figure 9 - Carbo/cisplatin/fluorouracil shelves.

- The computer area is where the pharmacist processes the records but, at the same time, where he/she may also be in contact with cytostatics, since he/she performs other tasks that may also cause contamination;

- The floor next to the computers is a site that may be exposed to some fluid splash, due to its proximity to the computers, being the place where the pharmacist stands and moves into the pharmacy for other tasks.

5.7.2 - Day-care hospital

The reception table is the place where the treatments to be given to the patients are received. They are removed from the hospital pharmacy transport equipment and placed on the table to be checked and delivered to be administered or, if necessary, stored for subsequently administration. The equipment required for the procedures is:

- The transport cart figure 10 - (a), is the equipment used to transport the treatments from the reception table to the patient;

- The waste bins figure 10 - (b), attached to the cart, are used to place the devices used to administer the treatment to the patients, and the personal protective equipment used by the nurses/half care nurses;

- The infusion pump figure 10 - (c), is an equipment used in various types of treatment in which strict administration of the drug drops is required. It may exist attached to the treatments transport or isolated. Nurses handle this equipment frequently. The fluid circulates through the infusion pump;

- The armchair figure 10 - (d), is an equipment consisting of 1 seat and 2 armrests. This is used for the patient to be seated to receive the treatment administration. Spillage may occur through the fluid transport tubes;

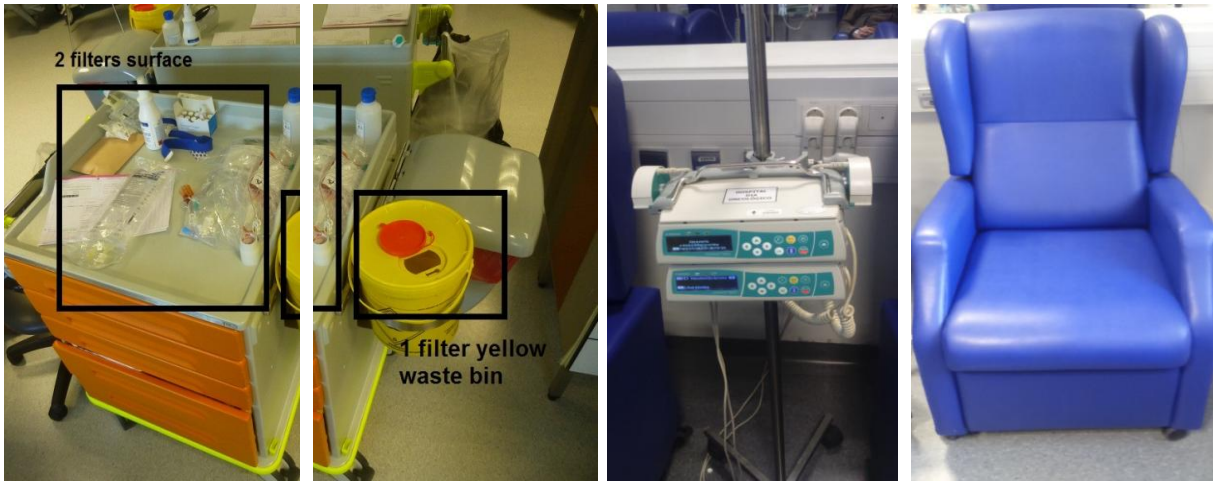

Figure 10 - (a) Treatment trolley, (b) Waste bin, (c) Infusion pump, (d) Armchair.

- The floor near the infusion pump is a place that may be exposed to some fluid splash and pillage due to its proximity to the infusion pumps. The presence of the nurse is frequent here, where several contacts are made with the infusion pump and with the equipment that has the drug circuit installed;

- The treatment support sample includes the infusion pump and the surface of the floor near the infusion pump. Except in hospital A, where only the infusion pump surface sample;

- The bathroom floor is used by all male patients, who are under treatment in medical oncology Day-care hospitals. Considering the characteristics of the user, it is possible to have floor contamination.

5.8 - Comparison of the methodology used by the 2010 and the 2015 studies in hospital B

In 2010, we have conducted a contamination study in some workplaces in the hospital pharmacy and medical oncology Day-care hospital of hospital B.

In the 2015 study, 3 hospitals are involved, including hospital B. Even if we have repeated the data collection in hospital B, the evaluation sites in the more recent study have much more locations than the one developed in 2010. The comparison is only possible for those locations where the same location was sampled.

The methodology followed in 2015 was the same as in 2010. The technique used for the sampling was "wipe sampling" used by Schierl, et al. (2009).

5.9 - The laboratory sample analysis techniques

Laboratory analyses of Pt and 5-FU were performed as described in detail in Schmaus et al. (2002) and Schierl et al. (2009).

The detection limit (LOD) for Pt was 0.01ng per sample and for 5-FU was 0.3ng per sample. For a cleaning area of 400 cm^2, detection limits were 0.025pg/cm^2 and 0.75pg/cm^2 respectively for Pt and 5-FU (Schierl et al., 2009). Pt is a metal that appears in the environment not only due to contamination with drugs containing Pt, but also due to other sources, such as the emission of exhaust catalysts from cars. Voltammetry measures only the total Pt and it is not possible to separate Pt from antineoplastic drugs and environmental sources.

Analytical methods in the analysis of the Pt in the laboratory, several equipment, among which the magnetic stirrer presented in (figure 11) are used. In the Pt analysis, 1 millilitre of HCl solution was used and, after the addition of hydrogen peroxide (H_2O_2) and sulfuric acid (H_2SO_4), the organic compounds were destroyed by ultraviolet radiation. The determination of the Pt concentration is performed by inverse voltammetry, as described in Ensslin, Pethran, Schierl, & Fruhmann (1994), Schmaus et al., (2002), and Schierl et al. (2009).

Figure 11 - a) Solution shaker, b) Test tubes, c) Equipment used in the laboratory to quantify Pt (Magnetic stirrer).

In order to analyze 5-FU in the laboratory, several devices were used, among which the gas chromatograph presented in (figure 12). 5-FU was analyzed in the laboratory through gas chromatography/mass spectrometry (GC / MS) (Schmaus et al., 2002) (Schierl et al., 2009). Methanol was used as organic solvent and 5-chlorouracil as an internal standard. Derivatization was performed by N-tert-butyldimethylsilyl-N-methyltrifluoroacetamide at 70°C. GC/MS was recorded in the selected ion mode with m/z 301 for FU and m/z 317 for CIU, Schierl et al., (2009).

Figure 12 - a) Test tubes, b) Exterior of the Equipment used in the laboratory to quantify 5-FU (Chromatograph), c) Inside.

5.10 - Statistical analysis

The data collected were treated and analyzed statistically by using SPSS, version 23 (Statistical Package for the Social Science, IBM).

Essentially, frequency distributions were made for most of the variables under study and associations between the variables were established using the chi-square test with the measure of association, and ratio of possibilities.

The chi-square test (χ^2) allows testing the homogeneity of the 2 groups under study regarding exposure effects in the workplace. This test was used because the 2 groups (exposed and control) are independent. Their elements were selected randomly and the observations are frequencies.

The cross-tabulated chi-square test (χ^2) was used to verify the independence of spill sites, causes of spills and exposure effects (nausea and vomiting, alopecia, headache, dizziness, dizziness and cutaneous hyperpigmentation). These data were crossed with the following questions: time of service in the task of manipulation of cytostatics? Do you have scheduled break intervals between preparation / administration periods? In the last 12 months have you attended training courses on cytostatic manipulation / administration? By your own initiative, you often read articles on cytostatics? Have you ever made any proposals for improving your practice?

CHAPTER 6 - RESULTS ANALYSIS AND DISCUSSION

6.1 - Questionnaire

6.1.1 - Sociodemographic characterization of the participants

The sample is composed from both exposed and control group, with a total 154 health professionals from 3 hospital centers. Among these, 74 worked in hospital A, 42 in hospital B, and 38 in hospital C (figure13).

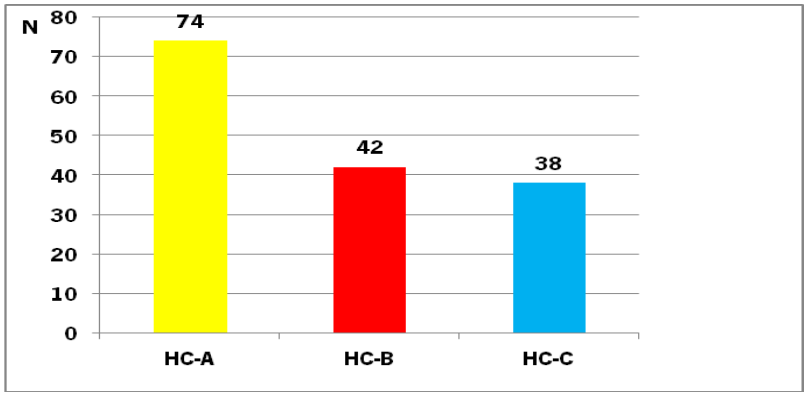

Figure 13 - Number of professionals for hospital centers A, B, C.

In figure 14, the distribution of the professionals over workplaces, where each one carries out their activity, can be observed. The sample included all the available professionals for each hospital service. Thus, 39 pharmacists and pharmacy technicians work in pharmacies, 21 in hospital A, 9 in hospital B and 9 in hospital C. Fifty seven nurses work in medical oncology Day-care hospitals: 35 in hospital A, 11 in hospital B, and also 11 in hospital C. Fifty six nurses work in the vascular surgery service: 18 in hospital A, 21 in hospital B, and 17 in hospital C. Two operational assistants work in the logistics department: 1 in hospital B and 1 in hospital C.

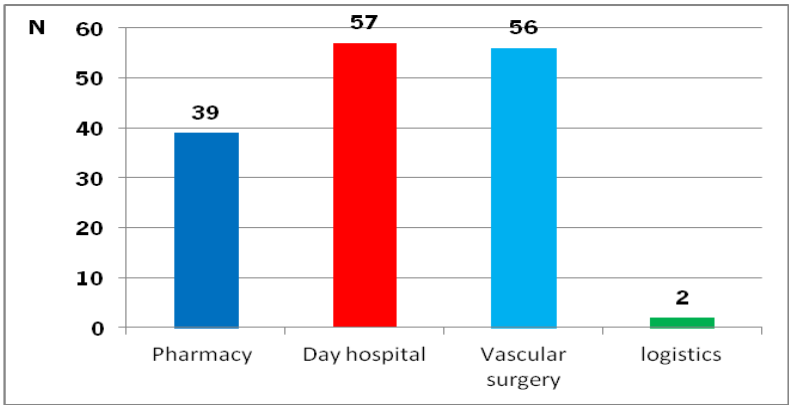

Figure 14 - Number of professionals per hospital service.

The majority of these professionals are female (129), 66 of whom work in hospital A, 33 in hospital B and 30 in hospital C. Regarding their academic training, 136 have higher education: 59 in hospital A, 39 in hospital B and 38 in hospital C.

Regarding their age, in figure 15 it is possible to observe that there is a smaller number of professionals at the extremes of the graphic, and that the largest number, at ages ranging from 25-30, corresponds to 35 professionals, and at ages ranging from 30-35, 33 professionals.

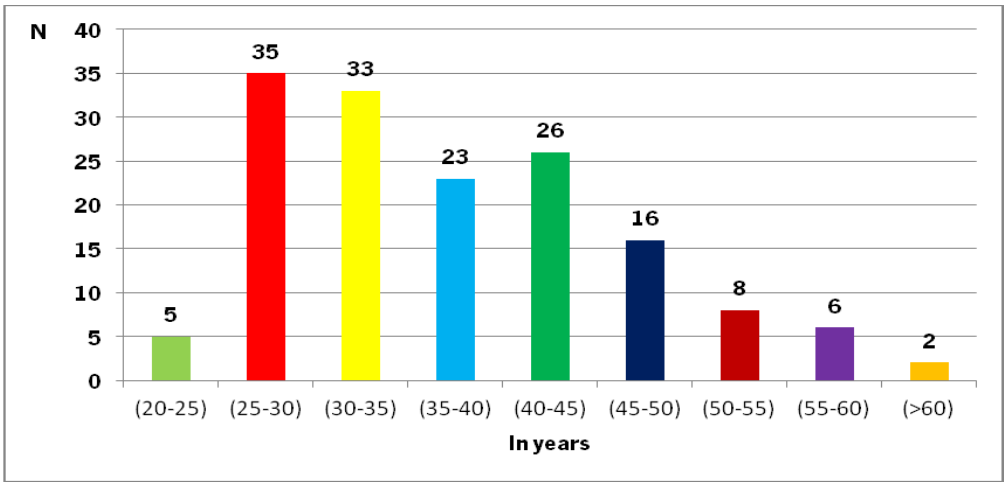

Figure 15 - Age of the health professionals of the sample.

In hospital A, the largest number of professionals is at these ages as well: 18 and 19, respectively. In hospital B, most professionals are in the 25-30 years range, with 10 professionals. On the other hand, in hospital C, the majority of professionals is at the ages ranging from 30-35 years and from 35-40 years, with 8 professionals in each range, (figure 16).

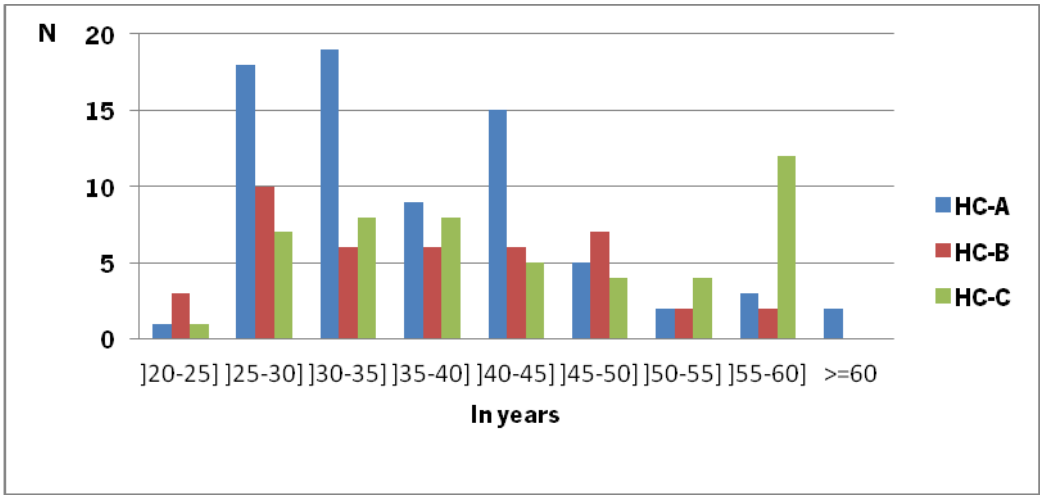

Figure 16 - Age of the professionals in hospital centers A, B, and C.

Obtained data show that most of these professionals are at fertile age, and 83 (56.9%) stated that they have descendants (42 in hospital A, 22 in B and 19 in C).

In relation to the number of descendants (figure 17), the most cited category was "1 descendant, with 39 professionals and 2 with 37, corresponding to 25.3% and 24%, respectively. It should be taken into account that in hospital A, the most mentioned was 1 with 23, in the percentage of 31.1%, as well as in hospital C, with 11, in the percentage of 28.9%. However, in hospital B, the most mentioned was 2 children, with 17 professionals (40.5%).

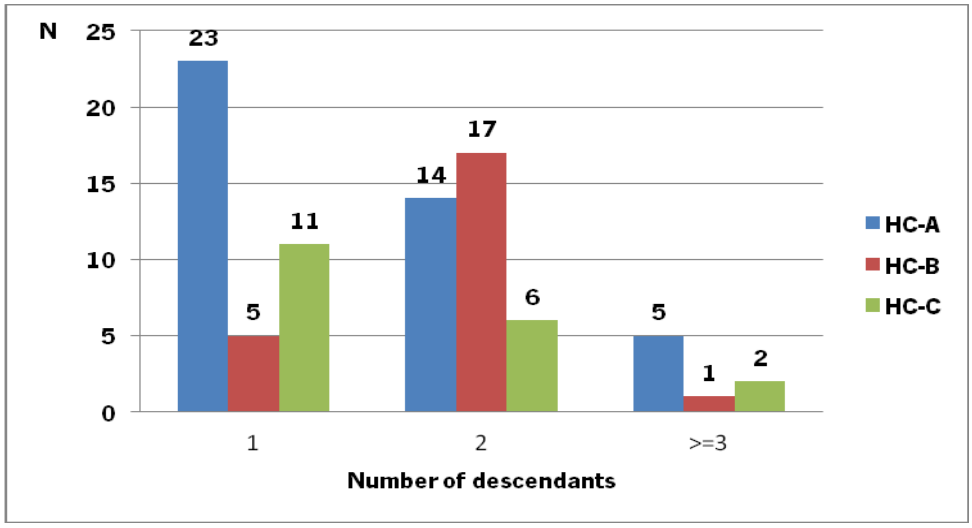

Figure 17 - Number of descendants of the professionals in hospital centers A, B and C.

Regarding pregnancy planning, (figure 18), 72 professionals, (46.8%), answered affirmatively, whereas in hospital A this number is 35, in the percentage of 47.3%; in hospital B the value is 19 in the percentage of 45.2%, and in hospital C 18 in the percentage of 47.4%.

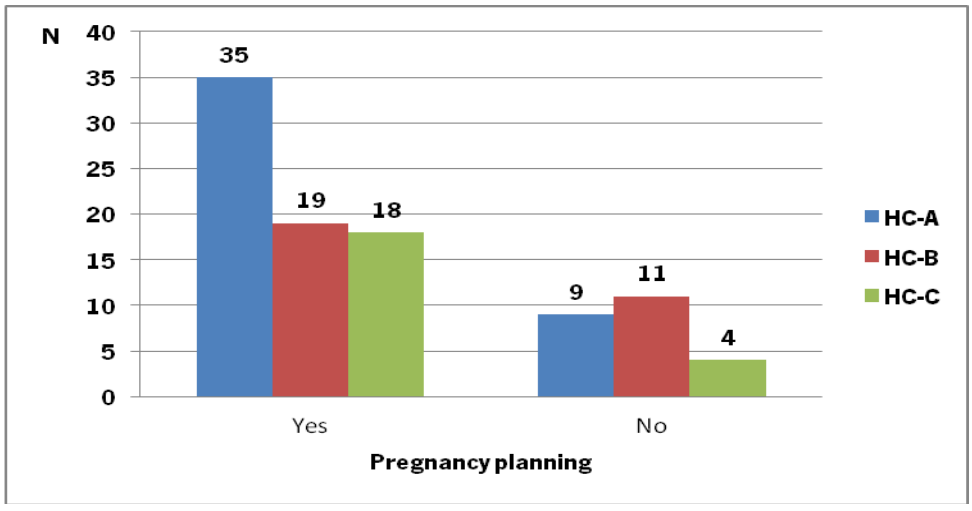

Figure 18 - Pregnancy planning of the staff of hospital centers A, B and C.

Twenty nine professionals, 18.8%, (figure 19) reported that the time until the pregnancy was equal to or less than 3 months. This time was also reported by the professionals of the 3 hospitals, with 13 in the percentage of 17.6% in hospital center A, 10 in the percentage of 23.8% in the hospital center B, and 6 in the percentage of 15.8% in hospital center C.

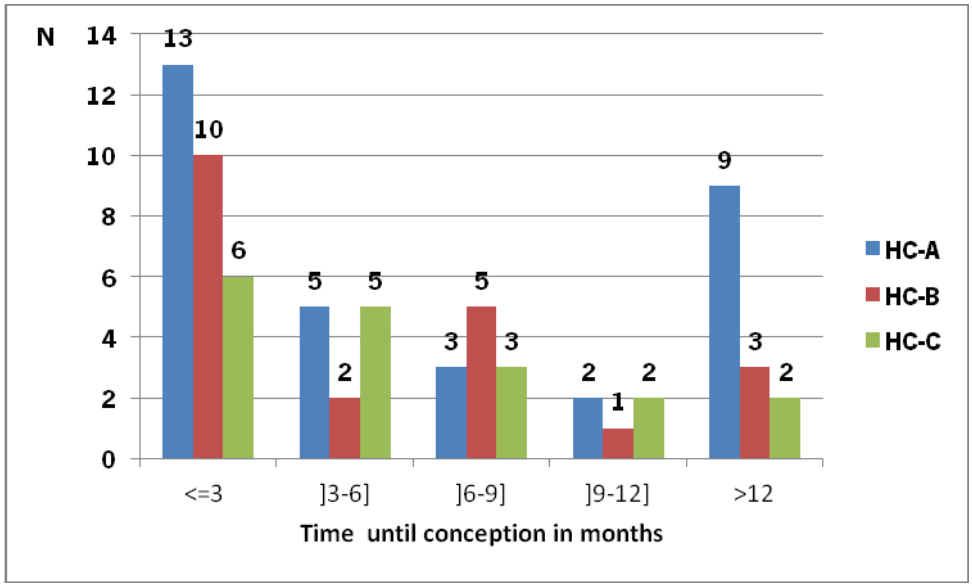

Figure 19 - Time until conception in months of the professionals of hospital centers A, B and C.

Also, 58 professionals from the three hospitals, in a percentage of 37.7%, stated that their first child was born when they were 30 years old or younger. Similarly, the professionals of hospital A, 32, in a percentage of 43.2%; those from hospital B, 16, in a percentage of 38.1%; and those from hospital C, 10, in a percentage of 26.3%, had their first child at an age below 30.

6.1.2 - Work organization

Regarding the total time of service in the health area, the interval of (5-10) years was the one that registered a greater percentage, 27.9%. This interval was also recorded in hospital A and hospital C, 36.5% and 23.7%, respectively, whereas in hospital B, the interval with the highest percentage was (1-5) years, 21.4%.

For the time of service only in the cytostatics handling task (figure 20), the value of 41 professionals is observed, in the percentage of 26.6%, for 2 or fewer years in that task. However, in hospital A, 28.4% of its professionals have 10 or more years of service, while in hospitals B and C, professionals have 2 or fewer years of service in the percentages of 33.3% and 42.1%, respectively.

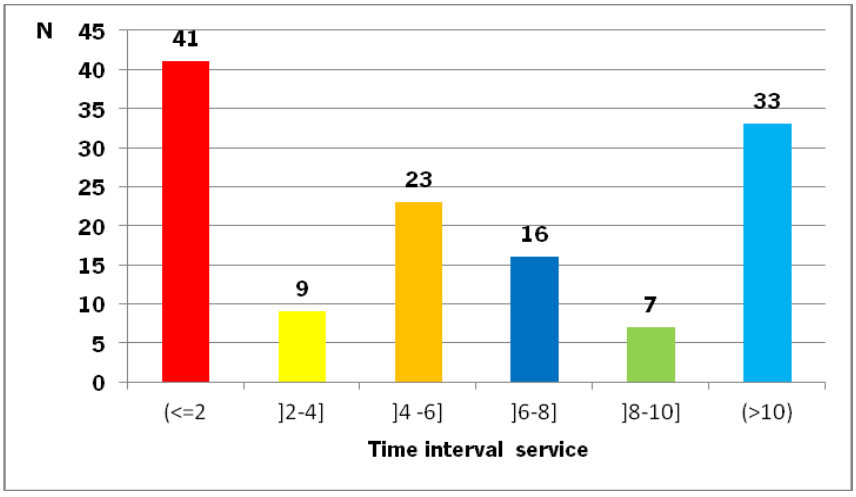

Figure 20 - Time of service in cytostatics manipulation tasks.

The average time of cytostatic manipulation (figure 21), ranging from 6 to 8 hours/day, was reported by 55 professionals, in a percentage of 35.7%. It should be taken into account that this interval was also reported by professionals in hospital A, in a percentage of 50%. However, in hospital B, the interval of 2 to 4 hours/day was reported, with the percentage of 21.4%, and in hospital C, the interval was less than or equal to 1, in a percentage of 42.1%.

Nearly 80% (79.9%) of the professionals (n=123), reported that they are aware of the exposure risk during their manipulation activity, namely cytostatics manipulation. However, the professionals in hospital A showed the highest risk perception, (n=64), followed by those from hospital C, with 32, and those from hospital B, with 26 professionals.

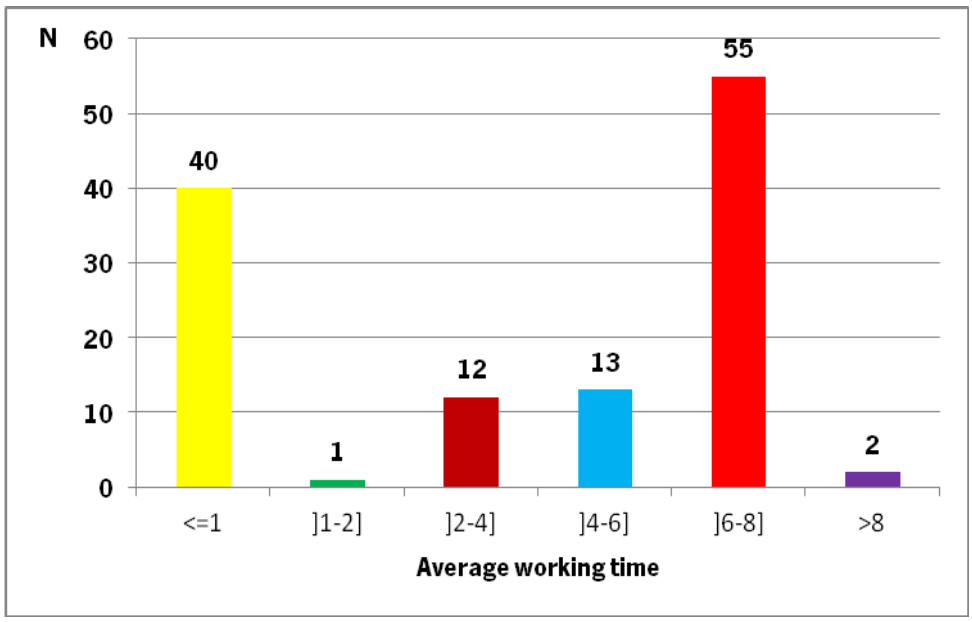

Figure 21 - Average time on cytostatic manipulation in the 3 hospital centers (hours).

Concerning the use of personal protective equipment (PPE) (figure 22), 133 (86.3%) professionals stated that they use them in their tasks. With 69 professionals, hospital A takes the lead, while in hospital C, the number of professionals that use it is 33, and in hospital B, 31.

Figure 22 - Personal Protective Equipment (PPE).

Regarding the use of personal protective equipment, the answers were different. The results are presented in table 2.

Table 2 - Use of personal protective equipment.

	Hospitals			
Personal Protective Equipment (PPE)	**A**	**B**	**C**	**Total**
Gloves	69	31	32	132
Masks	43	20	25	88
Goggles	8	3	13	24
Gowns	33	21	22	76
Hair protection	25	10	14	49
Footwear protection	23	10	12	45

The existence of an breaks/pauses planned between periods of cytostatics preparation and administration was reported by 58 of the respondents. In hospital C, 24 professionals reported that they took breaks, 23 in hospital A; and 11 in hospital B.

6.1.3 - Reported accident

Regarding the occurrence of spillages during cytostatics transport, manipulation and/or administration, 53 of the respondents answered affirmatively, 29 of hospital A, 12 of hospital B; and 12 of hospital C.

The locations where those spillages occurred are diverse and vary significantly, as can be seen in (figure 23). Thus, for the storage, the affirmative answers were 7, in a percentage of 4.5 percent.

Hospital A has 4 affirmative answers, corresponding to the percentage of 5.4%, hospital C has 2 responses, equivalent to the percentage of 5.3%, and hospital B has 1 response, equivalent to the percentage of 2.4%. For the shelf, the affirmative answers were 6, which correspond to the percentage of 3.9%. Hospital A presents 4 responses, equivalent to 5.4% of the professionals, hospital C has 1 response, which equates to the percentage of 2.6%, and hospital B also has 1 response, equivalent to 2.4%.

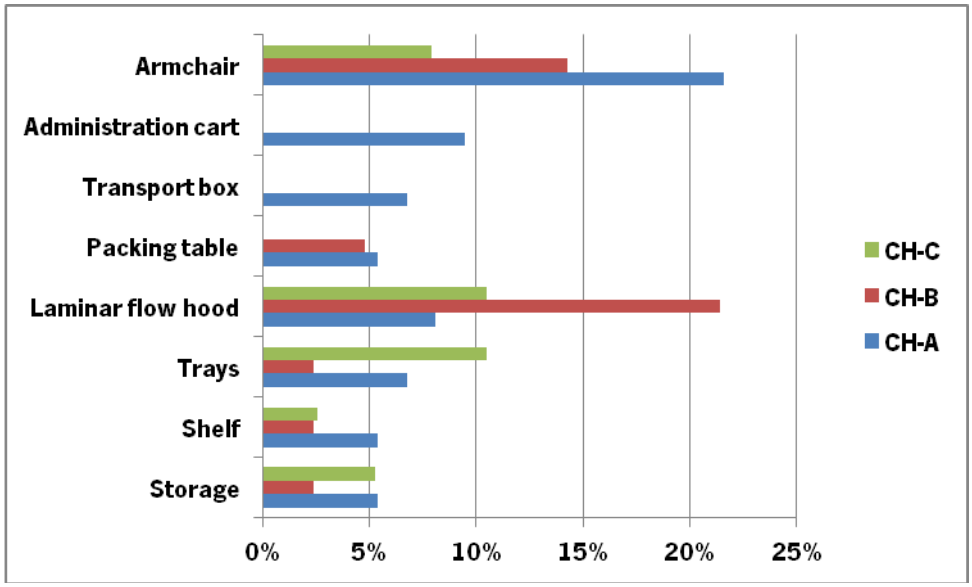

Figure 23 - Locations where spillages occurred.

On the tray, the number of spillages was 10, corresponding to 6.5%. In hospital A, its value was 5, equivalent to 6.8%, in hospital C, the value was 4, corresponding to 10.5%, and in hospital B, 1 spillage, equal to 2.4%. On the other hand, in the laminar flow hood, the number of spillages was 19, corresponding to 12.3%: 9 in hospital B, which corresponds to 21.4%; 6 in hospital A, corresponding to 8.1%; and 4 in hospital C, corresponding to 10.5%. On the packaging table, the number of spillages was 6 (3.9%). Hospital A shows 4 spillages, equivalent to 5.4%, hospital B shows 2, 4.8%, and hospital C does not show any spillages. In the transport box, the number of spillages was 5, equivalent to 3.2%. Hospital A was the only one where these 5 spillages occurred, corresponding to 6.8%. In the administration trolley, there were 7 spillages, which correspond to 4.5% of the professionals surveyed. Also in this case, hospital A was the only one showing these types of spills, 7 (9.5%). Finally, the armchair represents the place where more spillages occurred, 25 in total, equivalent to 16.2%. It should be taken into account that the highest number of spillages occurred in hospital A, 16, corresponding to 21.6%. There were 6 spillages in hospital B (14.3%), and 3 in hospital C (7.9%).

On the left, concerning the period of the day when these spillages occurred (M-morning, A-afternoon, M/A-morning/afternoon) figure 24 a), the morning period was reported by 35 professionals, 22.7

percent, as the most significant: hospital A with 14 professionals, (18.9%), hospital B with 10, (23.8%) and hospital C with 11, (28.9%).

On the right, regarding the time of the day when the spillages occurred figure 24 b), it can be seen that the 2nd and 4th hour are the times when they most occurred. There were 17 in each of these, (11%). At the first hour, hospital B registered 5, (11.9%), hospital A, 5, (6.8%), and hospital C, 2, (5.3%). At the second hour of the day, the following values were recorded: in hospital A, 9, corresponding to 12.2%; in hospital C, 4, (10.5%); and in hospital B, 4, (9.5%). At the third hour of the day, in hospital A, 9 spillages were again recorded, in the same percentage of 12.2%, in hospital C, 3, equivalent to 7.9%, and in hospital B, 1 spillage, corresponding to 2.4%. At the fourth and last hour of the day under study, it is verified that, in hospital A this period shows the highest number of spillages, 15, corresponding to 20.3%, in hospital C, 2 spillages, 5.3%, whereas in hospital B there was no reference.

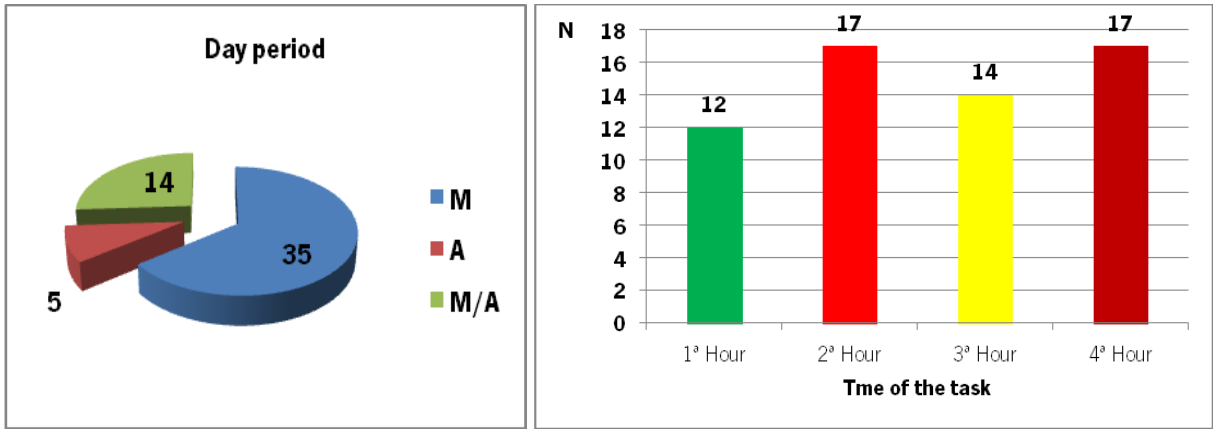

Figure 24 - a) Period of the day, b) Time when spillage occurred (M-morning, A-afternoon, M/A-morning/afternoon).

Regarding spillage causes, (figure 25), 6.5% is due to fine motor coordination according to 10 professionals. in hospital A, 6 professionals, 8.1%, in hospital C, 4 professionals, 10.5%, while in hospital B there was no reference. Concentration was reported as the cause of spillage by 4 health professionals, 2.6% of respondents. So, in hospital C, 2 professionals, 5.3%, answered affirmatively; in hospital B, 1 professional, 2.4%, and in hospital A, 1 professional, 1.4%. Stress was indicated by 17 professionals, which corresponds to 11 percent. Hospital C recorded 7 affirmative answers, corresponding to 18.4%; hospital A, also 7 answers, 9.5%; and hospital B, 3 affirmative answers, which is equivalent to 7.1%.

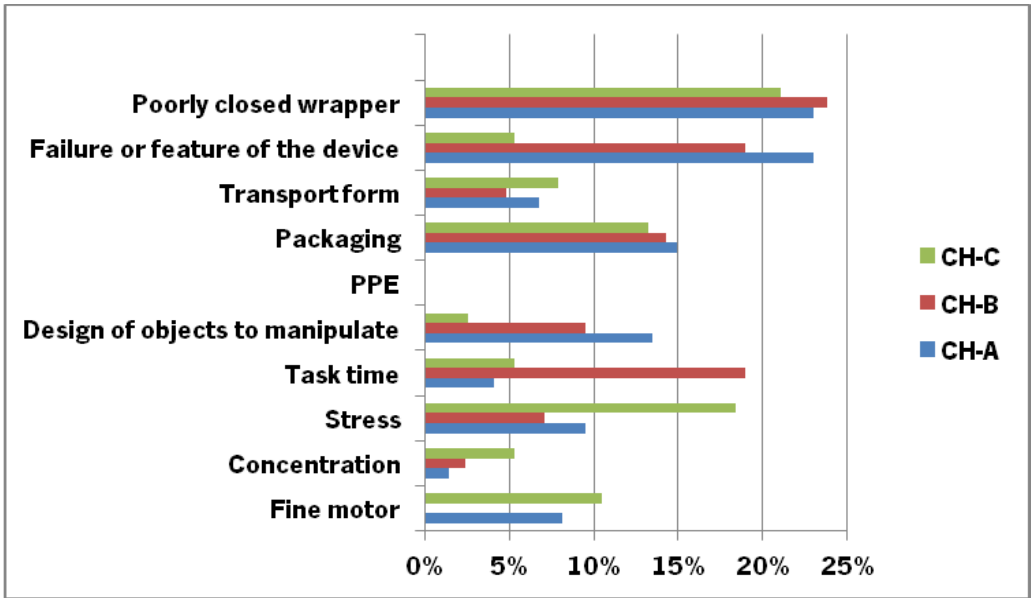

Figure 25 - Spillage causes.

Task time was mentioned as a cause of spillages by 13 of the respondents, 8.4%. Hospital B takes the lead, with 8 professionals answering affirmatively, 19.0%; hospital A, 3 professionals, 4.1%; and hospital C, 2 professionals, 5.3%. However, 15 of the respondents, 9.7%, considered the *Design* of the objects to be manipulated as the cause for the spillages: 10 professionals in hospital A, 13.5%; 4 in hospital B, 9.5%; and 1 in hospital C, 2.6%. It should be taken into account that the professionals involved in this study did not consider personal protective equipment (PPE) to be a cause of spillage. Regarding the packaging, 22 professionals, 14.3%, consider it as a cause of spillage. The number of affirmative answers is 11 in hospital A, which corresponds to 14.9%, 6 in hospital B, 14.3%, and 5 in hospital C, 13.2%. The type of transportation was indicated as a spillage cause by 10 hospital professionals, corresponding to 6.5%. 5 professionals of hospital A answered affirmatively, which is equivalent to 6.8%, 3 of hospital C, (7.9%) and 2 of hospital B, (4.8%). Device failure/feature was reported as the cause by 27 hospital professionals, which corresponds to 17.5%. In hospital A, 17 professionals (23%) reported failure as a spillage cause; in hospital B, 8 professionals, 19.0%; and in hospital C, 2 professionals, 5.3%. Finally, 35 respondents (22.7%), said that spillage occurred due to poorly enclosed wrap. The highest number of respondents was in hospital A, with 17 (23.0%), followed by hospital B with 10 (23.8%), and hospital C with 8 professionals (21.1%).

6.1.4 - Job training/motivation

Among the professionals who collaborated in this study, 78.6% reported that they carry out waste separation while performing their tasks. The professionals of hospital A answered affirmatively in a higher percentage (86.5%) followed by hospital C (81.6%) and hospital B (61.9%).

Regarding the frequency of training workshops on cytostatic manipulation/preparation (figure 26), only 34 professionals (22%) reported that they have attended training courses in the last 12 months. In this respect, hospital C leads with 13 professionals (34.2%), then hospital B with 11 (26.2%), and finally hospital A with 10 (13.5%).

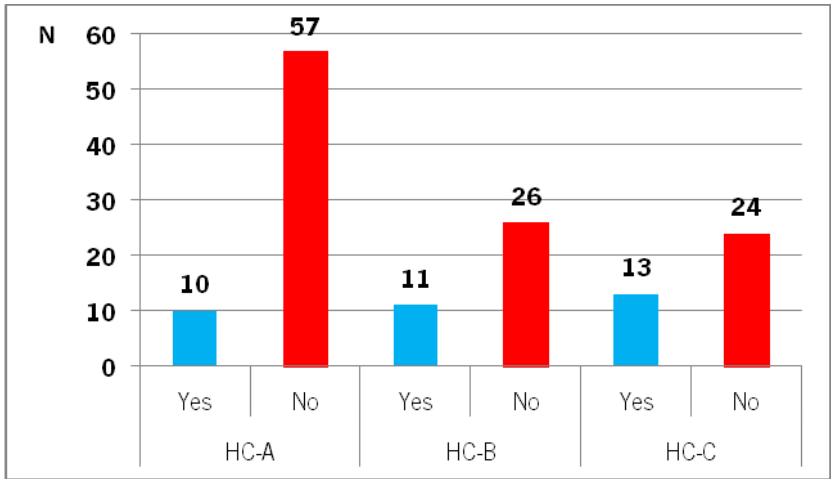

Figure 26 - Frequency of training workshops in the last 12 months.

Regarding the self-motivated reading of papers on cytostatics, fifty percent of the respondents answered affirmatively, with 44.7% in hospital C, 41.9% in hospital A, and 40.5% in hospital B.

However, regarding the presentation of proposals for improving practices, only 28.6% of the respondents submitted proposals: 39.5% in hospital C, 31.0% in hospital B, and 21.6% in hospital A. The most referenced proposal was in-service training, with 3 respondents (4.1%) in hospital A, while all other proposals were referenced only once in the 3 hospitals in the study.

6.1.5 - Self reported effects

Concerning the exposure effects results, they present the situation of "not experienced", "experienced" and "experienced a lot", this last two were added up and represented in figure 27, although some effects in a not very significant percentage. Thus, nausea and vomiting exposure effects were experienced by 16 professionals, 10.3% of respondents. This effect was experienced by 6 professionals, 14.2%, in hospital B, and 5 professionals in hospitals C and A, in the percentages of 13.1% and 6.7%, respectively.

The alopecia effect was "experienced" by 22 professionals, in the percentage of 14.3% of the respondents: hospital A with 15 professionals, in the percentage of 20.2%; hospital B with 5

professionals, in the percentage of 11.9%; and hospital C with 2 professionals, in the percentage of 5.2%.

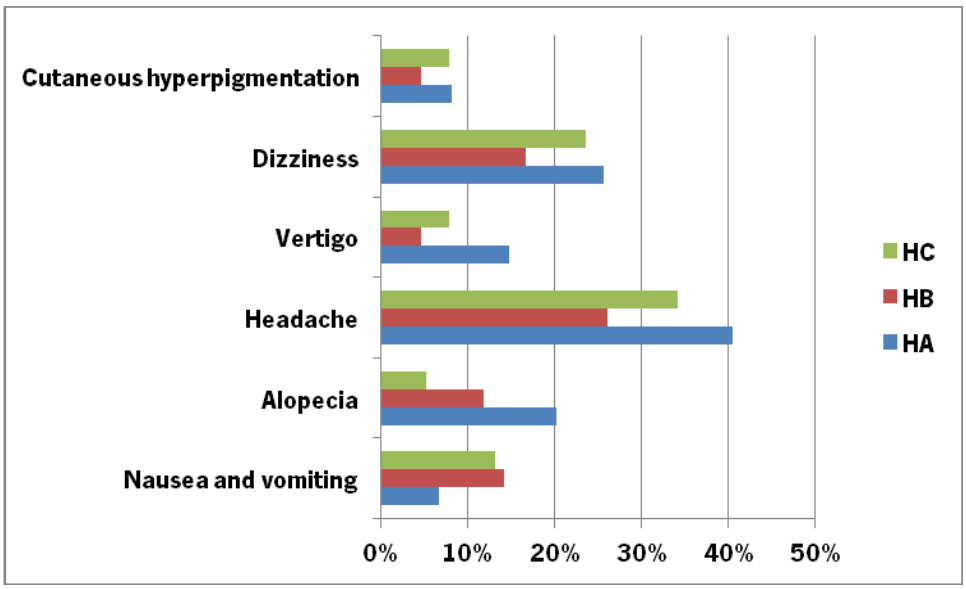

Figure 27 - Exposure effects reported by hospital centers staff A, B and C.

Headache was "experienced" by 54 professionals who answered affirmatively, in the percentage of 35%. Hospital A presents 30 professionals, in the percentage of 40.5%, hospital C, 13, 34.2%, and hospital B, 11, in the percentage of 26.1%.

On the other hand, vertigo was "experienced" by 16 professionals, 10.4% of the individuals surveyed. In hospital A, 11 professionals, in the percentage of 14.8%, in hospital C, 3 professional, which corresponds to 7.8%, and in hospital B 2, 4.7%.

The dizziness effect was "experienced" by 35 professionals, corresponding to the percentage of 22.7% of the professionals surveyed. The results of hospital A showed 19 professionals, in the percentage of 25.6%, hospital C, 9 professionals, 23.6%, and hospital B, also 7, but with a percentage of 16.7%.

Finally, the cutaneous hyperpigmentation effect was "experienced" by 11 professionals, corresponding to 6.5% of the respondents. In hospital A, 6 professionals, in the percentage of 8.1%, in hospital C, 3 professionals, equating to 7.8%, and in hospital B, 2 professionals, 4.7%.

6.1.6 - Exposure effects analyzed

The study of exposure effects included a sample of 154 health professionals. Among these, some manipulate/administer cytostatics, while others do not have any contact with these substances, been

the control group. The exposure effects under study were: nausea and vomiting, alopecia, headache, vertigo, dizziness and cutaneous hyperpigmentation.

6.1.6.1 - In the exposed group

The exposed group was composed of 98 health professionals (pharmacists, pharmacy technicians, nurses and logistics/transport employees) who work in the hospital pharmacies and in medical oncology Day-care hospitals, corresponding to 63.6% of the total sample. In this group, hospital A has 56 professionals, in the percentage of 75.7%, hospital B, 21, which equates to the percentage of 50%, and hospital C, 21, 55.3%.

The results of the answers of this group regarding the above-mentioned exposure effects are shown in figures 28 to 45, as well as those of the control group.

For the treatment and presentation of the survey data, and due to the results of the surveys, the "experienced" responses were combined to allow a more objective reading, leaving only two answers, "not experienced" and "experienced".

In (figure 28), we can observe the results of the nausea and vomiting side effect that was "experienced" by 13 health professionals in the group exposed, 13.2%, in the three hospitals under study. 4 in hospital A, 6 in hospital B, and 3 in hospital C. In the control group, this effect was "experienced" by 3 health professionals, 5.35%.

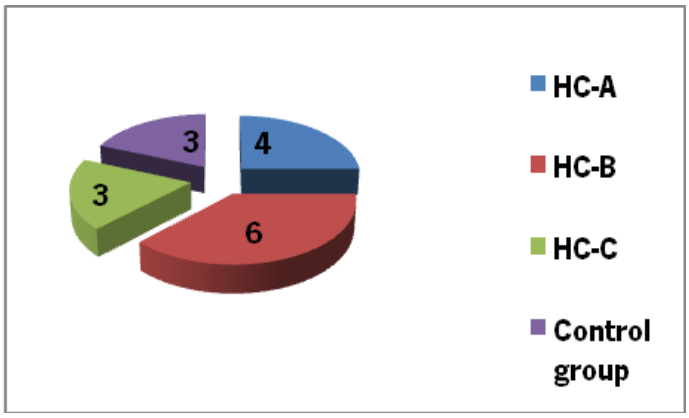

Figure 28 - Nausea and vomiting experienced in the 3 hospital centers.

In the exposed group (figure 29), there was a higher incidence of nausea and vomiting in relation to the control group (χ^2 (1) =2.629; p <0.05. There is a statistically significant difference in those that "experienced" the nausea and vomiting effect, which is almost 3 times higher (Odds ratio=2.867) in the exposed group, compared to the control group.

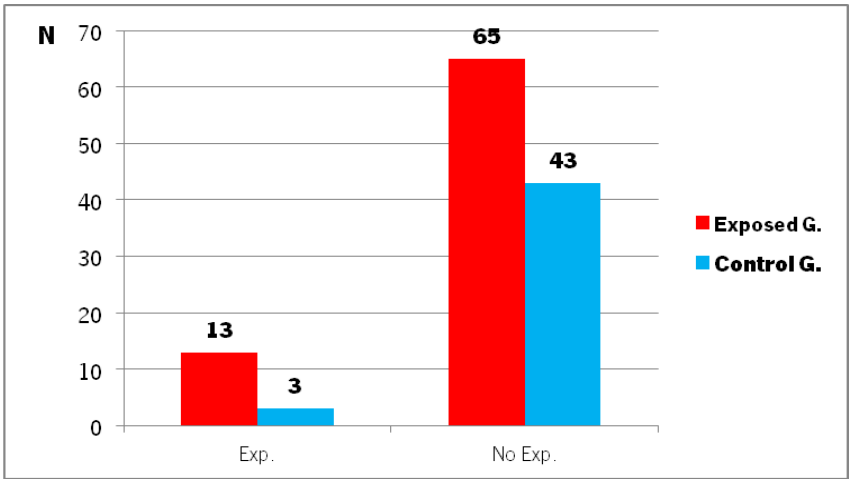

Figure 29 - Nausea and vomiting effect reported.

In the Day-care hospital (figure 30), there is also a higher incidence of nausea and vomiting compared to the hospital pharmacy (χ^2 (1) =0.011; p <0.05). There is a statistically significant difference in those that "experienced" the nausea and vomiting effect, which is 1 time higher (Odds ratio=1.067) in the Day-care hospital, compared to the hospital pharmacy.

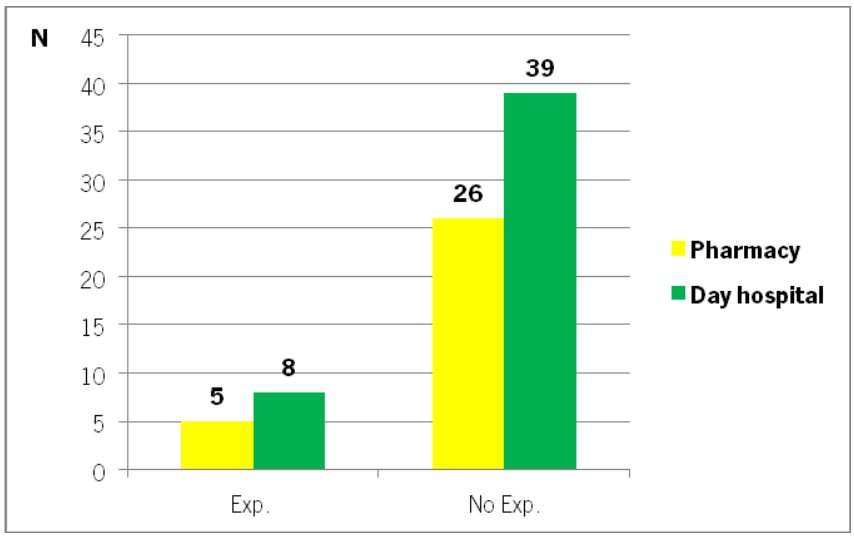

Figure 30 - Nausea and vomiting effect reported by pharmacy/hospital Day workers.

The alopecia effect (figure 31) was "experienced" by 20 health professionals in the exposed group, 20.4%. 14 in hospital A, 5 in hospital B and 1 in hospital C. The control group presents 2 professionals, 3.57%, who answered "experienced".

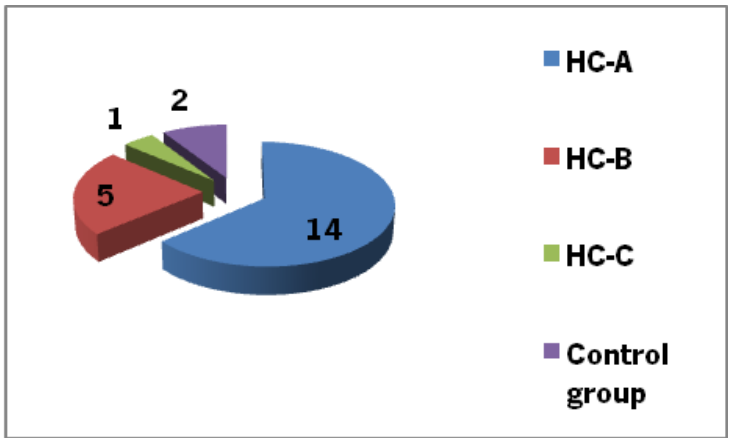

Figure 31 - Alopecia experienced in the 3 hospital centers.

In the exposed group (figure 32), there is a higher incidence of the alopecia side effect compared to the control group (χ^2 (1) =8.917; p <0.05). There is a statistically significant difference in those that "experienced" the alopecia effect, which is almost 8 times higher (Odds ratio=7.586) in the exposed group, compared to the control group.

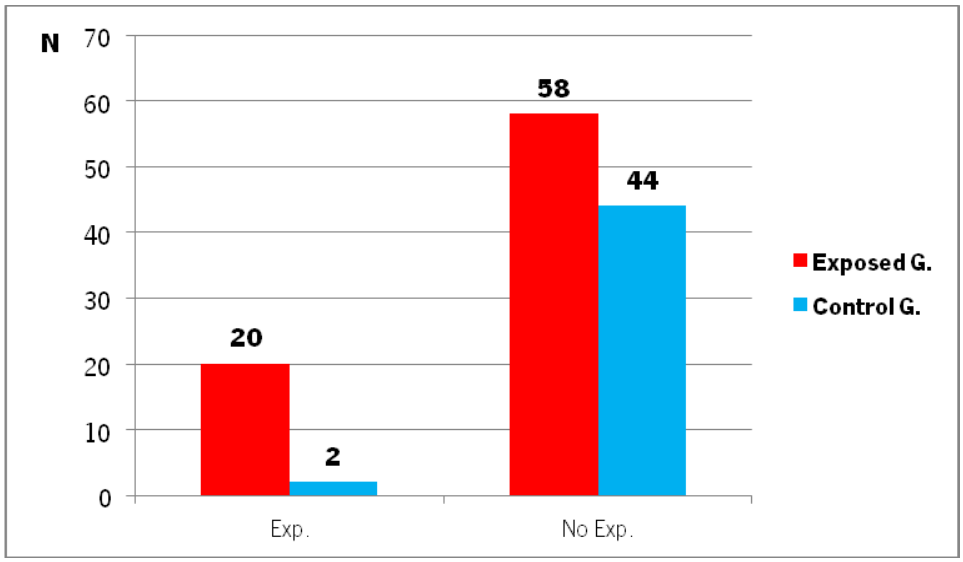

Figure 32 - Alopecia effect reported.

Likewise, in the Day-care hospital (figure 33), there is a higher incidence of the alopecia effect compared to the hospital pharmacy (χ^2 (1) =0.398; p <0.05). There is a statistically significant difference in those that "experienced" the alopecia effect, which is 1 time higher (Odds ratio=1.407) in the Day-care hospital, compared to the hospital pharmacy.

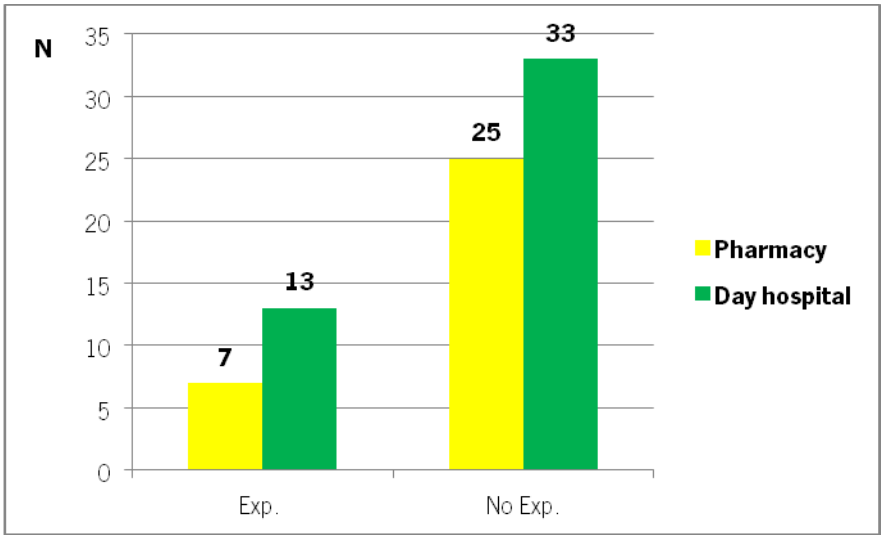

Figure 33 - Alopecia effect reported by pharmacy/hospital Day workers.

Headache was "experienced" by 52 health professionals in the group exposed, 53.1%, distributed as follows: 29 in hospital A, 11 in hospital B, and 12 in hospital C (figure 34). In turn, in the control group, 2 professionals 3.57% reported having "experienced" this side effect.

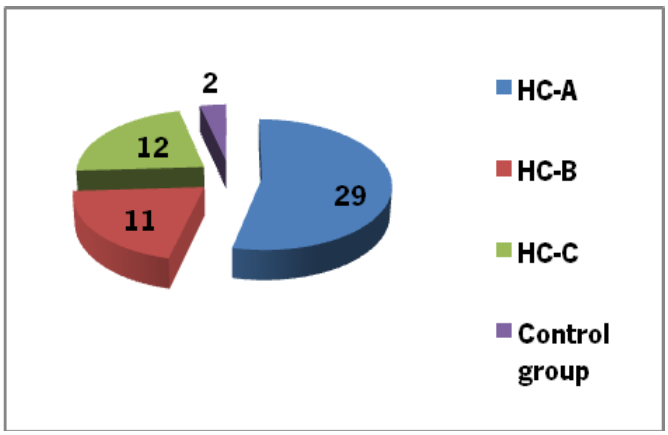

Figure 34 - Headache experienced in the 3 hospital centers.

In the exposed group (figure 35), there is a higher headache incidence, compared to the control group ($\chi^2(1) = 42.660$; $p > 0.001$). Although there is no statistically significant difference, the results for "experienced" the headache effect are almost 40 times higher (Odds ratio=39.448) in the exposed group, compared to the control group.

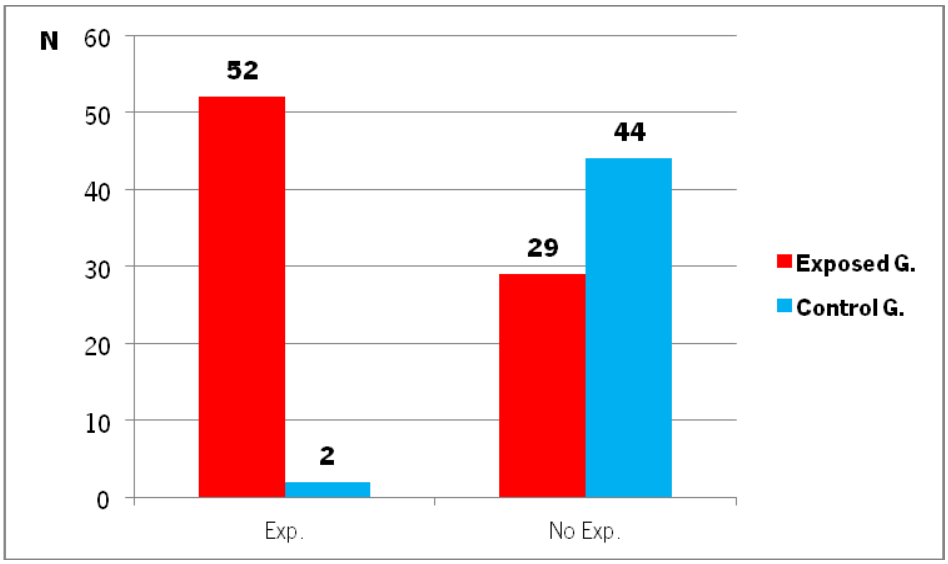

Figure 35 - Headache effect reported.

Similarly, in the Day-care hospital (figure 36), there is a higher headache incidence, compared to the hospital pharmacy (χ^2 (1) =2.156; p <0.05). There is a statistically significant difference in those that "experienced" the headache effect, which is slightly higher (Odds ratio=0.480) in the Day-care hospital, compared to the hospital pharmacy.

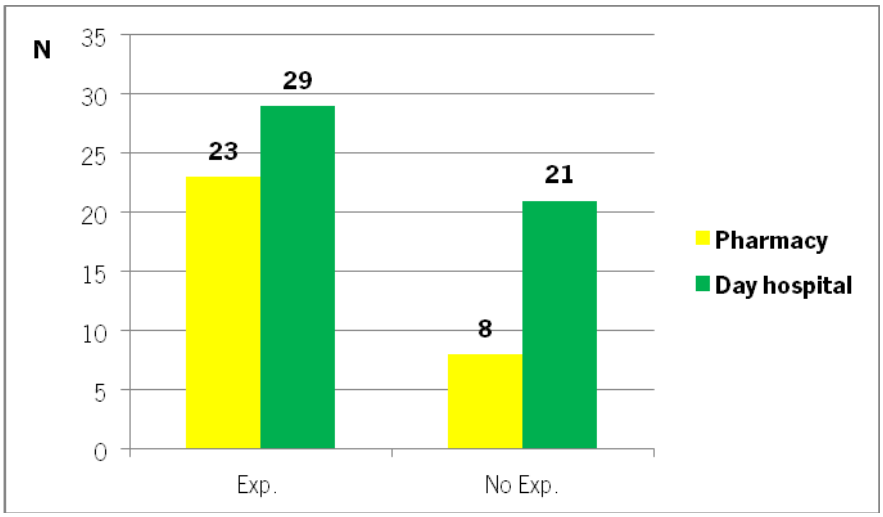

Figure 36 - Headache effect reported by pharmacy/hospital Day workers.

The vertigo effect (figure 37) was "experienced" by 15 health professionals in the exposed group, 15.3%, with 10 records in hospital A, 2 in hospital B, and 3 in hospital C. The control group presents 1 professional 1.78% who "experienced" this side effect.

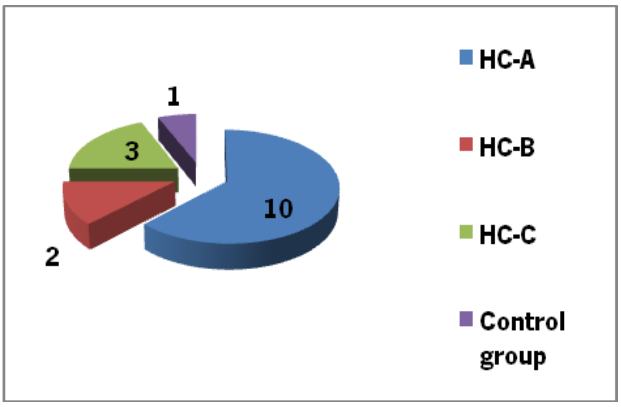

Figure 37 - Vertigo experienced in the 3 hospital centers.

In the exposed group (figure 38), there is a higher incidence of the vertigo side-effect compared to the control group (χ^2 (1) =7.560; p <0.05). There is a statistically significant difference in those that "experienced" the vertigo effect, which is almost 11 times higher (Odds ratio=10.887) in the exposed group, compared to the control group.

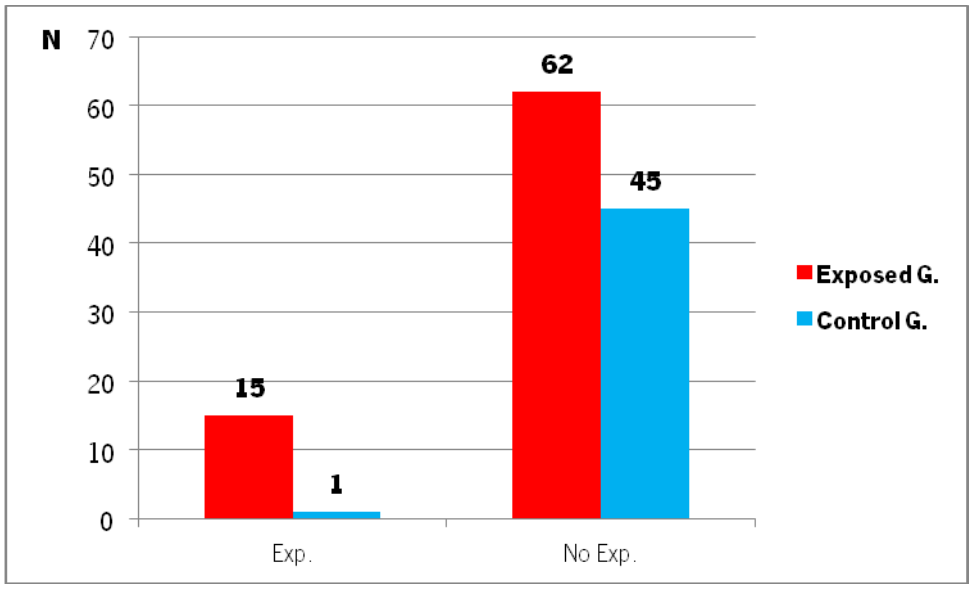

Figure 38 - Vertigo effect reported.

Similarly, in the Day-care hospital (figure 39), there is a higher incidence of dizziness compared to the hospital pharmacy (χ^2 (1) =3.138; p <0.05). There is a statistically significant difference in those that "experienced" the dizziness effect, which is 3 times higher (Odds ratio=3.294) in the Day-care hospital, compared to the hospital pharmacy.

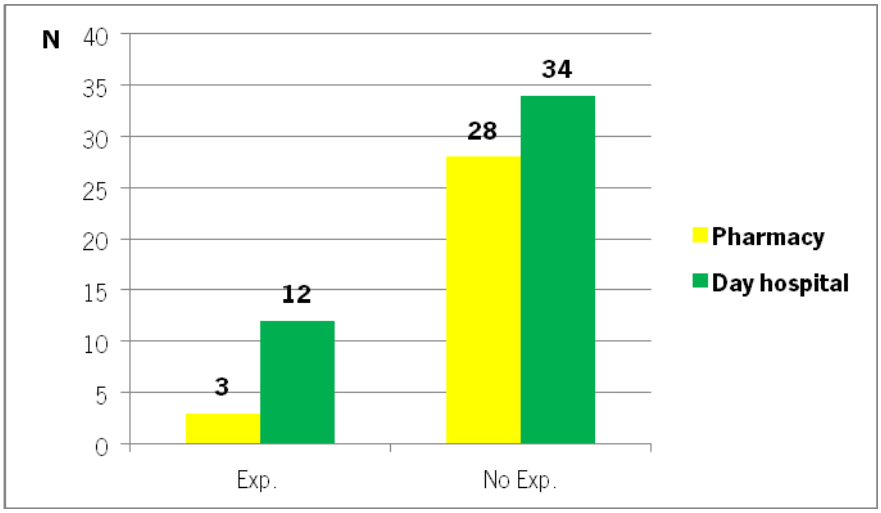

Figure 39 - Vertigo effect reported by pharmacy/hospital Day workers.

The dizziness effect (figure 40) was reported as "experienced" by 33 health professionals, 33.67% of the exposed group, with 18 records in hospital A, 7 in hospital B, and 8 in hospital C. In the control group, 2 professionals, 3.57%, experienced this effect.

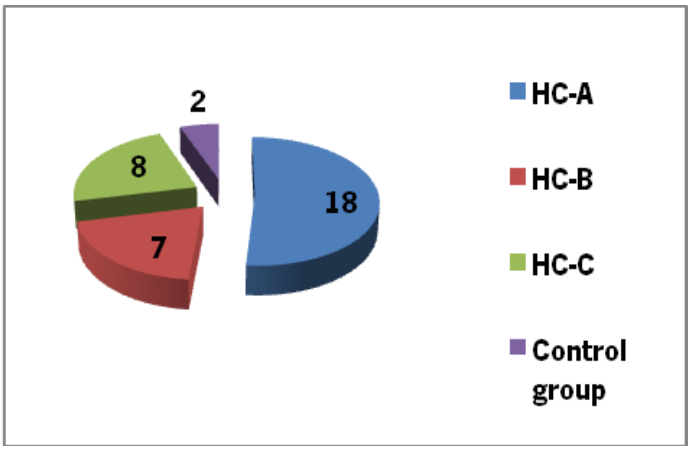

Figure 40 - Dizziness experienced in the 3 hospital centers.

In the exposed group (figure 41), there is a higher incidence of dizziness compared to the control group (χ^2 (1) =19.668; p <0.001). There is a statistically significant difference in those that "experienced" the dizziness effect, which is almost 16 times higher (Odds ratio=15.446) in the exposed group, compared to the control group.

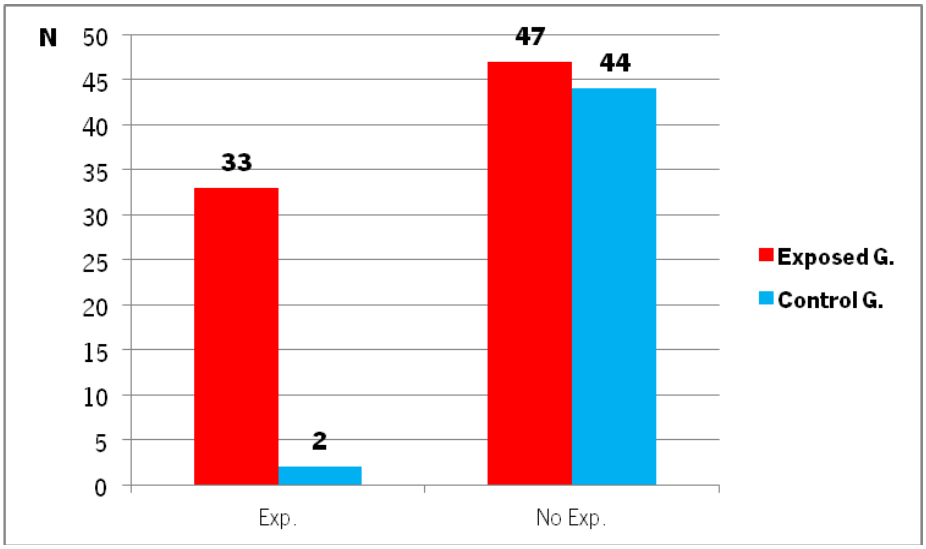

Figure 41 - Dizziness effect reported.

Also in the Day-care hospital (figure 42), there is a higher incidence of dizziness compared to the hospital pharmacy (χ^2 (1) =0.688; p> 0.05). Although there is no statistically significant difference, the results for "experienced" the dizziness effect are slightly higher (Odds ratio=0.680) in the Day-care hospital compared to the hospital pharmacy.

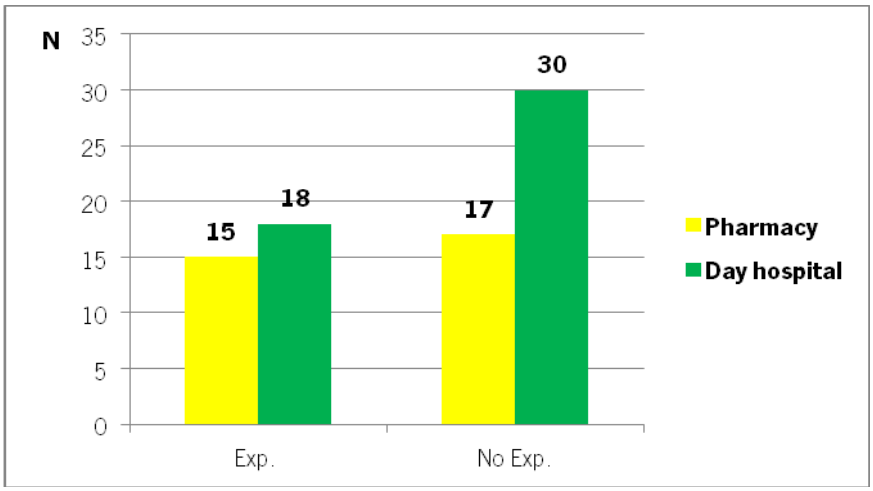

Figure 42 - Dizziness effect reported by pharmacy/hospital Day workers.

Finally, the cutaneous hyperpigmentation effect (figure 43), was reported by 10 health professionals of the exposed group as "experienced", 10.2%: 5 in hospital A, 2 in hospital B, and 3 in hospital C. In the control group, 1 professional, 1.78%, reported having "experienced" this side effect.

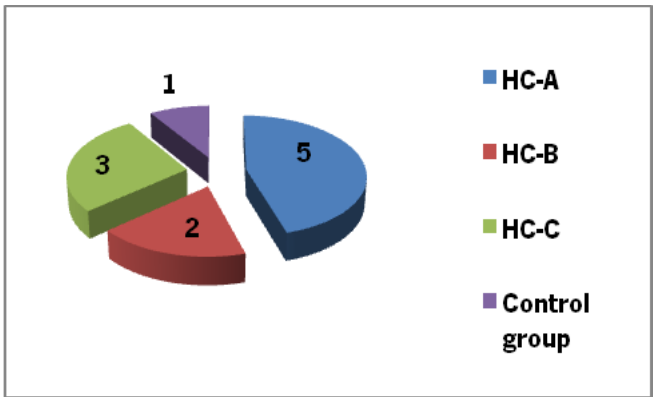

Figure 43 - Cutaneous hyperpigmentation experienced in the 3 hospital centers.

In the exposed group (figure 44), there is a higher incidence of the cutaneous hyperpigmentation side effect compared to the control group (χ^2 (1) =4.101; p <0.05). There is a statistically significant difference in those that "experienced" the cutaneous hyperpigmentation effect, which is almost 7 times higher (Odds ratio=6.716) in the exposed group, compared to the control group.

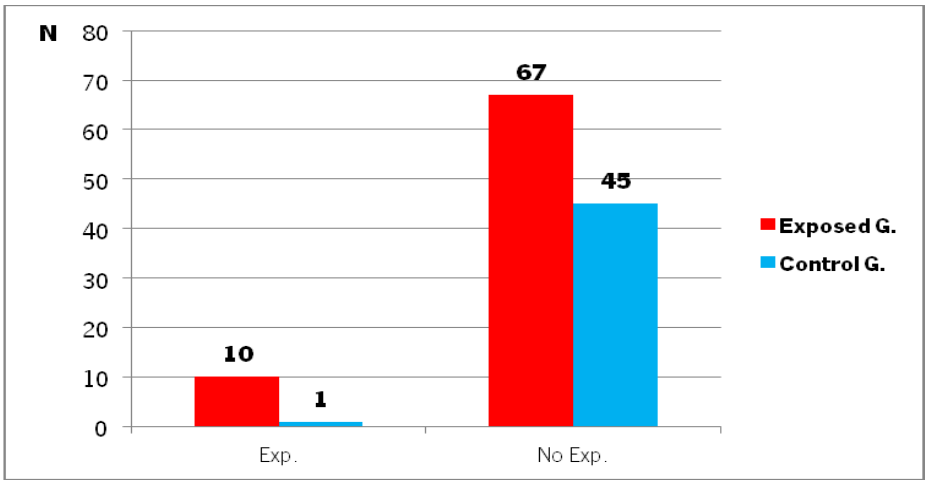

Figure 44 - Cutaneous hyperpigmentation effect reported.

Still in the Day-care hospital (figure 45), there is a higher incidence of the cutaneous hyperpigmentation effect compared to the hospital pharmacy (χ^2 (1) =0.447; p> 0.05). Although there is no statistically significant difference, the cutaneous hyperpigmentation effect is slightly higher (Odds ratio=0.634) in the Day-care hospital compared to the hospital pharmacy.

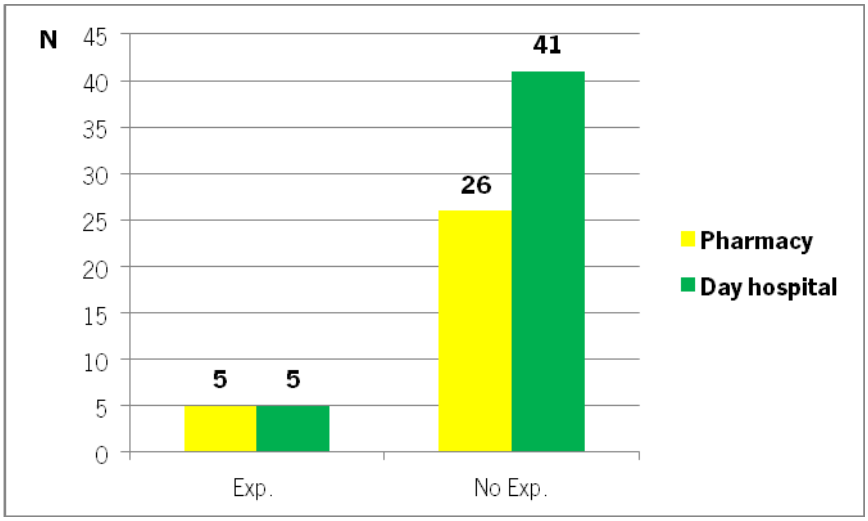

Figure 45 - Cutaneous hiperpigmentation effect reported by pharmacy/hospital Day workers.

6.1.2.2 - In the control group

The control group was composed of 56 nurses that work in the vascular surgery department, which is equivalent to 36.4% of the hospital population. These nurses are distributed throughout hospital A, 18, which corresponds to the percentage of 24.3%, hospital B, 21, 50%, and hospital C, 17, in the percentage value of 44.7%. In this group, as expected, 96.5% percent answered that they have not experienced any of these side effect under study. However, 3 nurses responded affirmatively.

Thus, in hospital A, 1 nurse answered affirmatively to the six exposure effects, meaning that he/she had "experienced" nausea and vomiting, alopecia, headache, vertigo, dizziness and cutaneous hyperpigmentation. In this case, from the questionnaire responses, it can be inferred that, considering the time spent in the health service (15 to 20 years), and that spending more than 10 years in cytostatics handling where spillages can occur due to fine motor coordination and personal protective equipment (PPE), that this professional has already manipulated cytostatics and, due to the complaints presented, this professional may have been placed in another health department, in this case, vascular surgery.

The other 2 cases were referred by nurses in hospital C. The first reported that he/she "experienced" nausea and vomiting, and headache effects, and the second indicating that he/she "experienced" nausea and vomiting, alopecia and dizziness effects. These 2 nurses, contrary to the previous one, have little time of service and did not report having manipulated cytostatics. Thus, it can be inferred that these complaints are not associated with cytostatic manipulation. In hospital B, all respondents replied that they have "not experienced" any exposure effects.

6.1.7 - Cross-tabulation statistical analysis of the spills questionnaire

The spills were analyzed through the chi-square (χ^2) cross-tabulation statistical test between the sites where cytostatics are handled, the causes that can lead to the spills and the exposure effects, and the following issues: “Time of service in the task of handling of cytostatics?", “Do you have scheduled break intervals between preparation/administration periods?", "In the last 12 months have you attended training courses on cytostatic manipulation / administration?", “By your own initiative, do you often read articles on cytostatics?" and “Have you ever made any proposals for improving your practice?".

6.1.7.1 - Locations where spillages occurred

The cross-tabulation statistical test results (table 3) show that the most significant sites for spills were the laminar flow hood and the trays. The other reported site was the armchair.

Table 3 - Chi-square Independence Test Result ($p<0.05$) for spills locations.

Questions/Location	**Storage**	**Self**	**Trays**	**Laminar flow hood**	**Packing table**	**Transport box**	**Administration cart**	**Armchair**
Time of service in the task of handling of cytostatics?	a)	a)	a)	a)	a)	a)	a)	p= 0.003
Do you have scheduled break intervals between preparation / administration periods?	a)	a)	p= 0.047	p= 0.024	a)	a)	a)	p= 0.001
In the last 12 months have you attended training courses on cytostatic manipulation / administration?	a)	a)	a)	p=0.049	a)	a)	a)	a)
By your own initiative, do you often read articles on cytostatics?	a)	a)	p= 0.004	p= 0.002	a)	a)	a)	a)
Have you ever made any proposals for improving your practice?	a)	a)	p= 0.000	p= 0.001	a)	a)	a)	a)

a) Not statistically significant

The professionals who reported the laminar flow hood, as a spill location, considered pertinent for the improvement of their work, scheduled break intervals between preparation/administration periods, training courses on cytostatic manipulation/administration, reading articles on cytostatics and presenting proposals for improving practice.

The professionals who reported on the trays, as spill locations, also considered pertinent for the improvement of their work, scheduled break intervals between preparation/administration periods, reading articles on cytostatics and present proposals for improving your practice.

6.7.1.2 - Spillage causes

The table 4 shows the cross-tabulation statistical test results. The most significant reported cause for spills poorly was poorly enclosed wrap, device fault/feature and packing. The other reported causes were the stress, task time, design of objects to be manipulated and transport form.

Table 4 - Chi-square Independence Test Result ($p<0.05$) for causes.

Questions/ Causes	**Concentration**	**Stress**	**Task time**	**Design of objects to be manipulated**	**Packing**	**Transport form**	**Device fault / feature**	**Poorly enclosed wrap**
Time of service in the task of handling of cytostatics?	a)	a)	a)	a)	a)	a)	p =0.005	p=0.037
"In the last 12 months have you attended training courses on cytostatic manipulation / administration? "	a)	a)	a)	a)	a)	a)	a)	p=0.038
By your own initiative, do you often read articles on cytostatics?"	a)	a)	p=0.018	a)	p=0.022	a)	p=0.015	p=0.006
Have you ever made any proposals for improving your practice?"	a)	p=0.042	a)	p=0.012	p=0.000	P=0.043	p=0.037	p=0.000

a) Not statistically significant

The professionals who reported the poorly enclosed wrap, as a spill cause, considered pertinent for the improvement of their work, the time of service in the task, training courses on cytostatic manipulation/administration, reading articles on cytostatics and also reported to have presented proposals for improving practice.

The professionals who reported the device fault/feature, as a spill causes, also considered pertinent for the improvement of their work, the time of service in the task, reading articles on cytostatics and presenting proposals for improving their practice.

The professionals who reported the packing, as a spill causes, considered pertinent for the improvement of their work, reading articles on cytostatics and present proposals for improving practice.

6.1.7.3 - Exposure effects

The table 5 shows the cross-tabulation statistical test results. The most significant reported exposure effects of spills were the headache followed by dizziness.

Table 5 - Chi-square Independence Test Result ($p<0.05$) for exposure effects.

Questions/Exposure effects	Nausea and Vomiting	Alopecia	Headache	Vertigo	Dizziness	Cutaneous hyperpigmentation
By your own initiative, do you often read articles on cytostatics?"	a)	a)	p=0.011	a)	a)	a)
Have you ever made any proposals for improving your practice?"	a)	a)	p=0.001	a)	p=0.013	a)

a) Not statistically significant

The professionals who reported the headache, as exposure effect, considered pertinent for the improvement of their work, reading articles on cytostatics and present proposals for improving practice. This last one was also pointed by the professionals who reported dizziness, as exposure effect.

6.2 - Results of the environmental monitoring

The results of this study were analyzed according to the threshold guidance values (TGV) defined by Schierl et al. (2009).

There are no legal threshold limit values (TLV) for cytostatic drugs yet defined, although there is a directive setting exposure limit values for only a few drugs (Directive 2004/37/EC). These values apply only to ambient air concentrations and not to surface contamination or skin contact. Mainly, because it

is extremely difficult to establish a relationship between the presence of the contaminant on the surface and its absorption by the skin or other mucous membranes. The introduction of guideline values can be a useful tool to classify the sampling results. However, the search for appropriate monitoring parameters remains a challenge (Schierl et al., 2009).

Thus, level of contamination is defined according to the study developed by Schierl et al., (2009), where a colour code (green, yellow and red) for contamination was implemented. The TGV1 was set according to the 50th percentile of pt and 5-FU. Values below TGV1 mean low levels of contamination (green colour). The TGV2 was defined according to the 75th percentile and presents the threshold of high contamination levels (red colour). Intermediate values, i.e., higher than (TGV1) and lower than (TGV2), were identified as yellow. The values for (TGV1) and (TVG2), for Pt and 5-FU, are shown in table 6.

Table 6 - Proposed TGV (TGV1 and TGV2) for Pt and 5-FU (reproduced from Schierl et al., 2009).

TGV	**Definition**	**Platinum (Pt) pg/cm²**	**5-Fluorouracil (5-FU) pg/cm²**
TGV1	Percentile 50	0,6	5
TGV2	Percentile 75	4	30

In our study 112 samples were collected, (56 of each drug), of which 45 (40.1%) are contaminated, i.e. the results of these samples are higher than TGV1. In hospital A, 38 samples were collected and 13 (33.3%) were contaminated. In hospital B, 44 samples were collected and 16 (36.3%) of these samples were contaminated. Finally, in hospital C, where 30 samples were collected, 16 (53.3%) were contaminated.

6.2.1 - Results for Platinum

Concerning Pt, the study results on drug contamination in the workplace environment are presented in tables 7 and 8, and it can be seen that in all the sites under evaluation in the 3 hospitals there is a disparity of values among the different sampling areas, as can be observed in the Tables. In these 3 hospitals, the results were obtained from 56 samples. Among these, 14 are contaminated at a high-level (red), 9 are with intermediate-level contamination (yellow) and the others with low contamination (green), but with values higher than LOD and lower than TGV1. These high level contamination sites require immediate intervention, followed by the sites with intermediate level of contamination. Thus, the percentage of sites contaminated by Pt and requiring intervention is 41%.

6.2.1.1 - Pharmacies

Table 7 shows the results of the hospital pharmacies of the 3 hospitals, where 37 samples were collected: 12 from hospital A, 14 from hospital B, and 11 from hospital C. The 6 sites marked in (red) are considered contaminated, since they exceed the guidance value (TGV2). The 7 sites marked (yellow) are also contaminated, but in an intermediate level, according to the guidance value (TGV1). Therefore, we conclude that 13 sites (35.1%) of the hospital pharmacies, are contaminated by Pt-drug residues.

The hospital pharmacy of hospital A, where 12 samples were collected, shows high-level contamination (red) on the floor, in front of the laminar flow hood (LFH) 211.1 pg/cm², on the packing table 4.3 pg/cm², and on the shelf 21.7 pg/cm². Before the start of the task, an intermediate-level contamination (yellow) guidance was recorded in the laminar flow chamber 2.8 pg/cm², in the transfer 1.6 pg / cm², and in the gluing machine 3.1 pg/cm².

Table 7 - Concentrations (in pg/cm²) of Pt in hospital pharmacies.

			Hospitals		
Sites	**Sample sites**	**Sampling area (cm²)**	**A**	**B**	**C**
Pt-01	Pharmacy: Laminar Flow Hood (inside); before task	600	2.8	0.3	10.0
Pt-02	Pharmacy: Laminar Flow Hood (inside); middle of task	600	0.6	0.1	31.7
Pt-03	Pharmacy: Laminar Flow Hood (inside); end of task	600	0.6	0.3	100.0
Pt-04	Pharmacy: Floor in front of Laminar Flow Hood	900	211.1	0.2	0.0
Pt-05	Pharmacy: Transfer	600	1.6	0.2	0.3
Pt-06	Pharmacy: 3 Trays	500	0.1	3.0	0.1
Pt-07	Pharmacy: Reception table	400	-	0.5	-
Pt-08	Pharmacy: Packaging table	400	4.3	0.3	1.6
Pt-09	Pharmacy: Gluing machine	225	3.1	-	-
Pt-10	Pharmacy: Capsule transport	666	0.1	-	-
Pt-11	Pharmacy: Transport bag	4120	-	0.0	0.1
Pt-12	Pharmacy: Shelf (carbo/cisplatin)	600	21.7	0.8	0.1
Pt-13	Pharmacy: Waste bin	2080	-	0.0	-
Pt-14	Pharmacy: Computers area	400	0.1	0.1	0.2
Pt-15	Pharmacy: Floor near computers	900	0.2	0.1	1.7
Pt-16	Pharmacy: Storage location	600	-	0.1	-

However, the hospital pharmacy of hospital B (14 samples) was less contaminated and shows intermediate-level contamination (yellow) in the 3 trays, 3.0 pg/cm², and on the shelf, 0.8 pg/cm². The remaining samples are green in colour, with very low contamination, but higher than LOD.

The hospital pharmacy in hospital C, (11 samples) shows contamination in the laminar flow hood of 10.0 pg/cm² before the start of the task, 31.7 pg/cm² at mid-task, and 100.0 pg/cm² at the end of the task, (red) because they exceed the guidance value (TGV2). Considering the intermediate-level contamination (yellow) and the guidance value (TGV1), 1.6 pg/cm² is verified in the packaging table, and 1.7 pg/cm² on the floor next to the computers.

6.2.1.2 - Day-care hospitals

Table 8 shows the medical oncology Day-care hospitals' results in the 3 hospitals, where 19 samples were collected - 7 in hospital center A, 8 in hospital center B, and 4 in hospital center C. The 8 sites marked in red are considered contaminated because they exceed the reference value (TGV2). The 2 sites marked in yellow are also contaminated, but in an intermediate level, according to the guidance value (TGV1). Thus, Pt contamination was detected in 10 samples, in the percentage of 52.6% in the medical oncology Day-care hospitals.

In the medical oncology Day-care Hospital A, 7 sites were sampled and it was verified that the floor near the infusion pump had 25.0 pg/cm², the armchair 4.2 pg/cm² and the bathroom floor 450.0 pg/cm², showing a high-level contamination (red) since it exceeds the guidance value (TGV2). The infusion pump shows an intermediate-level contamination (yellow) (TGV1), 0.9 pg/cm².

Table 8 - Concentrations (in pg/cm²) of Pt in Day-care hospitals.

			Hospitals		
Site	**Sample sites**	**Sampling area (cm²)**	**A**	**B**	**C**
Pt-17	Day Hospital: Reception table	600	0.1	0.1	0.1
Pt-18	Day Hospital: Tray	900	-	0.1	-
Pt-19	Day Hospital: Transport cart	828	0.2	0.2	-
Pt-20	Day Hospital: Waste bin	1164	0.2	0.0	22.8
Pt-21	Day Hospital: Infusion bomb	532	0.9	-	-
Pt-22	Day Hospital: Treatments support	754	-	38.5	6.6
Pt-23	Day Hospital: Floor near the infusion bomb	400	25.0	-	-
Pt-24	Day Hospital: Armchair	1725	4.2	1.9	-
Pt-25	Day Hospital: Bathroom floor	400	450.0	750.0	0.3
Pt-26	Day Hospital: Bathroom door handle (inside)	450	-	7.3	-

In the medical oncology Day Hospital B, 8 samples were also collected and a high-level contamination (red) was verified in the treatment support 38.5 pg/cm², on the bathroom floor 750.0 pg/cm² and on the bathroom door handle (inside) 7.3 pg/cm², since it exceeds the guidance value (TGV2). The armchair shows an intermediate-level contamination (yellow) (TGV1), 1.9 pg/cm².

In the medical oncology Day-care Hospital C, 4 samples were collected that show a high-level contamination (red): in the waste bin 22.8 pg/cm^2, and on the treatment support 6.6 pg/cm^2, since it exceeds the guidance value (TGV2). Notice that the floor of the bathroom of this Day-care hospital is not contaminated by Pt 0.3 pg/cm^2. This place does not correspond in truth to the bathroom, because in this hospital patients are treated with Pt-drugs in bed and urinate into a container, which is in the room whose floor was protected by a plastic canvas. The sample was collected by wiping the surface of the canvas of a single patient.

6.2.2 - Results for 5-fluorouracil

Tables 9 and 10 show the 5-FU results in hospital pharmacies and Day-care hospitals in hospitals A, B and C. 56 samples were obtained in the 3 hospitals analyzed. Among these, there are 9 that are high-level contaminated (red) (TGV2), 13 with intermediate-level contamination (yellow) (TGV1), and the others with low contamination (green), but with values higher than LOD and lower than TGV1. These sites require immediate intervention in the high-level of contamination areas, followed by the intermediate level. Therefore, there are 22 sites requiring intervention, 39.2%.

6.2.2.1 - Pharmacies

Table 9 shows the results of the hospital pharmacies in the 3 hospitals where 37 samples were collected: 12 in hospital center A, 14 in hospital center B, and 11 in hospital center C. The sites marked in red are considered high-level contaminated, since they exceed the guidance value (TGV2), reaching the number of 6, in the present case. 8 sites are also marked in yellow, therefore contaminated as well, but in an intermediate level according to the guidance value (TGV1). Through this data we can conclude that 14 (37.8%) of the hospital pharmacies' samples are contaminated with 5-FU.

The 12 samples collected in the hospital pharmacy in hospital A show an intermediate-level (yellow) contamination inside the laminar flow hood (LFH) in the middle of the preparation task (8.8 pg/cm^2) and on the shelf (16,7 pg/cm^2).

In hospital B, the 14 samples collected at the hospital pharmacy show high-level contamination (red) (TGV2) inside the laminar flow hood (LFH) at the end of the task (179.3 pg/cm^2) and on the shelf (48.7 pg/cm^2). However, intermediate contamination (yellow) (TGV1) exists in the laminar flow hood showing in the middle of the task 14.2 pg/cm^2, on the floor next to the laminar flow hood 10.1 pg/cm^2, the transfers 17.0 pg/cm^2, and the 3 trays 12.0 pg/cm^2.

Table 9 - Concentration (in pg/cm²) of 5-FU in hospital pharmacies.

Site	Sample sites	Sampling area (cm²)	Hospitals		
			A	B	C
FU-01	Pharmacy: Laminar flow hood (inside); before the task	600	1.0	4.5	125.0
FU-02	Pharmacy: Laminar flow hood (inside); middle of task	600	8.8	14.2	75.0
FU-03	Pharmacy: Laminar flow hood (inside); end of the task	600	3.8	179.3	46.7
FU-04	Pharmacy: Floor in front of the Laminar flow hood	900	1.3	10.1	0.9
FU-05	Pharmacy: Transfer	600	nd	17.0	2.0
FU-06	Pharmacy: 3 Trays	500	nd	12.0	34.0
FU-07	Pharmacy: Reception table	400	-	3.8	-
FU-08	Pharmacy: Packaging table	400	nd	0.8	6.5
FU-09	Pharmacy: Gluing machine	225	2.7	-	-
FU-10	Pharmacy: Capsule transport	666	nd	-	-
FU-11	Pharmacy: Transport bag	4120	-	1.1	0.5
FU-12	Pharmacy: 5-FU shelf	600	16.7	48.7	2.6
FU-13	Pharmacy: Waste bin	2080	-	1.7	-
FU-14	Pharmacy: Computers area	400	nd	1.0	1.3
FU-15	Pharmacy: Floor near computers	900	1.1	nd	10.0
FU-16	Pharmacy: Storage location	600	-	nd	-

nd: below 0.2 ng/sample

In hospital center C, the 11 samples collected present high-level contamination (red) (TGV2) in the hospital pharmacy at the following points: before the start of the task, in the laminar flow hood 125.0 pg/cm²; in the middle of the task, in the laminar flow hood 75.0 pg/cm²; and on the 3 trays 34.0 pg/cm². At the end of the task, in the laminar flow hood it shows 46.7 pg/cm². As for the intermediate contamination (yellow) (TGV1), this is verified on the packaging table (6.5 pg/cm²) and on the floor next to the computers (10.0 pg/cm²). The samples were collected in the middle of the task. Intervention at contaminated sites should be primarily at high-level contamination sites, followed by intermediate-level sites.

6.2.2.2 - Day-care hospitals

Table 10 shows the results in the medical oncology Day-care hospitals in the 3 hospital centers, where 19 samples were collected: 7 in hospital center A, 8 in hospital center B and 4 in hospital center C. The 3 sites marked (red) show a high-level contamination (TGV2), while the 5 sites marked (yellow) are contaminated at an intermediate-level (TGV1). Thus, we can detect 5-FU contamination in 8 samples, in the percentage of 42.1%, in the medical oncology Day-care hospitals.

In the medical oncology Day-care hospital of hospital center A, the bathroom floor, with 1228 pg/cm², is high-level contaminated (red), exceeding the guidance value (TGV2).

Table 10 - Concentration (in pg/cm²) of the 5-FU in Day hospitals.

			Hospitals		
Site	**Sample sites**	**Sample area (cm²)**	**A**	**B**	**C**
FU-17	Day-care hospital: Reception table	600	0.5	nd	2.7
FU-18	Day-care hospital: Tray	900	-	nd	-
FU-19	Day-care hospital: Transport cart	828	0.4	0.8	-
FU-20	Day-care hospital: Waste bin	1164	nd	3.1	-
FU-21	Day-care hospital: Infusion bomb	782	0.4	-	-
FU-22	Day-care hospital: Treatment support	886	-	162.2	20.9
FU-23	Day-care hospital: Floor near infusion bomb	400	2.3	-	-
FU-24	Day-care hospital: Armchair	1725	0.9	9.4	23.6
FU-25	Day-care hospital: Bathroom floor	400	1228	146.8	14.3
FU-26	Day-care hospital: Bathroom door handle (outside)	450	-	6.2	-

nd: below 0.2 ng/sample

In the medical oncology Day-care hospital of hospital center B, the treatment support (162.2pg/cm²) and the bathroom floor (146.8 pg/cm²) show a high-level contamination (red), since these exceed the guidance value (TGV2). The armchair (9,4 pg/cm²) and the bathroom door handle (outside) (6,2 pg/cm²) show an intermediate-level contamination (yellow) (TGV1).

In the medical oncology Day-care hospital of hospital center C, the treatment support (20.9 pg/cm²), the armchair (23.6 pg/cm²) and the bathroom floor (14.3 pg/cm²) show an intermediate-level contamination (yellow), exceeding the guidance value (TGV1).

Priority intervention should be carried out at high-level contamination sites and later at intermediate-level contamination ones.

6.3 - Impact of working procedures on contamination

In our study, the procedures are similar in the 3 hospital centers, although with small differences that can contribute to the reduction of the contamination in the workplaces.

The cytostatic preparation is carried out within the laminar flow hood. At the base of the laminar flow hood, in its central zone, there is a tissue covering the bottom, called work field, which is usually removed every 2 hours, except in case of spillage. Also within the laminar flow hood, we can find carriers, syringes, vials, spigots, containers or buckets for cytostatic waste, delivery systems and small compresses generally soaked in 70% alcohol to clean the rubbers of vials, ampoules, needles, syringes and connections during preparation.

The drugs are transferred into the preparation room on a tray. In hospitals B and C, where the number of trays is not sufficient, the same tray is used to transfer the drugs of several patients, entering and leaving the preparation room several times. In hospital A, each patient has a tray with the corresponding identification label. It goes in and out only once, and it is later cleaned at the end of the task. Drugs and all material, when sent into the preparation room, are first sprayed with 70% ethyl alcohol before entering the clean room in hospital A. In hospitals B and C, these procedures are not always met.

Inside the preparation room, pharmacists or pharmacy technicians follow the procedures given in the manual to carefully prepare with slow movements and prick the vial rubber at a 45° angle to the rubber surface, or 90°, if the spikes have a double bevel. It introduces a certain amount of serum as a safety barrier, to avoid spillage of the drug.

After preparation, the pharmacists take the drugs outside the room on a tray through the transfer. These drugs may be packaged inside the preparation room, in hospital C, into a plastic bag and thermal glued. They can also be received outside the room, where they will be packed in a plastic bag and glued through thermal glue or other gluing system, in hospitals A and B. Subsequently, the drugs are placed in a bag, properly arranged, to be sent to the Day-care hospital, and later administered to the patients.

Hospital A professionals, who are working in the preparation, perform their task for a period of approximately one hour at the end of which they will be replaced by others. For those in hospitals B and C, the task period is of two hours, followed by a break. After preparing and completing their assignment, these professionals enter the transition zone, where they remove the personal protective equipment, throwing them in the bin, followed by disinfection, washing their hands and arms. In this zone there are dumpsters to place all the material that was in contact with cytostatics.

Hospital A, B and C present some different procedures, namely:

- Regarding the cleaning of the laminar flow hood at the end of the task, samples are collected prior to the start of the task to verify compliance with this procedure. In hospital B, this procedure is applied in accordance with the results of 0.3 pg/cm^2 for Pt and 4.5 pg/cm^2 for 5-FU. In turn, in Hospital A, the results varied for Pt 2.8 pg/cm^2, higher than the TGV1, and 1.0 pg/cm^2 for 5-FU. However, in hospital C, the results present levels of contamination above TGV2: 10 pg/cm^2 for Pt and 125 pg/cm^2 for 5-FU. These results reveal that the cleaning

procedures of the laminar flow hood at the end of the task are different. Considering the values obtained, it is to assume that hospitals B and C should improve cleaning procedures at the end of the task;

- Hospital A uses one tray per patient and per treatment, while Hospitals B and C use one tray for multiple patients and treatments. This procedure seems to impact on the observed values for the contamination of hospital A, which is low for Pt 0.1 (pg/cm^2) and 5-FU (nd), while in hospitals B and C the values are much higher;

- The change of preparation technician in hospital A takes place after one hour of work, while in hospitals B and C this change takes place after two hours. This change seems to contribute for reducing the spillage because, this way the technician had one hour of pause.

Thus, according to the data from the questionnaire, we can say that there is a correlation with the results of the samples, in the laminar flow chamber and in the patient's chair, with the reported spillage sites. These sites were referred to as where the spills occur in greater number and the samples present contamination significant contamination levels. There is also correlation in other places, such as the packing table and the shelf. For these sites, the results of the samples also present contamination levels.

6.4 - Results comparison between the 2010 and 2015 studies in hospital center B

A surface sampling has already been performed in 2010, in hospital B, enabling a comparison of the contamination between the obtained results in 2010 and the results obtained in the current study. The 2010 samples were collected at 6 sites for Pt and 5-FU (Silva, 2011), while in the current study were collected at 20 sites for each of these drugs. Therefore, there is a difference of the number of sampling sites between the two collections. The sites that are common in 2010 and 2015 are: the pharmacy, 3 sites; laminar flow hood, floor in front the laminar flow hood and transfer, and Day-care hospital, and reception table. However, 2 sites in the first collection (support table of the laminar flow hood and patient support table) were not sampled in the second collection since they are not present in the current work context.

The results of the samples collected in May 2010 and in the current study, in the hospital under study, are presented in table 11, both regarding the hospital pharmacy. In the medical oncology Day-care hospital the results are presented in text. These results were obtained through a collaboration with

the laboratory of the University of Munich and are presented according to the colour code of the proposed TGV (Schierl et al., 2009), explained before in section 6.2.

6.4.1 - Hospital B

In table 11, the results are presented for hospital pharmacy and for the 2 drugs under study, Pt and 5-FU.

Table 11 - Concentration of Pt and 5-FU, in the pharmacy of hospital B.

	2010		Current study	
	Pt	5-FU	Pt	5-FU
Sample site	**pg/cm²**	**pg/cm²**	**pg/cm²**	**pg/cm²**
Laminar Flow Hood, inside mid-task (30x20)cm²	292.5	4375.0	0.1	14.2
Floor in front of Laminar Flow hood (40x40)cm²	1457.5	193.0	0.2	10.1
Transfer	13.0	199.3	0.2	17.0

Thus, in 2010, 3 sites were contaminated by Pt which are considered critical ones and therefore marked in red, namely: the interior of the laminar flow hood with 292.5 pg/cm², the floor in front of the laminar flow hood with 1457.5 pg/cm² and the transfer with 13.0 pg/cm².

Also, for 5-FU, according to the colour code identified above, there are three critical sites marked in red, which are: the interior of the laminar flow hood with 4375.0 pg/cm², the floor in front of the laminar flow hood with 193.0 pg/cm² and the transfer with 199.3 pg/cm².

Under the current study, in the hospital pharmacy, Pt is present in 3 sites, in green: on the laminar flow hood with 0.1 pg/cm², floor in front of laminar flow hood with 0.2 pg/cm² and transfer with 0.2 pg/cm².

As to the results of 5-FU, they present a greater number of sites with concentrations requiring intervention, since they exceed the admissible values. Thus, in the hospital pharmacy, three critical sites, in yellow, were found: the laminar flow hood at the middle of the task with 14.2 pg/cm², the floor in front of the laminar flow hood with 10.1 pg/cm², and transfer with 17.0 pg/cm², which require non-urgent intervention.

6.4.2 - Day-care hospital B

The results of the 2010 and 2015 studies, in the medical oncology Day-care hospital of hospital B, are presented in the following paragraphs.

In the first study, contamination by Pt was detected at the receiving table (3.5 pg/cm^2) with values higher than TGV1 and lower than TGV2.

Regarding 5-FU, in the Day-care hospital, there are one intermediate-level (higher than TGV1 and lower than TGV2) contaminated sites, the reception table with 8.0 pg/cm^2.

Under the 2015 study, the medical oncology Day-care hospital recorded Pt with contamination lower than TGV1 in the reception table (0.1 pg/cm^2). For 5-FU, in the medical oncology Day-care hospital, no value was detected (nd) because the value is below (0.2 pg/cm^2). These sites do not require priority intervention.

Comparing the results of the 2015 study with those of the 2010 study, we found that Pt and 5-FU obtained values lower than (TGV1) in the only comparable site (reception table), while the 2010 results were higher than TGV1 and lower than TGV2.

Regarding the 2015 study, there are 3 common places in the hospital pharmacy and 1 in the Day-care hospital. It should be noted that the results of the 2015 study reported concentrations much lower than the previous study, both in the hospital pharmacy and in the medical oncology Day-care hospital. These values should be associated to several factors, among which it is highlighted in the hospital pharmacy:

- The new physical facilities, as well as all the equipment installed in the preparation room, (laminar flow hood);

- The preparation is now centralized;

- The replacement of nurses in the preparation task by pharmacists and pharmacy technicians in the 2015 study. These professionals revealed better job train for cytostatic manipulation tasks;

- Improvements in the procedures, namely at the level of organization, packaging, cleaning and transportation.

The medical oncology Day-care hospital also contributed with some factors for the improvement of results in 2015. These include the following:

- The physical facilities in the medical oncology Day-care hospital are new (infusion pump, armchairs), as well as all the equipment installed. Thus, their time of use is still very little and cleaning of these equipments may be more effective in the removal of contaminates;

- There is evidence that during treatment, the use of the closed drug transfer device reduces the contamination (Nygren, Gustavsson, Ström, Eriksson, et al., 2002) (Clark & Sessink, 2013);

- Improvements in the procedures (cleaning, closed transfer system, use of personal protective equipment);

- Use of personal protective equipment, such as the use of gloves which, in case of contact with the drug, can be promptly removed;

- The experience revealed by the nurses, since they participated in the 2010 study and continue exercising their functions in the 2015 study;

- The development of training programs regarding the on manipulation of cytostatics.

6.5 - Results discussion

6.5.1 - About the survey

Regarding the survey, the focus of the results were spillages that were reported by 53 professionals (Sorsa & Anderson, 1996); (Sottani et al., 2012). In the hospital pharmacy, spillages occurred in the laminar flow chamber, while in the medical oncology Day-care hospital, they occurred on the patient's chair. The most reported cause for spillages was the poorly closed wrap. Considering that spillages are a potential exposure source, health professionals handling cytostatics must, as their primary objective, reduce or eliminate such incidents.

Therefore, in order to reduce spillages in both the laminar flow hood and the armchair, or at other sites, it is expectable that these professionals should have ongoing training on cytostatics preparation and administration, and that they perform such tasks with high attention/concentration and responsibility. In turn, the poorly closed wrap is an incorrect procedure and considered to be a non-compliance. This situation occurs due to some factors that can contribute to such occurrences, as well as the stress and pressure caused by the work itself. Also, in this case, attention/concentration and responsibility factors are preponderant.

The sites where spills occur were analyzed by the chi-square cross-tabulated statistical test with different questions.

The “laminar flow hood”, the statistical testing proves (table 3) there is a significant association between scheduled breaks between preparation/administration periods (p=0.024), training courses on cytostatic manipulation/administration (p=0.049), reading articles on cytostatics, (p=0.002) and presenting proposals for improving practice (p=0.001) so they are dependent.

Statistical testing proves (table 3) that there is a significant association between scheduled breaks between preparation/administration periods (p=0.047), reading articles on cytostatics (p=0.004) and presenting proposals for improving practice (p=0.000) and the “trays”.

Regarding the "armchair" the statistical test (table 3) proves that there is a significant association between service time in the task of manipulating cytostatics (p=0.003), scheduled breaks between preparation/administration periods (p=0.001).

Regarding the causes of the spillage, the "poorly enclosed wrap" the statistical test (table 4) proves that there is a significant association between service time in the task (p=0.037), training courses on cytostatic manipulation/administration (p=0.038), reading articles on cytostatics (p=0.006) and presenting proposals for improving practice (p=0.000).

Statistical testing proves (table 4) that there is a significant association between "device fault/feature" and service time in the task of handling cytostatics (p=0.005), reading articles on cytostatics (0.015) and presenting proposals for improving practice (p=0.037).

All the exposure effects under study were experienced by health professionals, with headaches and dizziness being the most commonly reported.

In table 5 it can be seen that there is a significant association between “headache” and reading articles on cytostatics (p=0.011), and presenting proposals for improvement practices (p=0.01).

Regarding "dizziness", the statistical test shows evidence that there is a significant association, between this condition and presenting proposals for improvement practices (p=0.013).

6.5.2 - In hospital pharmacies

In the 3 evaluations carried out in the laminar flow hood at the hospital pharmacy of hospital C, high-level contamination was detected for Pt and 5-FU. It should be noted that the first samples collected

before the start of the day's task have values of 10.0 pg/cm² for Pt and 125.0 pg/cm² for 5-FU. The results of the second and third samples for Pt are: 31.7 pg/cm² and 100.0 pg/cm², and for 5-FU, 75.0 pg/cm² and 46.7 pg/cm². Also, in the hospital pharmacy in hospital A, intermediate-level Pt contamination was detected in the flow hood, in the first sample collected before the start of the day's task (2,8 pg/cm²). These results are in agreement with the studies conducted by Brouwers et al., (2007) and Yoshida et al., (2009), and allow to conclude that the laminar flow hood cleaning has not been well performed or that the products used are not the most suitable for the removal of drugs from the surfaces. Still in the hospital pharmacy of hospital center A, 5-FU intermediate-level contamination was detected inside the laminar flow hood in the sample collected in the middle of the task. In hospital B, the hospital pharmacy has high-level contamination in the laminar flow hood at the end of the task, and intermediate-level contamination in the middle of the task by 5-FU. High contamination-levels within the laminar flow hoods were also reported previously by Connor et al., (1999) for fluorouracil (1.58 ng/cm² and 32.18 ng/cm²), and for Pt (0,22 pg/cm² and 32,7 pg/cm²) (Brouwers et al., 2007), as well as (Crauste-Manciet, Sessink, Ferrari, Jomier, & Brossard, 2005) (Yoshida et al., 2009).

Laminar flow hood cleaning is an important procedure to limit accumulation of residual contamination. Thus, there are several products, among which sodium hypochlorite (Lamerie et al., 2013), a very widely used and very effective product. However, it can damage the surfaces. Isopropyl Alcohol (IPA) and sodium dodecyl sulfate (SDS) are also used in surface cleaning. According to Lamerie et al., (2013) and Anastasi et al., (2014) the combination of these two products is an effective cleaning solution on stainless steel and glass surfaces. The results for the laminar flow hood revealed an association between the existence of scheduled pause intervals between preparation/administration periods, by operators initiative, read articles on cytostatics and presenting proposals for improving your practice.

These results allow a comparative analysis between the results of hospitals A, B and C, and with the results from studies by the other authors mentioned in this article. The results in this study for Pt and 5-FU in pharmacies are shown in table 12, as well as the minimum level and maximum level values in other authors' studies.

Table 12 - Comparison of Pt and 5-FU results in the 3 hospitals, with those of the referenced authors.

Sample site	Cytostatic	Hospital			Other studies	Other studies contamination levels	
		A	B	C			
		pg/cm²	pg/cm²	pg/cm²		Min pg/cm²	Max pg/cm²
Pharmacy: Laminar Flow Hood (inside) before task	Pt	2.8	0.3	10.0	-	-	-
	5-FU	1.0	4.5	125.0	-	-	-
Pharmacy: Laminar Flow Hood (inside) mid-task	Pt	0.6	0.1	31.7	(Brouwers, et al., 2007).	0.22	32.7
	5-FU	8.8	14.2	75.0	(Connor et al., 1999).	1580	32 180
Pharmacy: Laminar Flow Hood (inside) end of task	Pt	0.6	0.3	100.0	-	-	
	5-FU	3.8	179.3	46.7	-	-	
Pharmacy: Floor in front of the Laminar Flow Hood	Pt	211.1	0.2	0.0	(Schierl et al., 2009), (Schmaus et al., 2002).	1.48	55
	5-FU	1.3	10.1	0.9	(Schierl et al., 2009), (Connor et al., 1999).	20.50	1 110
Pharmacy: Transfer	Pt	1.6	0.2	0.3	(Schierl et al., 2009).	1.67	-
	5-FU	nd	17.0	2.0	(Schierl et al., 2009), (Viegas et al., 2014).	22.50	13 700
Pharmacy: 3 Trays	Pt	0.1	3.0	0.1	-	-	-
	5-FU	nd	12.0	34.0	-	-	-
Pharmacy: Reception table	Pt	-	0.5	-	-	-	-
	5-FU	-	3.8	-	-	-	-
Pharmacy: Packaging table	Pt	4.3	0.3	1.6	(Schierl et al., 2009).	1.76	-
	5-FU	nd	0.8	6.5	(Schierl et al., 2009).	9.66	-
Pharmacy: Gluing machine	Pt	3.1	-	-	-	-	-
	5-FU	2.7	-	-	-	-	-
Pharmacy: Transport capsule	Pt	0.1	-	-	-	-	-
	5-FU	nd	-	-	-	-	-
Pharmacy: Transport bag	Pt	-	0.0	0.1	(Brouwers, et al., 2007).	0.285	74.5
	5-FU	-	1.1	0.5	(Schierl et al., 2009).	18.92	-
Pharmacy: Shelf	Pt	21.7	0.8	0.1	(Schierl et al., 2009), (Schmaus et al., 2002)	4.35	14
	5-FU	16.7	48.7	2.6	(Schierl et al., 2009), (Schmaus et al., 2002)	80	737
Pharmacy: Waste bin	Pt	-	0.0	-	-	-	-
	5-FU	-	1.7	-	-	-	-
Pharmacy: Computer area	Pt	0.1	0.1	0.2	-	-	-
	5-FU	nd	1.0	1.3	-	-	-

Table 12 - Comparison of Pt and 5-FU results in the 3 hospitals, with those of the referenced authors (continuation).

Sample site	Cytostatic	Hospital			Other studies	Other studies contamination levels	
		A	B	C		Min	Max
		pg/cm²	pg/cm²	pg/cm²		pg/cm²	pg/cm²
Pharmacy: Floor near computers	Pt	0.2	0.1	1.7	(Odraska et al., 2014), (Brouwers et al., 2007).	4.4	11.9
	5-FU	1,1	nd	10.0	(Connor et al., 1999).	nd	2 310
Pharmacy: Storage	Pt	-	0.1	-	-	-	-
	5-FU	-	nd	-	-	-	-

On the floor, in front of the laminar flow hood of the pharmacy of hospital center A, high-level Pt contamination (211.1 pg/cm²) was detected, as well as in the pharmacy of hospital center B, but this at an intermediate 5-FU contamination level (10.1 pg/cm²). However, these results are lower than those reported by (Connor et al., 1999), 1.11 ng/cm²; (Schmaus et al., 2002), 42 pg/cm² and (Schierl et al., 2009), 20.25 pg/cm² for 5-FU and higher than those of Schmaus et al., (2002) and Schierl et al., (2009) for Pt (55 pg/cm² and 1,48 pg/cm²) respectively.

The transfer of the pharmacy of hospital center A shows a Pt intermediate-level contamination of 1.6 pg/cm², while the pharmacy of hospital center B also shows an intermediate-level contamination, but by 5-FU (17,0 pg/cm²). Similarly, Schierl et al., (2009) presented similary contamination results, 1.67 pg/cm² for Pt and 22.50 pg/cm² for 5-FU. However, Viegas et al., (2014) detected 5-FU contamination in 2 hospitals, but with higher results, 13.7 ng/cm² and 11.17 ng/cm².

On the 3 trays in the pharmacy of hospital B, intermediate-level contamination by Pt and 5-FU of 3.0 pg/cm² and 12.0 pg/cm² respectively, was detected. However, hospital pharmacy C has high-level contamination with 5-FU (34.0 pg/cm²) on the 3 trays. It should be noted that Berruyer et al., (2015) found no contamination for several drugs (ciclophosphamide, ifosfamide and methotrexate). The contamination presented at the different sites of the hospital pharmacies under study is in agreement with those reported by Schierl et al., (2009). It should be noted that hospital center A had no contamination of the trays. This hospital center has different practices and procedures compared to hospital centers B and C. Hospital center A uses a tray for each treatment, i.e. each tray only enters once in the clean room of the preparation unit and is placed later for cleaning, which takes place at the

end of the shift/day. The results for the 3 trays, revealed an association between the existence of scheduled pause intervals between preparation / administration periods, reading articles on cytostatics and present proposals for improving practice.

The packaging table in the pharmacy of hospital center A show high-level Pt contamination of 4.3 pg/cm^2. The pharmacy of hospital center C also had contamination by Pt (1.6 pg/cm^2) and by 5-FU (6.5 pg/cm^2) on the packaging table, but at an intermediate-level. Schierl et al., (2009) present on the post-preparation bench 1.76 pg/cm^2 for Pt and 9.66 pg/cm^2 for 5-FU. The results for the packaging table revealed an association between the present proposals for improving practice.

The gluing machine shows Pt contamination of 3.1 pg/cm^2. These results are in agreement with (Schierl et al., 2009), for other hospital pharmacies' sites.

In the transport bag, the contamination results are low for Pt and 5-FU. Thus, for Pt, the highest value was detected in hospital pharmacy C (0.1 pg/cm^2) and for 5-FU the highest value was detected in hospital pharmacy B (1.1 pg/cm^2). Brouwers et al. (2007) detected higher values for Pt (0.285 pg/cm^2 and 74.5 pg/cm^2), and Schierl et al. (2009) detected higher values for 5-FU (18.92 pg/cm^2).

The storage shelves in the pharmacy of hospital center A were contaminated with Pt (21,7 pg/cm^2) and with 5-FU (16.7 pg/cm^2), the first showing a high-level and the second an intermediate-level contamination. Also, on the pharmacy shelves of hospital B, intermediate-level contamination was detected by Pt (0.8 pg/cm^2) and high-level contamination by 5-FU (48.7 pg/cm^2). These results are higher than those reported by Schmaus et al., 2002 (Brouwers et al., 2007) (Schierl et al., 2009) for Pt: 14.0 pg/cm^2, 5.7 pg/cm^2 and 4.35 pg/cm^2, respectively, and lower for 5-FU: 737 pg/cm^2 (Schmaus et al., 2002) and 80 pg/cm^2 (Schierl et al., 2009). The results for the storage shelves revealed an association between the reading articles on cytostatics, as well as, present proposals for improving practice.

Also, the floor next to the computers shows contamination with Pt and with 5-fluoouracil: 1.7 pg/cm^2 and 10,0 pg/cm^2 respectively. This result refers to the floor of the pharmacy, where the computer is very close to the transfer and shelves. Thus, (Brouwers et al., 2007) (Odraska et al., 2014) shows higher values for Pt: 11.9 pg/cm^2 and 4.4 pg/cm^2 respectively. For 5-FU (Connor et al., 1999) shows non detected (ND) and 2,31 ng/cm^2. This contamination may be due to some spillage or possible runoff of the contaminated flasks.

6.5.3 - In Day-care hospitals

The Day-care hospitals in the present study also have several sites where Pt and 5-FU contamination has been detected.

The waste bin shows contamination only in hospital C, Pt 22.8 pg/cm², much lower than 77.0 pg/cm² of (Schmaus et al., 2002), and much higher than 5.1 pg/cm² of the study by (Kopp, et al., 2013). The results obtained in this study for 5-FU are lower than those presented by (Kopp, et al., 2013) (208 pg/cm²).

Table 13 shows the Pt and 5-FU study values in the medical oncology Day-care hospitals, for the 3 hospitals, the minimum level and maximum level values found in other authors' studies.

Table 13 - Comparison of Pt and 5-FU results in the 3 hospitals with those of the referenced authors.

Sample site	**Cytostatic**	**Hospital**			**Other studies**	**Other studies contamination levels**	
		A	**B**	**C**			
		pg/cm²	**pg/cm²**	**pg/cm²**		**Min pg/cm²**	**Max pg/cm²**
Day Hospital: Reception table	Pt	0.1	0.1	0.1	-	-	-
	5-FU	0.5	nd	2.7	-	-	-
Day Hospital: Tray	Pt	-	0.1	-	-	-	-
	5-FU	-	nd	-	-	-	-
Day Hospital: Transport cart	Pt	0.2	0.2	-	-	-	-
	5-FU	0.4	0.8	-	-	-	-
Day Hospital: Waste bin	Pt	0.2	0.0	22.8	(Kopp et al., 2013), (Schmaus et al., 2002)	5.1	77.0
	5-FU	nd	3.1	-	(Kopp et al., 2013)	-	208
Day Hospital: Infusion pump	Pt	0.9	-	-	(Kopp et al., 2013)	7.8	-
	5-FU	0.4	-	-	(Kopp et al., 2013), (Viegas et al., 2014)	11.3	41 300
Day Hospital: Treatments support	Pt	-	38.5	6.6	-	-	-
	5-FU	-	162.2	20.9	-	-	-
Day Hospital: Floor near infusion pump	Pt	25.0	-	-	(Kopp, et al., 2013)	12.7	-
	5-FU	2.3	-	-	-	-	-
Day Hospital: Armchair	Pt	4.2	1.9	-	(Kopp et al., 2013)	1.3	-
	5-FU	0.9	9.4	23.6	(Connor et al., 1999).	700	13 900
Day Hospital: Bathroom floor	Pt	450.0	750.0	0.3	(Kopp et al., 2013)	-	192
	5-FU	1228	146.8	14.3	(Kopp et al., 2013)	71.3	-

Table 13 - Comparison of Pt and 5-FU results in the 3 hospitals with those of the referenced authors (continuation).

Sample site	Cytostatic	Hospital			Other studies	Other studies contamination levels	
		A	B	C			
		pg/cm²	pg/cm²	pg/cm²		Min pg/cm²	Max pg/cm²
Day Hospital: Bathroom door handle (inside)	Pt		7.3	–	-	-	-
	5-FU	-	6.2	-	-	-	-

The infusion pump was sampled only in Day-care hospital A, and the contamination detected for Pt was 0.9 pg/cm², significantly lower than the study by (Kopp, et al. , 2013), which found 7.8 pg/cm² for Pt and 11.3 pg/cm² for 5-FU. Also, Viegas et al., (2014) detected 41.3 ng/cm² of 5-FU contamination at the infusion pump in one of the hospitals, being the highest of the study. The result of this study may be associated with the procedures for the exchange of gloves, when turning the system on/off, and a proper cleaning of the infusion pump and armchair at the end of the task. The floor near the infusion pump was sampled only in Day-care hospital A, presenting 25.0 pg/cm² of Pt contamination. This contamination is higher than that of the study by (Kopp, et al., 2013), with 12.7 pg/cm² for Pt, and lower than the study developed by (Kiffmeyer et al., 2013) where there is contamination on the Day-care hospitals' floors was of 26 ng/cm². This contamination may occur due to spillage on the Day-care hospitals' floors.

The treatments support was sampled at Day-care hospitals B and C, and it is shown a two drug contamination in these hospitals. This site is contaminated by Pt (38.5 pg/cm² and 6.6 pg/cm²) and 5-FU (162.2 pg/cm² and 20.9 pg/cm²), respectively. Considering that this site is equivalent to the two previous sites, i.e., (infusion pump and floor next to the infusion pump), it can be seen that the contamination is much higher in these hospitals compared to hospital A. The infusion pump results, as well as the treatments support results, can be associated with possible spillages during the drug administration, inadequate procedures in the tasks accomplishment and the cleaning procedure at the end of the task (Acampora et al., 2005) (Hon et al., 2013). The infusion pump is a device that is often handled by nurses during cytostatic administration (Hon et al., 2011), who do not always use gloves as a protective equipment (Kopp, et al. 2013).

In the armchair, Pt contamination was also detected in Day-care hospitals A and B, with 4.2 pg/cm² and 1.9 pg/cm², and 5-FU in the Day-care hospitals B and C, with 9.4 pg/cm² and 23.6 pg/cm², respectively. These results are higher when compared to those of the study by (Kopp et al., 2013),

which presents 1.3 pg/cm² for Pt, although 5-FU contamination was not detected. However, in their study, Connor et al., (1999) presented 5-FU contamination values much higher than those in the 3 centers under study (0.70 ng/cm² and 13.9 ng/cm²), as did Dal Bello et al., (2016). Janes et al., (2015) also detected cyclophosphamide contamination of 159 pg/cm². The results for the armchair revealed an association between the time of service in the cytostatic manipulation task, as well as the existence of scheduled pause intervals between preparation / administration periods.

The patient's bathroom floors in the 3 Day-care hospitals show high-level and intermediate-level contamination, except in Day-care hospital C for Pt since in this Day-care hospital, patients do not use the bathroom, as mentioned in (6.2.1.2). Thus, in Day-care hospitals A and B, Pt contamination is of 450 pg/cm² and 750 pg/cm², respectively. These results are higher than those reported by Kopp et al., (2013) for Pt (192 pg/cm²). 5-FU contamination was also detected in Day-care hospitals A, B and C, respectively 1228 pg/cm², 146.8 pg/cm² and 14.3 pg/cm². These results are superior to those found in the study by (Kopp et al., 2013), with the value of (71.3 pg/cm²) for 5-FU. However, they are in agreement with Hedmer et al., (2008) and Sottani et al., (2012) who also detected high-level contamination on the patient's bathrooms floor. The floor contamination may be due to urine spillage when the patient is using the toilet or, possibly when the bottles are being filled with urine, and by aerosol formation during cleaning as well (Hedmer et al., 2008). Formation of aerosols may result from the procedure. Considering that the concentration of antineoplastic drugs in the urine is high, a small amount of urine can cause a high-level contamination on the surface (Hedmer et al., 2008).

The inside bathroom handle in Day-care hospital B shows a high-level contamination with Pt (7.3 pg/cm²) but outside it shows a 5-FU intermediate-level contamination (6.2 pg/cm²). As there are no results in the bibliography regarding this site to allow us to compare, we use the refrigerators' doors as an example. Thus, these results are lower than those reported by (Hedmer et al., 2005) for cyclophosphamide (11ng/cm²) and (Brouwers et al., 2007) for Pt (26.3 pg/cm²) on the pharmacies' refrigerators' doors.

The nurses of hospital B that participated in the 2010 and 2015 studies are professionals with experience in the administration of cytostatics (Connor and McDiarmid, 2006), and can contribute to significantly reduce the probability of occurrence of error.

In a brief summary, we found that the results obtained for Pt in this study, compared with the authors mentioned above, are higher in the following sites: on the floor next to the laminar airflow chamber, on

the packaging table, on the carbo/cisplatin shelf, in the waste bucket, in the infusion pump, in the armchair and on the bathroom floor. On the other sites, the results show lower values or very close to the ones presented by the mentioned authors. It should be taken in account that in several sites it was not possible to compare them.

For 5-FU, we also found that the results obtained in this study, compared with those of the cited authors, are higher only on the bathroom floor. However, in other places, the results have lower values than the studies of the mentioned authors. It should be noted that in several places it was not possible to establish a comparison of the results.

6.5.4 - Main remarks

The results presented on the chemical contamination and its impact on the work environment and the possible exposure of the professionals who handle and administer cytostatics (Pt and 5-FU), as well as the exposure effects on these professionals, can contribute to devise some corrective measures that can be implemented in order to reduce or eliminate risks to the environment, and of course, to health professionals. This is the first study in Portugal combining the collection of detailed information on working practices etc., with environmental monitoring of the work surfaces in order to assess potential occupational exposure of the pharmacists, pharmacy technicians and nurses.

In this study, contamination was detected in the laminar flow hood, before the beginning of the task, at the middle of the task and at the end of the task. In the studies of (Connor et al., 1999; Brouwers et al., 2007; Yoshida et al., 2009), contamination was detected in the laminar flow hood (LFH). As described, we can assume that the laminar flow hood is an equipment susceptible to contamination. The following procedures must be implemented in order to reduce/eliminate contamination at these sites:

- The laminar flow hood should be cleaned at the end of the shift or at the end of the day, taking into account the quantity of preparations produced;

- Cleaning should be carried out with products suitable for surface decontamination, considering the material they are made of (Lamerie et al., 2013; Anastasi et al., 2014) and using the appropriate protective equipment;

- Implement scheduled break intervals between preparation / administration periods;

- Providing appropriate training to professionals who handle and administer cytostatics. This training should be documented by collecting signatures.

Contamination was also detected on the bathrooms floors. Similarly, in their studies, (Kopp et al., 2013; Hedmer et al., 2008; Sottani et al., 2012) detected floor contamination. We can infer that bathroom floors are suitable places for contamination. The following procedures must be implemented in order to reduce/eliminate contamination at these sites:

- Clean the bathrooms floors more frequently and with the most suitable products;

- Propose as a rule of good health practice that men use the bathroom in the sitting position to urinate, thus avoiding the projection of urine splashes or urine drops to the floor.

In order to apply the "sitting position to urinate" measure, a strategy should be implemented by nurses and auxiliaries to sensitize patients to the benefits of this measure. As the patient informs the nurse or assistant that he intends to go to the bathroom, the latter should take the time and explain the advantages of the measure. Thus, the patient should be sensitized to the comfort of this position, less risk of urinating on their cloths and greater hygiene in the bathrooms.

Contamination was also detected on the trays. However, in the study by Berruyer et al., (2015) contamination was not detected, but Schierl et al., (2009) report that it exists in other pharmacy sites. Thus, we can assume that the trays may be contaminated, depending on the applied practices. To reduce/eliminate contamination on trays, the following procedures must be implemented:

- Each tray should be used only once, i.e., it enters and leaves the clean room only once;

- After use, it should be set aside for cleaning at the end of the shift. Alternatively, if reuse is required, then it should be properly cleaned and decontaminated;

- The tray sent into the clean room should carry drugs only for one treatment, for one patient, i.e. one tray per patient/treatment;

- implement scheduled break intervals between preparation / administration periods;

- Providing appropriate training to professionals who handle and administer cytostatics.

Regarding training only 22% of professionals reported had workshop training in last twelve months. In their study (Connor & McDiarmid, 2006) also suggest that health professionals should be provided with training at least once a year. In order to improve procedures, the following actions must be taken:

- The employer must promote training workshops for pharmacists, pharmacy technicians, nurses and auxiliaries, so that they are aware of the risks they may be exposed to;

- Professionals should attend training workshops to improve the preparation/administration procedures and comply with the safety standards defined in each organization;

- Require the compulsory attendance at a training workshop at least once a year, because only then will there be more responsible professionals in the performance of their professional activity, resulting in greater safety for organizations.

In this study, personal protective equipment (PPE) was stated as being used by a high percentage of professionals. However, there are still professionals who do not use them, being probably exposed to exposure effects (Kaijser, 1990). Similarly, (Connor & McDiarmid, 2006) suggest the importance of the use of equipment in cytostatic manipulation. Thus, to improve procedures, the following actions must be carried out:

- Always use appropriate personal protective equipment for cytostatics in any situation of contact with such drugs, whether in preparation, administration or transportation;

- Change gloves after each task completed. This procedure is essential in reducing the spread of contamination.

This study also shows that the results of hospital B improved significantly compared to the study by (Silva, 2011). This may be due to the following conditions:

- The new physical facilities in the hospital pharmacy and in the medical oncology Day-care hospital;

- Centralized cytostatics production;

- Replacement of dangerous products by others less dangerous to health, but keeping efficiency, such as the use of the spike, as a substitute for the needle.

The technological evolution also allowed to improve the results in the hospital pharmacy and the medical oncology Day-care hospital in hospital B. This was be due to the following actions:

- Change the old laminar flow hood for a new one;

- Changes in equipment procedures;

- Use of the closed system in the administration of the treatment to the patient in the Day-care hospital.

Considering the results of this study and comparing them with those of the study of hospital B, (Silva, 2011), and considering that the first study raised the awareness and the perception of health professionals handling cytostatics, the following conclusions can be drawn:

- Environmental monitoring should be carried on regular basis;

- The impact of the proposed improvements should be assessed.

6.6 - Recommended procedures for handling and administration practices of cytostatics

Health professionals that prepare and administer cytostatics should know the procedures set for their hospital.

The procedures are not the same in the hospitals of this study. In table 14, the procedures used in each hospital can be observed.

Table 14 - Procedures in 3 hospitals.

	Hospitals		
Procedures	**A**	**B**	**C**
Pharmacists, pharmacy technicians and nurses should wear all the recommend personal protective equipment.	x	x	x
The laminar flow hood should be cleaned at the end of the task, with products suitable for removal of the prepared drugs.	x	x	x
During preparation, the pharmacy technician should close the bottle well after removing some of the drug.	x	x	x
Remove the packaging from the drug, before sending it to the preparation room.	x	x	x
Spray the drugs and other materials with 70% alcohol, before sending them to the interior of the preparation room.	x	a)	a)
Use one tray per patient and treatment, when sending the drugs to the preparation room;	x		

Table 14 - Procedures in 3 hospitals (continuation).

	Hospitals		
Procedures	**A**	**B**	**C**
The pharmacy technicians must be replaced every 60 minutes.	x		
The treatment should be preceded with serum, thus avoiding the spill of the drug.	x	x	x
There is a risk of nurses neglecting to use personal protective equipment when administering cytostatics. This should be enforced.	x	x	x
Nurses should wear new gloves when starting the treatment of a patient and remove them after system-wide binding.	x	x	x
The chair protection is removed and folded to the inside and replaced with another sanitizer. If no other protection is applied, the chair should be cleaned.	x		

a) In hospitals B and C, spraying of the drug with 70% alcohol does not always occur. However, this spraying takes place inside the clean room.

6.7 - Study limitations

The initial objective of this study was to cover three regions of the country, i.e., at least a hospital in each region. However, the present study was only developed in 3 hospital centers, all in the northern region of the country.

Another limitation was related to the lack of national laboratories certified and accredited to carry out the analytical determinations of cytostatic drugs in wipe samples. This required sending the samples to a laboratory outside the country with all the logistics constrains associated with it.

CHAPTER 7 - CONCLUSIONS AND FUTURE PERSPECTIVES

7.1 - Conclusions

This study allows us to evaluate the working conditions in the places where cytostatics are manipulated and administered, regarding the adopted procedures, the use of personal protective equipment, the professionals' self-reported exposure effects and the environmental chemical contamination at each of the analyzed locations.

The methodology applied in this study allowed a careful and rigorous observation of the adopted procedures, the reading of the procedures manual and the respective records, and it was verified that the professionals of these organizations work according to the written procedures.

The sampling technique was applied rigorously and according to the defined standards and all samples were taken by one trained person. A questionnaire was also applied to evaluate the self-reported exposure effects and other situations inherent to the daily tasks in pharmacies and Day-care hospitals.

The analysis of the results obtained show that the values in many of the workplaces are higher than those of the proposed guidance values (Schierl et al., 2009). This fact causes a potential risk, due to the environmental contamination of the workplaces. These sites can be considered as potential sources of exposure, resulting from the contamination detected in the collected samples of Pt and 5-FU.

Regarding the procedures, the absence of contamination on the trays of hospital center A was verified. This is probably due to sending the trays into the clean room with the drugs only once, namely a tray per treatment and per patient, unlike hospitals B and C. In addition, another procedure considered preventive was to pack the drug, after preparation, outside the clean room. Thus, the exposure of the packaging material to contamination and the spread thereof to other locations may be reduced.

Spills occur at different workplaces in health facilities. Thus, health professionals who handle/administer cytostatics reported in the survey that the laminar flow hood, trays and armchair are the sites where the highest percentage of spills occur.

Professionals self-reported that the spillages occurred predominantly in the morning, at the 2nd and 4th hour of the day. The most mentioned cause for the occurrence of spillage is due to the poorly

closed wrap. This non-compliance is likely to be related to the intention to use the same vial in future preparations and some pressure at the workplace. This incident may also be related to the performance of health professionals who prepare and administer cytostatics. This may also be related to stress and some pressure in the workplace.

The collaborators of the hospitals under study use the personal protective equipment recommended for their tasks. However, in the Day-care hospitals, nurses do not always use them, since there is a feeling that the exposure is unusual and inconsequential, unlike in hospital pharmacy professionals.

Nurses, pharmacists and pharmacy technicians in hospitals centers, in general, have not attended training workshops on cytostatics for the last 12 months and only half of the respondents read, by their own initiative, posters on cytostatics. In-service training was the most mentioned contribution to the continuous improvement/good practices in the performance of their tasks in hospital pharmacies and in Day-care hospitals.

The most reported spill causes were poorly enclosed wrap and the device fault/feature.

It should be taken into account that the self-reported side-effects headache and dizziness are the most reported effects by professionals.

In this study, 40.1% of the samples reveal contamination by Pt and by 5-FU. The largest number of contaminated samples occurs in hospital C, while the smallest number occurs in hospital A. Day-care hospitals are the health facilities where the highest percentage of contaminated samples was found, 52,6% by Pt, and 42,1% by 5-FU. Day-care hospitals are the places where the highest levels of contamination were detected on the bathroom floors in hospitals A and B. In the hospital pharmacies, contamination was detected in the laminar flow hoods before the start of the task, in hospital centers A and C. It should be noted that in hospital C, high-level contamination was detected in the 3 samples collected in the laminar flow hood. This may be due to the ineffectiveness of the cleaning measures.

The results provided by the presented data can make an important contribution to the improvement of the working environment in hospital centers, as well as to improve the awareness for the manipulation and administration of cytostatics either by the collaborators or the hospital management.

The results show the chemical contamination, its impact on the work environment and the possible exposure of the professionals who manipulate and administer cytostatics (Pt and 5-FU). The corresponding exposure effects allow to propose possible corrective measures to be implemented,

aiming to reduce or eliminate environmental risks, and to benefit the professionals' health as well. Thus:

- The cleaning and decontamination of the laminar flow hoods must be carried out carefully, at the end of the shift;

- The trays should be cleaned, decontaminated and used only once. If reuse is necessary, this should be done only after cleaning and decontamination. Also, regarding the work method, one tray should be used only for one treatment/patient;

- The bathroom floor should be cleaned more frequently (every hour, if possible) as well as the door handles. The use of the toilet, in the sitting position to urinate, should be implemented as a measure for the health of male patients;

- In-service training should include at least one workshop per year;

- Perform environmental monitoring to assess the impact of the implemented improvements and carry out at least one environmental monitoring per year.

Ideally, it is necessary to consider the hypothesis of a hospital with a high number of patients in need of treatment, to acquire a robot to prepare these drugs, so the heath professional can reduce their exposure.

7.2 - Future perspectives

In Portugal, health professionals who manipulate and administer cytostatics show interest in knowing the actual conditions of cytostatics exposure, since studies in this area are incipient. Thus, it is relevant to respond to the interests of health professionals. For this, it should be carried out a study, with extensive research, throughout the country, preferably. In order to give adequate response to this purpose, an analytical laboratory with appropriate facilities should be established in Portugal.

Another perspective is related to the business component. In this context it is intended to identify and study public or private companies that handle cytostatics. For example, sampling vials at the end of the production line.

An interesting challenge to carry out and considering the results of this study, it would be to conduct a biological study of the blood and urine of the professionals of the 3 considered hospitals. Thus, it

would be possible to establish a relation between the level of environmental contamination and the biological markers. Additionally, it would be also possible to compare the blood and urine results and determine if the latest, a non-intrusive technique, is sufficient accurate to infer the environmental exposure to cytostatic.

Another interesting line of research that can be explored in the future is the study of the combined effects, i.e., try to determine if combined exposure to cytostatic and other environmental contaminants exists in current hospital conditions and if this combined exposure presents additional health risks for these professionals.

On job training is also an important aspect of prevention. The present study showed evidence that health professionals seek further knowledge about their work in order to improve their practice. So, it would also be interesting to devise an on-job training program to ensure that the safer techniques and procedures are used by every hospital and their staff.

Poorly enclosed wrap and the device fault/feature where reported as the main spill causes. So, another interesting study would be to determine which features of the device are contributing to this fact and conduct an ergonomic study to improve their usability and ensure spill free devices.

Finally, it should be noted that environmental exposure to cytostatics has been receiving little attention from the Portuguese Government. So, it would be also important to extended this research to a larger number of Portuguese hospitals where cytostatic are handled.

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APPENDICES

APPENDIX I - CHECKLIST FOR PROCEDURES VERIFICATION IN HOSPITAL PHARMACIES AND MEDICAL ONCOLOGY DAY-CARE HOSPITALS

CHECKLIST FOR PROCEDURES VERIFICATION IN HOSPITAL PHARMACIES AND DAY-CARE HOSPITALS

Hospital Pharmacy	Yes	No
Does the pharmacy have a locker room?		
Does the pharmacy have signage?		
Does the pharmacy have emergency showers, hand and face wash, etc?		
Do the employees change their clothes and shoes?		
Do they wear pants and a tunic (surgery unit suit)?		
Do they wear clogs or others?		
Do they wash their hands?		
Do they wear gloves when in contact with cytostatics?		
Are the gloves adequate to the task?		
Besides the referred equipment, do the pharmacy technicians, who handle the preparations, wear: P3 type mask, scrub hair protection, a 2nd pair of gloves, sterile tunic, plastic feet covers?		
Are all the products sent into the clean room disinfected with alcohol at 70%?		
Are the products sent on trays into the clean room?		
Is the tray used once and then decontamination at the end of the work shift?		
Are the trays separated, i.e., are the used ones in one place and then not used in another?		
Is the transfer support table the same one for sending and receiving the drug?		
Are all products disinfected with alcohol at 70% before entering the clean room?		
Does the tray with the drug have the patient's identification at the entrance and exit of the room?		
Is the drug properly packed when it leaves the room?		
After leaving the clean room, is the drug packaged in a bag and labeled?		
Does the pharmacist put the drug into the package?		
Are all these procedures validated by the pharmacist?		
Is the drug transport to the administration sites carried out in a cart or a bag?		
Is the transport carried out through the transfer from the preparation room, since the administration room is contiguous?		
Is the transport carried out by another process? If so, which one?		
Is there a red bin where to place all the materials that were in contact with cytostatics?		
- Clean Room -		
Do pharmacy technicians, before entering and after leaving the clean room, pass through the transition zone to do proper disinfection?		
Do pharmacy technicians take out the protective equipment when they come in and out of the clean room?		
Are the different drugs suspended in a carrier within the chamber?		
In the preparation, is a small amount of serum used as a protective barrier in case of spillage?		
In the preparation, do the vials have Spikes?		
Is the drug withdrawn from the vial with syringes?		

Is the cleaning of the vials made with a moistened compress with alcohol to eliminate excesses?		
Can filling up also be done in an automatic way (infusion pumps)?		
Does the laminar flow chamber (LFC) have a protective absorbent cloth and is there a plastic to prevent contact with the chamber in the lower part of it?		
Is the cloth protection replaced after 1, 2, 3 hours or at the end of the shift?		
In case of spillage, is it also replaced?		
And is the chamber cleanup made immediately?		
And under normal conditions, does LFC cleaning occur at the end of the shift?		
Is there a red bucket where to place the materials that were in contact with cytostatics?		
Is there a bin where to place the materials that have not been in contact with cytostatics?		
Are the pressures controlled and are they positive?		
At the observation time, did any spillage occur?		
Is it forbidden to eat and drink in the clean room?		
Does the preparation technician perform any repetitive movement?		
Day-care Hospital	**Yes**	**No**
Are the drugs received in the nursing room?		
At their reception, are gloves and plastic protection being used?		
Are they checked and separated by patient?		
Are they administered immediately?		
Is the transport to the patient made by a cart?		
Are the drugs suspended in carriers?		
Does the nurse wear gloves and mask when administering cytostatics?		
Does the nurse disinfect after contact with cytostatics?		
Is the chair covered?		
Is the coating replaced after the patient's treatment?		
If it has no coating, is it disinfected? How?		
Does the half care nurse wear gloves?		
After the treatment, is all material that was in contact with cytostatics placed in the red bin?		
And the rest in another bin?		

APPENDIX II - QUESTIONNAIRE FOR CYTOSTATICS HANDLING/ ADMINISTRATION

INFORMED CONSENT

Project Title: Handling of cytostatic-drugs in hospitals: Study of the impact on the contamination of the occupational environment

Person responsible for the project: João Oliveira da Silva **Contact:** 919424875 **email:** joaoadaufe@gmail.com

Responsible Advisor: Professor Pedro Arezes, Dr. Rudolf Schierl and Professor Nélson Costa.

This document, called **Informed Consent**, Free and Clarified, contains important information regarding the study for which it was addressed, as well as what to expect if you decide to participate in it. Please carefully read all the information contained herein. You should feel entirely free to ask any question.

Some research aims:

- To evaluate the impact of platin and 5-FU (5-FU), in two dimensions, in the measurement of environmental values and in the verification of self-reported symptoms among exposed workers and a control group;

- To quantify the concentrations of the products referred to in the workplace in a hospital environment;
- To observe and record the working methods and practices of cytostatics manipulation/administration in order to evaluate the possible relation between these and the results obtained in the laboratory analyses;
- To develop and implement a worker survey on the existence of self-reported symptoms potentially associated with exposure.

Expected duration of participation: The expected response time to the present questionnaire is 5 minutes.

Procedures: You will be presented with a questionnaire, which you will have to answer, after which there will be an analysis of your answers, whose data will be collected and the results reported in the referred project. The data will be presented together and your identification will be entirely confidential.

Voluntary participation: Your participation is voluntary and you may refuse to participate. If you decide to participate in this study, it is important to know that you can quit at any time without any kind of consequence.

Risks: There is no risk involved in your participation in this study under any condition.

Benefits: Your participation in this study is strictly voluntary. Therefore, the participants will not be remunerated or compensated financially. Although there are no direct benefits to the participants of this study, it may have indirect benefits, as it is contributing to evaluate and eventually improve the conditions of your workplace and you may also be proud to know that you contributed to the process of the research activities. The results of this study will be available later and you may have access to them.

Reliability Statement: The results of this research may be published for information and benefits of this and other studies, although their identity remains anonymous. You will be informed about any change in the nature of this study, being free to give up during the course of the research. For answers to any questions regarding this study and your rights, you may speak with the researcher involved.

Under the exposed above, I, the undersigned, agree to participate in the referred study as an interviewee. I declare that I have been correctly informed and clarified about the right of confidentiality and anonymity. I also declare that I authorize the use of the information obtained, in the dissemination of the study through scientific work.

_____

Responsible Researcher

_____

Responsible Advisor

_____

Interviewee Signature

This questionnaire was developed within a research project developed in the Doctoral Program in Industrial and Engineering Systems and aims to characterize the task of manipulating/ administering cytostatics.

Your answers will be kept in strict anonymity and will be used exclusively for academic purposes.

Thank you for your cooperation.

QUESTIONNAIRE

1 - Place where you work

Hospital pharmacy ☐ Day-care hospital ☐ Gynecology/Other ☐

Logistics/Transport/Storage ☐

2 - Gender Male ☐ Female ☐

3 – Education 9th Grade ☐ 12th Grade ☐ Higher Education ☐

4 - Age

]20 – 25] ☐]25 – 30] ☐]30 – 35] ☐]35 – 40] ☐

]40 – 45] ☐]45 – 50] ☐]50 – 55] ☐]55 – 60] ☐ > 60 ☐

5 - Descendants? Yes ☐ No ☐

5.1 How many? 1 ☐ 2 ☐ >= 3 ☐

5.2 Did you plan your pregnancy? Yes ☐ No ☐

5.3 Time until conception (months).

<= 3 ☐]3 – 6] ☐]6 – 9] ☐]9 – 12] ☐ >12 Months ☐

5.4 Your first child was born when you were at the age of (age in years):

<= 30☐]30 – 35] ☐]35 – 40] ☐ > 40 ☐

6 – Time of service in the health area (years).

<=1 ☐]1 – 5] ☐]5 – 10] ☐]10 – 15] ☐]15–20] ☐

]20 – 25] ☐]25 – 30] ☐]30 – 35] ☐]35 – 40] ☐ > 40 ☐

7 - Time of service in cytostatics manipulation/administration (years).

<=2 ☐]2 – 4] ☐]4 – 6] ☐]6 – 8] ☐]8 – 10] ☐ >10 Years ☐

8 - Average time (hours) of cytostatics manipulation/administration per day.

<= 1 ☐]1 – 2] ☐]2 – 4] ☐]4 – 6] ☐]6 - 8] ☐ >8 ☐

9 - When you are handling cytostatics, are you aware of the risks that you are exposed to?

Yes ☐ No ☐

10 - While you perform your task, do you use Personal Protective Equipment?

Yes ☐ No ☐

10.1 Which?

Gloves ☐ Mask ☐ Goggles ☐ Tunic ☐ Scrub hair protection ☐ Plastic feet cover ☐

11 - Are there scheduled intervals/breaks between preparation/administration periods?

Yes ☐ No ☐

12 - While transporting/handling/administering cytostatics, has any spillage occurred?

Yes ☐ No ☐

12.1 Where?

Storage ☐ Shelf ☐ Tray ☐ Laminar flow hood ☐ Packaging table ☐

Transport box ☐ Administrative cart ☐ Armchair ☐

12.2 What time of day?

Morning ☐ Afternoon ☐

12.3 At what time relative to the time of the task (hour)?

At the 1st hour? ☐ At the 2nd hour? ☐ At the 3rd hour? ☐ At the 4th hour? ☐

13 - Spillages can occur due to different factors. Point some that were the source of the error.

Fine motor coordination ☐ Concentration ☐ Stress ☐ Time spent on the task ☐

Design of the objects to be manipulated ☐ The PPE`s ☐ Packaging ☐

Form of transport ☐ Device fault / Feature ☐ Poorly enclosed wrap ☐

14 - During cytostatic preparation/ administration, is the residues separation performed?

Yes ☐ No ☐

15 - In the last 12 months have you attended training courses on cytostatic manipulation/administration?

Yes ☐ No ☐

16 - By your own initiative, how often do you read articles on cytostatics?

Yes ☐ No ☐

17 - Have you ever submitted any proposals for improving your practice?

Yes ☐ No ☐

17.1 Which?

_____

_____

18 - Exposure effects from cytostatic manipulation may be diverse. Of the following, indicate the one(s) you have already experienced. To do this, use a scale from 0 to 2 points, where 0 means "not experienced" and 2 "experienced a lot".

A - Nausea and vomiting. 0 2 ☐☐☐

B - Alopecia (Hair loss). 0 2 ☐☐☐

C - Headache. 0 2 ☐☐☐

D - Vertigo. 0 2 ☐☐☐

E - Dizziness. 0 2 ☐☐☐

F – Cutaneous hyperpigmentation 0 2 ☐☐☐