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## The occupational risks and health effects resulting from exposition to cytotoxic drugs preparation

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### Abstract

Health professionals dealing with cytotoxic drugs are exposed to occupational hazards, which need to be controlled and reduced to the lowest possible level. The research intends to analyse the effect on the health of the manipulators and the main risks exposition in the preparation of cytotoxic drugs. To achieve this aim, a quantitative analysis was carried out based on data collected through the application of a survey developed for cytotoxic drugs manipulators in Portuguese Oncology institutions. The main results show some symptoms for general manipulators, the occurrence of accidents in the past and more training is required as important. The number of accidents is not connected with more training needs and proceedings lack of knowledge by manipulators. The research intends to contribute to the manipulation of cytotoxic drugs by health professionals, proposing the necessity of better and good practices implemented and organised throughout the CTX manipulation process that must be transversal between different oncology institutions.

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*Keywords:* Occupational Cytotoxic Drugs; Risks; Manipulator health.

### 1. Introduction

Health professionals responsible for preparing and administering cytostatic (CTX) are at risk of adverse effects on their health. Several studies have confirmed the existence of widespread contamination of the environment and work surfaces [1]. Therefore, there is a high concern about handling this type of drugs, due to the occupational risks that

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may arise from the exposure to which the pharmacy professionals are subject [2]. Chemical risks can manifest themselves through systematic contact with potentially dangerous antineoplastic drugs through teratogenic, mutagenic, and carcinogenic manifestations [3]. In this context, the authors propose an empirical study that intends to answer the following research question: What are the health effects and the main occupational risks in the preparation of cytotoxic drugs? The main objective of this paper is to analyse data about the health effect and self-diagnosis of the manipulators and also the occupational exposure risks during the preparation of cytotoxic medicines, attending the study in Portuguese hospital institutions that prepare the CTX. In Portugal, Infarmed licenses the opening of each centralized cytotoxic preparation unit (CCPU), but there is no uniform procedure manual for all hospitals, which could be considered a negative practice. Currently, each hospital has its own manual based on international guidelines without a minimal uniformization standard between institutions [4]. This study may be relevant for the development of procedures and preventive measures that allow working with the lowest possible risk and the health of Portuguese CTX manipulators, attending their own opinion.

This paper is structured in section 1 with an introduction followed the section 2 about occupational exposure of CTX drugs. Section 3 deals with the research methodologies, and section 4 describes the research results and discussion. Section 5 contains some Recommendations and scope for new research and conclusions in section 6.

## **2. Occupational risks exposure of cytostatic drugs preparation**

### *2.1. Risk analysis approach*

In addition to the cancer patients exposed to genotoxic effects on normal cells by virtue of treatment of their pathology, many workers are also exposed to these drugs in their manipulation activity. Among these professionals stand out are the following: the professionals in hospital pharmacies responsible for their preparation, those who provide support the manipulators, those who transport the therapy to the administration rooms, and finally the nursing professionals responsible for the administration of cytostatic therapy [5].

Previous studies revealed that a significant percentage of workers showed episodes of exposure related to breakage/rupture of CTX ampoules and bags (43%), spillage of their contents (39%) or stings with contaminated cutters (13%) [6]. This is evidenced by several studies using exposure biomarkers that demonstrate the presence of CTX on its metabolites, such as in the urine. Although vertical laminar flow chambers are used, contamination of the chamber's outer surfaces and relatively distant areas by aerial dispersion of the agent and transfer through contaminated hands and objects has been demonstrated [7]. In addition, it was detected the contamination of walls, floors, benches and of the most diverse equipment and objects of work [8].

With the insertion of the current sealed ampoules, there was a substantial improvement over the use of the old ones, which had to be broken for content extraction. However, the external surface of these ampoules is constantly contaminated, contributing to skin exposure to these agents [9]. Some CTX solutions can pass through the syringes directly into the hands of the worker. It was also detected contamination of the outer surface of the packages containing CTX, before opening, suggesting that protection is necessary even during unpacking [10]. In several studies the presence of CTX has been demonstrated in various body regions, especially at the hands and forehead level [11]. These studies demonstrate that the safety procedures and personal protective equipment are insufficient to prevent skin exposure, with a consequent risk of absorption. Besides, the enunciated chemical risks related to preparation CTX tasks are the most expressive, and other risks frequently neglected [5]. These risks can be determined by analysing the handle workplace, applying for example the methodology “Job Hazard Analysis”, such as: ergonomic risks related to musculoskeletal disorders (uncomfortable places); psychosocial risks related to stress, exhaustion, depression (repetition tasks, continuous technical exigency, working for large hours) [2].

### *2.2. Risk Assessment contents*

Some national and international organisations suggest that a risk assessment should be carried out whenever a new activity started or a change in procedures, equipment and substances occurs [4]. This general principle of prevention is assumed as the basic methodology of the risk management process. In this context a key element of the risk assessment process is the existence of the Safety Data Sheets (SDS) of the hazardous substances used in the activity.

Each hospital institution is required to have SDS available to all hazardous agents in the workplace and must be done a process to monitor and update the SDS database [1]. The SDS defines the appropriate handling precautions, including protective equipment, means of control and spill management [12].

In order to reduce the exposure risk, the Decree-Law 301/2000 [13] of November 18, which transposes into national law the requirements of Directive 90/394/EEC [14], article 5 presents the procedures that the employer must ensure. The risk to workers exposed is a consequence of the toxicity intrinsic to each drug, exposure magnitude (cumulative effects across exposures or acute exposures) and individual sensitivity [15]. The most obvious danger that the professionals are subject to is the very handling of drugs with high toxicity, being in a situation of chemical risk. These chemical risks can be manifested through systematic contact with these potentially dangerous medicinal products through mutagenic and teratogenic manifestations [4]. These drugs constitute an etiological factor of hives and dermatitis. For most of that substances are not safety data, such as Occupational Exposure Limit Values [2].

Therefore, the effects of continuous low dose exposure (chronic exposure) cannot be evaluated. It is recommended that workers do not stay more than two hours in the handling and there should be in a registry, where the entries and exits in the clean room are discriminated [1]. However, in Spain, through the National Institute of Occupational Safety and Health, a technical note of prevention was issued to CTX, "NTP 740: Occupational exposure to cytostatic in the sanitary field", where it refers the limit value of exposure to the manipulators of this type of drugs [16]. The risk assessment of activities involving CTX can be structured by identifying exposed workers, CTX used, exposure means and specific activities where risk is manifested CTX [1].

### 2.3. Preventive measures advised

There are some standards adjustable for CTX handlers, published by INSHT, in addition NTP 740 cited, such as [16]: NTP 1051, replaced by NTP 1134, Occupational exposure to cytostatic compounds: safe systems for their preparation; NTP 233 Biological safety cabins; and NPT 1135 Hazardous drugs: administration and available equipment. After a correct risk analysis and risk assessment, the health risks should be reduced by applying preventive measures and adequate medical supervision to personnel working with these products, considering all relevant factors for each workplace [4]. Since cytotoxic agents have been shown to cause adverse effects on the health of those who administrate and manipulate them, a set of preventive measures must be taken. The first measure was the centralization of the preparation of these substances in hospital pharmacies that follow procedures and preventive measures, such as the use of laminar flow chamber, use of appropriate clothing, and double pair of gloves [17]. These drugs should be stored in a separate area from other substances and should be well ventilated. The prevention measures are the key for the risks controls, namely [18]: Initial and periodic risk assessment (e.g. Workplace Hazard Assessment Form); Preparation of work procedures (reception, transportation and storage of CTX, how to act in case of the leakage, breaks and splashes); Description of the specifications of a centralized cytostatic preparation unit (CCPU); Training for employees; Registration of CTX exposure and occurrence of accidents; The requirement to use of personal protective equipment (PPE); Management of hazardous waste; And health surveillance.

## 3. Research methodology - Materials and methods

The bibliography identifies some health problems in preparing CTX drugs by health professionals [4]. The problem in this issue is based on inadequate preventive measures and inefficient health conditions application by cytostatic handlers in Portugal. Attending to the main objective and the problems issue described in this research, the CTX handles opinions are important and could give a different perspective [5]. According to some special knowledge about the Portuguese scenario in the area, some research hypotheses (H) have been formulated:

- H<sub>1</sub>: The occurrence of accidents is associated with knowledge of the current standard.
- H<sub>2</sub>: There are differences regarding risk by sociodemographic/professional variable, manipulators rotation, occurrence of accidents, number of working hours per day and manual of procedures.
- H<sub>3</sub>: There are differences in health effects/symptoms by sociodemographic/occupational variables (gender, age and length of service), type of mask used and occurrence of accidents.

The authors used a quantitative research methodology for the research [19]. Based on bibliographical and documentary research, a survey was developed in Google docs, which contained 69 questions structured by the following groups: I-Personal/Hospital characterization (9 questions); II-Workplace methodology at UCPC (8 questions); III-Safety at UCPC/procedures: Collective Protection Equipment (19 questions); IV-Safety at UCPC/procedures: Personal Protective Equipment (19 questions); V-Costs of Personal Protective Equipment (7 questions); VI-Handles health (7 questions); VII- Exposition risk characterization (10 questions). The survey was subjected to a pilot test [20], before application, by 4 different technical Health and Safety at Work related with the oncology area in different Portuguese Oncology institutions.

Before the survey handled application, all study aims [19], informed consent and the data collection plan were presented to the chief executive officer (CEO) of the 36 hospital institutions in Portugal, and in some cases to the Director of Pharmaceutical Services, Ethics Commission and Research Centres. These hospitals that participated in this study are listed in the Plan of the National Program for Oncological Diseases 2015 developed by Miranda et al. [21], in the installed capacity and activities in oncology in Hospitals National Health Service Report. The hospitals are organised according to the “Administração Regional de Saúde (ARS)” to which they belong. Of the 36 institutions in the area, 18 were permitted to apply the questionnaire, 6 gave an unfavourable opinion and 12 did not respond. For the application of the survey, after the respective institutions issued the opinion, a message was sent by email to the person indicated by each institution, where the purpose of the study was duly clarified, and the anonymity and confidentiality of the data collected and in which oncology institution were guaranteed. Besides that, were asked to all CTX handlers to complete the survey. The application of this survey ran from June to September 2017 and data results were treated in software SPSS version 25. It was produced descriptive and inferential statistical information.

From the 18 institutions that authorized the questionnaire, a sample was constituted of 83 CTX manipulators who work in Portuguese hospitals, the majority female (73.5%; n=61). Most of the manipulators are pharmacy technicians (n=70; 84.3%) and the rest are pharmacists (n=13; 15.7%). The manipulator of CTX varies between 1 month and 20 years, with an average of 8.0 years. Approximately 89% of the respondents (n=74) attended specific courses to be CTX manipulators, and most of them (n=68; 91.9%) made short courses, which were mostly provided by the institution where they work (n=59; 79.7%). Most of the manipulators have a specific course to be manipulators and was administered by the institution where they work, according to ASHP [1].

#### **4. Discussion results and research test hypothesis**

This section presents and discusses the results obtained through the survey. It begins with the descriptive analysis of the health of the manipulator and the occupational risks, later, and it is followed for the test of the hypotheses [22]. Regarding the manipulator health is presented in a descriptive analysis. This analysis focuses more specifically on: Periodicity of the health surveillance; medical examinations carried out, health effects since they hold positions in the CCPU, the symptoms number, attitude towards health problems, the importance of the contraindication.

##### *4.1. Handler health results*

The frequency of health surveillance of handlers that integrate this study, the most common is the annual surveillance (74.7%; n=62), but the medical examinations carried out by most of the respondents are: blood count (88%; n=73); urinalysis (80.7%; n=67); clinical chemistry analysis (66.3%; n=55); tumour markers (53%; n=44).

In addition, the manipulators that perform functions in the CCPU 29% (n=24) do not present any complaint about the health effects. Despite this, the most frequent complaints were headache or dizziness (64.4%; n=38), sore throat (61%; n=36), and allergic or dermatological reactions (37.3%; n=22). For each manipulator was recorded the number of health effects, and the results of the effects number ranging from 1 to 4, more commonly, have two distinct symptoms (30.1%; n=25). There were also 22.9% (n=19) manipulators with one symptom, 13.3% (n=11) with three symptoms and 4.8% (n=4) manipulators with 4 symptoms at least. Regarding the attitude manipulators to the health symptoms mentioned above, 33.9% (n=20) did not take any action. Of the remaining patients, 25.4% (n=15) reported to the hierarchical superior and the Doctor of Occupational Medicine. The same number reported only to the Doctor of Occupational Medicine and the remaining 15.3% (n=9) reported to the hierarchical superior.

The importance degree attributed by the manipulator to the contraindication of CTX manipulation, according to Table 1, all manipulators considered extremely important in the case of being pregnant or suspected of pregnancy, and 98.8% if they were breastfeeding. They also considered this contraindication very important and extremely important (6% and 92.8%) if they suffer from an autoimmune disease. In the case of suffering from allergies, the answers are more dispersed, although, mainly, it is very or extremely important. In the case of having undergone cancer treatment, 96.4% consider the contraindication of CTX manipulation as extremely important, and 85.5% attribute this degree of importance if they have congenital malformations. This culminates in average values comprised between 4,19 and 5, which translates into the high importance attributed by the manipulators to the contraindication of the manipulation of CTX in certain personal situations [5]. Manipulators are aware of the limitations and contraindications of CTX manipulation, especially in the bone marrow and reproductive organs, and may lead to serious side and collateral effects, as many of the agents are carcinogenic, mutagenic and teratogenic, and certain CTXs cause skin lesions and due to its irritant, vesicant or allergenic action [3].

Table 1. Degree of importance in which the manipulation of cytostatic is considered contraindicated.

	Nothing important (1)	Little important (2)	Relatively important (3)	Very important (4)	Extremely important (5)	I don't know/ I don't have information	Mean (standard deviation)
If you are pregnant	-	-	-	-	83 (100%)	-	5 (0)
If you suspect being pregnant	-	-	-	-	83 (100%)	-	5 (0)
If you are breastfeeding	-	-	-	1 (1.2%)	82 (98.8%)	-	4.99 (0.11)
If you suffer from an autoimmune disease	-	-	1 (1.2%)	5 (6.0%)	77 (92.8%)	-	4.92 (0.32)
If you usually suffer from allergies	-	3 (3.6%)	16 (19.3%)	26 (31.3%)	38 (45.8%)	-	4.19 (0.88)
If you made cancer treatment	-	-	-	1 (1.2%)	80 (96.4%)	2 (2.4%)	4.99 (0.11)
If you have congenital malformations	-	-	2 (2.4%)	2 (2.4%)	71 (85.5%)	8 (9.6%)	4.92 (0.36)

#### 4.2. Occupational risk results

According to Gouveia [23], CTX handlers must receive initial, continuous, periodic training to perform their duties properly. However, in Table 2, most manipulators (80.7%; n=67) revealed that the CCPU where they perform functions does not provide training actions on the risks of manipulating CTX, and most of them (98.8%; n=82) felt the need for safety training of CCPU. Insufficient or inadequate training may lead to the inherent risk of improper use or non-use of Personal Protective Equipment (PPE) and lack of knowledge of prevention and control procedures, leading to intoxication, infertility or congenital defects [24]. Based on findings, it appears that most handlers CTX (80.7%; n=67) had already suffered some kind of work accidents related to the handling of CTX. Attending the type of accidents suffered, the manipulators selected as the most common: spills, splashes and bites (25.4%; n=17) and spills and splashes (10.4%, n=7). However, the remainder have multiple accidents. And the contact with the drugs, the majority refers to the skin (59.7%; n=40), followed by skin and hands (23.9%; n=16).

Table 2. Sample distribution with regard to training courses on the risks arising from the manipulation of cytostatics (n=83).

	Answer type	N	%
The institution provides training/awareness about the risks involved in handling cytostatics	Yes	16	19.3
	No	67	80.7
Feels the need to have safety level training of CCPU	Yes	82	98.8
	No	1	1.2

Based on findings, it appears that most handlers CTX (80.7%; n=67) had already suffered some kind of work accidents related to the handling of CTX. The type of accidents suffered, the manipulators selected as the most common: spills, splashes and bites (25.4%; n=17) and spills and splashes (10.4%, n=7). However, the remainder have multiple accidents. The most contact with the drugs refers to the skin (59.7%; n=40), followed by skin and hands (23.9%; n=16). The characterization of the risk degree of exposure in the chemotherapy manipulation can be observed:

- The risk of exposure to aerosol inhalation, most manipulators consider it undesirable (65.1%; n=54) and 22.9% (n=19) consider it unacceptable;
- The direct contact of the drug with the skin or mucous 47% (n = 39) considered undesirable and for 39.8% (n=33) it is unacceptable that this happens;
- The accidental injection, most of the manipulators considered undesirable (75.9%; n=63) and 14.5% (n=12) considered it unacceptable;
- The development of cancer is unacceptable to 71.1% (n=59) of the manipulators and 20.5% (n=17) undesirable;
- The occurrence of immune-suppression is unacceptable for most of the manipulators (68.7%; n=57) and 24.1% (n=20) consider this risk undesirable;
- The occurrence of allergic reactions, the majority (50.6%; n=42) considered the risk undesirable and 24.1% (n=20) unacceptable;
- The tissue injury is unacceptable for 65.1% (n=54) of the manipulators and undesirable for 22.9% (n=19);
- The mutagenicity is unacceptable for 72.3% (n=60) of the manipulators of this study, and 15.7% (n=13) consider this risk to be undesirable;
- The infertility is an unacceptable risk for 66.3% (n=55) of the respondents and for 25.3% (n=21) is undesirable;
- Finally, menstrual dysfunction presents a reduced risk for 41% (n=34) of the 61 (73.5%) female manipulators, but an undesirable risk for 43.4% (n=36) and unacceptable for "only" 9.6% (n=8).

Thus, in general, manipulators consider the risk of cancer development, occurrence of immune-suppression, occurrence of tissue injury, mutagenesis and infertility to be unacceptable. Then, a new variable was operationalized, which was called "Risk" and resulted from the average of the responses of each respondent in each of the situations described above in the table 1. The risk assessment was as follows: Insignificant - 1; Reduced - 2; Undesirable - 3 and Unacceptable - 4. The score of each item included in the risk ranges from 1 to 4. Table 3 shows the risk variable's variation, mode, median, mean and standard deviation. Thus, the assessment attributed to the risk is comprised of 1.6 to 4 points. The median obtained was 3.40 points, which allows concluding that 50% of the manipulators present a risk below this value and 50% higher. The mean value obtained was 3.27 with a standard deviation of 0.54.

Table 3. Variation, measures of central tendency and standard deviation of the risk variable.

	Minimum	Maximum	Median	Average	Standard deviation
Risk	1.60	4.00	3.40	3.27	0.54

In addition, about the material in the unit to deal with occupational accidents, contains the following information:

- In the case of CTX spills, all handlers refer to the existence of a spill kit in the units where they perform functions and their respective manual, as referred to in the NHS guideline ASHP [1]; namely, all areas of cytotoxic handling there should be a spill kit;
- Most of the manipulators (66.3%; n=55) also mention the existence of chemical inhibitors and/or antidotes in case of CTX spills. However, there are 7 manipulators unaware of its existence and for 21 they do not exist;
- Most handlers (94%; n=78) say he knows how to act in case of spillage according to the current standard, however there are 3 who answered no and 2 did not know;
- Also, 94% of the handlers report an existence of a specific document for register accidents, but the rest replied that they do not know if this document exists in their CCPU;
- As for professionals who do not handle CTX but work in this unit, the majority of respondents (90.4%, n=75) think they are at chemical risk;
- Most CTX handlers report that the material and disposal from the handling are placed in a hazardous hospital waste container (Group IV- "Specific" Hospital Waste includes empty bottles of cytotoxic/needles used, spikes, contaminated wraps, bottles (serum or water) contaminated with cytotoxic agents" [25]).

#### 4.3. Corroboration of research hypotheses

The 1<sup>st</sup> research hypothesis

“The occurrence of accidents is associated with the knowledge of the current norm”, it was used the Fisher's exact test, because the assumptions of applicability of the chi-square test of independence were not validated. In addition, to obtain a table data, the individuals who answered “do not know” in the question were excluded relative to the current standard. The findings of Table 4 show that 63 handlers of 65 who have already suffered accidents are knowledgeable of the current standard. However, of the 16 who did not suffer accidents, only 1 handle did not know the current standard. The p-value was 48.8%, higher than the level of significance assumed (5%), so it is concluded the variables are not statistically significant [22]. The occurrence of accidents in the institution where they work were not associated with the current standard knowledge. Thus, it is concluded that the 1<sup>st</sup> research hypothesis was not validated.

Table 4. Observed frequencies and p-value of the Fisher test between the variable accidents and current norm.

		Knowledge of the current norm		Total	P-value
		Yes	No		
Have you ever had an accident?	Yes	63	2	65	0,488
	No	15	1	16	
Total		78	3	81	-

#### The 2<sup>nd</sup> research hypothesis

“There are differences regarding risk by sociodemographic/professional variable, manipulator rotation, the occurrence of accidents, number of working hours per day and manual of procedures”. This hypothesis will be supported, for its validation, by the application of non-parametric tests [22]. This is because the normality assumption of the dependent variable is not fulfilled and the groups by the independent sample are less than 30 cases. The authors used the Mann-Whitney and the Kruskal-Wallis tests. The age variable was operationalized in four age groups: 21 to 30 years, 31 to 35 years, 36 to 40 years and 41 to 50 years. The variable time that you are manipulator was operationalized in three categories: less than 5 years, 5 to 10 years and more than 10 years. The findings of these tests are found in the Table 5. Since all the p-value obtained is greater than 5%, it is concluded that there is not enough statistical evidence to affirm that the risk is different or depend by gender, age, occupation, time of manipulator, specific course and course given by the institution, rotation of manipulators and existence of manual procedures. The p-value of the number of working hours per day obtained is less than 5%, then the risk is different in terms of the number of hours of daily work. Thus, it is concluded that the 2<sup>nd</sup> research hypothesis was partially validated.

Table 5. Risk comparison by socio-demographic and professional variables: inferential analysis. (\*, Significant at 5% level)

Variable	Statistical test	P-value
Gender	Mann-Whitney	0,608
Age	Kruskal-Wallis	0,688
Occupation	Mann-Whitney	0,706
How long are you manipulator?	Kruskal-Wallis	0,887
CTX specific for Handling Course	Mann-Whitney	0,820
Course given by the institution	Mann-Whitney	0,877
Manipulators rotation	Kruskal-Wallis	0,202
Number of working hours per day	Kruskal-Wallis	0,015*
Procedures manual	Mann-Whitney	0,159

The results show that the median of the highest risk is 3.6 when working 7 hours per day. Closer is the one who works 2, 4 and 6 hours. From the analysis of this figure, it is verified that the manipulators that work 7 hours per day present greater median risk.

#### And the 3<sup>rd</sup> research hypothesis

"There are differences in the effects/symptoms on health by sociodemographic/professional variable (gender, age and length of service), type of mask used and occurrence of accidents". There was a need to apply non-parametric

tests once the normality assumption and number of cases per independent sample were verified, and the Mann-Whitney test and the Kruskal-Wallis test were applied [22]. The presentation of the results of these tests is done in Table 6. The tests obtained two values of less than 5%: the type of mask used and the occurrence of accidents. Thus, there is sufficient statistical evidence to state, at the 5% significance level, that the effects felt are different regarding the type of mask used. From the analysis (Figure 1a), it is observed in the manipulators that use the mask of class P2 present fewer effects/symptoms.

Table 6. Comparison of the number of effects/symptoms by sociodemographic, professional variable, mask type and occurrence of accidents: inferential analysis. (\*, Significant at 5% level)

Variable	test	p-value
Gender	Mann-Whitney	0.745
Age	Kruskal-Wallis	0.084
Time that is manipulator	Kruskal-Wallis	0,177
Type of mask used	Kruskal-Wallis	0.001 *
Already suffered accidents	Mann-Whitney	0.026 *

There is also sufficient statistical evidence to state that at the significance level of 5%, the effects are different regarding the occurrence of accidents (see Table 6). By the analysis of Figure 1b), it is verified that it is the manipulators that have already suffered accidents that present more health effects/symptoms.

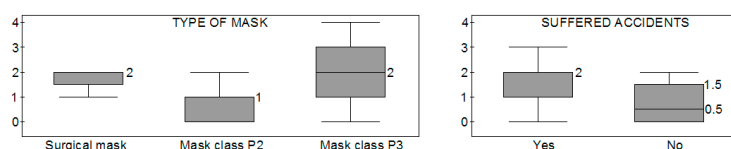


Figure 1. a) Diagram of extremes and quartiles of the number of health effects/symptoms by type of mask used. b) Diagram of extremes and quartiles of the number of health effects/symptoms attending to the occurrence of accidents.

With the result of the test of the 3rd research hypothesis partially validated, the third specific objective was partially achieved, namely in the verification if there are differences in the health effects of the worker according to the professional profile, working conditions (type of mask used) and the occurrence of accidents.

#### Research hypothesis final considerations

In the form of a summary, the first research hypothesis was not validated. However, the second and third research hypotheses have been partially validated. This makes it possible to conclude that most of the manipulators, in case of an accident, know how to proceed according to the current standard in their institution. In addition, the occurrence of accidents is not related to the knowledge of the standard [4]. However, the perception of manipulation risk does not vary with respect to the age range, professional category, time of service as a manipulator, specific course [5] and course given by the institution, manipulators rotation and existence of manual procedures [4]. The risk felt by the manipulators varies as to the number of hours of daily work, and the manipulators that work 7 hours a day present a greater risk. The health effects/symptoms presented by the manipulators are not different in relation to the sociodemographic/professional variable (gender, age and length of service). The same does not happen about the type of mask used and the occurrence of accidents. Handlers that use P2 class mask have fewer effects/symptoms. Also, the sensed effects are different attending the occurrence of accidents, being the manipulators that already suffered accidents that present more effects/symptoms in the health.

## 5. Recommendations and scope for further research studies

The research allows to propose the following recommendations and adequate proceedings for cytotoxic handles:

- Bet on training and awareness, as it denotes a need for training by professionals;



- Alert the professionals for the importance of adopting measures that allow minimizing the risk of exposure, requirement of measures and laws that determine the time of exposure;
- Safeguarding the importance of a preventive attitude in the workplace and promoting an organisational culture of security, trying to make risk assessment understood as a serious, continuous and priority reality.
- Implementation of a manual of procedures for the manipulation of CTX in all Hospitals, as there should be legislation on the good practices of handling this type of drugs;
- Preliminary Hazard Analysis (PHA) application in earlier stages of CTX uses by handlers for prevent hazards events with adjustable preventive control measures for risk monitorization.
- Installation of video cam to control the cytostatic preparation with an intelligent video recording (DrugCam®) [26].

It is also important to point out that it is necessary to intervene in the institutions to develop quality and efficiency in the work of the manipulators, trying to anticipate the risks, mitigate their occurrence, and act at the level of the risk groups [16]. It is necessary to look beyond the figures for immediate expenditure, focusing on future income. Although it is a sensitive matter, it is important that it be addressed and debated, trying not to ignore the problem. This section concludes with suggestions for future research. Thus, as a future line of research, it is proposed to develop more research studies in this area, namely on:

- Worker safety in handling antineoplastics;
- Norms and procedures on the use of antineoplastics in conjunction with workers directly or indirectly involved in exposure to this type of drugs;
- Occupational risks, as there are risks of occupational exposure in all activities carried out at the CCPU;
- More detailed studies on non-compliance with good practices in the health of professionals who handle and prepare antineoplastic chemotherapeutics;
- Health education contributes to biosafety, taking a deeper view on the theme and facilitating professionals' awareness of the theme.

## 6. Research conclusions

According to the results, the manipulators consider the health surveillance performed annually to be of great importance. The symptoms that have manifested most in CTX manipulators are headache or dizziness, and throat irritation. However, in the face of these effects, most manipulators took no action. Additionally, the average of the manipulators considers of extreme importance the existence of contraindications stipulated to the accomplishment of these procedures in special the pregnancy. Although most institutions do not conduct training on the risks involved in handling CTX, many manipulators feel the need for them.

Many handlers have already suffered work accidents, the most common being spills, accidental bites and splashes, mostly considering the skin as the way of contact. For each manipulator the risk was calculated, measured on a scale of 1 to 4 points, where 1 corresponds to "Insignificant", 2 "Reduced", 3 "Unacceptable" and 4 "Unacceptable", as the average risk in various situations. The mean obtained was 3.27 points, with a standard deviation of 0.54 points, representing a risk between the undesirable and unacceptable. The paper can be concluded that the occurrence of work accidents is independent of the manipulator's knowledge about the current norm. In addition, the risk felt by the handlers is different from the daily working time. However, manipulators working 7 hours a day are at increased risk [5]. Finally, the authors conclude that the effects felt are different as to the type of mask used and the occurrence of accidents. Handlers that use P2 class mask have fewer health effects/symptoms. However, manipulators that have already suffered accidents have more health effects/symptoms.

Nevertheless, it should be noted that the interpretation of these results should consider the following limitations: the number of manipulators that exist in all hospitals in Portugal is unknown; and another limitation stems from the main obstacle that was the absence of responses by all hospitals for the availability of the study, having been necessary enough insistence. Furthermore, despite the difficulties in obtaining answers to the questionnaires, and knowing the importance of these drugs for the oncological patient and the risk to the manipulators [2], it is considered appropriate and well-founded the accomplishment of this study, contributing as a form to alert for the existence and need to implement good practices organised throughout the process of handling CTX [4].

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