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REVISIÓN
Artículo bilingüe inglés/castellano

Evidence of exposure to cytostatic drugs in healthcare staff: a review of recent literature

Evidencia de la exposición a fármacos citostáticos del personal sanitario: revisión de la literatura reciente

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Abstract

Objective: Provide updated evidence and learn about the actions that must be implemented in order to prevent the occupational exposure to cytostatic drugs.

Method: A bibliographic search was carried out on the MEDLINE, COCHRANE PLUS and WEB OF SCIENCE databases, with the terms "surface contamination", "cytostatic drug", "drug preparation", "occupational exposure", "safe handling" and "closed-system transfer device", within the 2010-2015 period.

Results: Thirteen articles were selected for review. These articles are from hospitals in U.S.A., Canada, Japan, Australia, Spain, Portugal and Germany. In all of them, surface contamination by cytostatic agents was found in over 15 different surfaces, with concentrations ranging from 1.69 ng/cm^2 to 4-784 µg/cm^2. The specific drugs were cyclophosphamide, ifosfamide, 5-fluorouracil, methotrexate, paclitaxel, cisplatin, gemcitabine, and docetaxel. Closed-system transfer devices can reduce the contamination in work surfaces significantly, but do not eliminate it.

Conclusions: Presence of contamination by cytostatic drugs was confirmed in many hospitals across all 5 continents. In all cases, contamination was found in the cabinet, on the floor in front of the cabinet, and in other places of the Hospital Pharmacy. The drug most frequently found is cyclophosphamide. Closed-system transfer devices can reduce the contamination in work surfaces significantly, but do not eliminate it.

Resumen

Objetivo: Disponer de la evidencia más actual y conocer las medidas a aplicar para evitar la exposición laboral a citostáticos.

Método: Se realizó una búsqueda bibliográfica en las bases de datos MEDLINE, COCHRANE PLUS y WEB OF SCIENCE con los términos "surface contamination", "antineoplastic drug", "drug preparation", "occupational exposure", "safe handling" y "closed-system transfer device" para el periodo 2010-2015.

Resultados: Se seleccionaron 13 artículos para la revisión. Estos artículos corresponden a hospitales de USA, Canadá, Japón, Australia, España, Portugal y Alemania. En todos ellos se ha encontrado contaminación por fármacos citostáticos en más de 15 superficies distintas con concentraciones que van desde los 1,69 ng/cm^2 hasta 4,784 µg/cm^2. Los fármacos determinados han sido ciclofosfamida, ifosfamida, 5-fluorouracilo, metotrexato, paclitaxel, cisplatino, gemcitabina y docetaxel. El sistema cerrado reduce la contaminación de las superficies de trabajo significativamente, pero no la elimina.

Conclusiones: Se verifica la presencia de contaminación por fármacos citostáticos en numerosos hospitales de los 5 continentes. En todos los casos se ha encontrado contaminación en la cabina, en el suelo frente a la cabina y en otros lugares de la farmacia. El fármaco más frecuentemente encontrado es la

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macy. The drug most frequently found was cyclophosphamide. The most effective action used to reduce contamination was the closed-system transfer devices (CSTDs).

KEYWORDS
Cytostatic drugs; Surface contamination; Occupational exposure; Safe handling.

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ciclofosfamida. El sistema empleado más eficaz para reducir la contaminación es el uso de dispositivos cerrados de transferencia (CSTD-closed system transfer device).

PALABRAS CLAVE
Fármacos citostáticos; Contaminación superficial; Exposición laboral; Manipulación segura.

Farm Hosp. 2016;**40(6)**:604-621

Introduction

Cytostatic drugs are cytotoxic substances designed and used to cause cell dysfunction, thus inhibiting cancer cell growth through the alteration of their metabolism and by blocking cell division and reproduction. This damage is not selective for tumour cells, but it affects all cells in the body, causing adverse toxic effects that are mostly hematopoietic, renal, liver, digestive and dermal.

Their use started in the 50s decade, after observing aplastic anemia cases in soldiers exposed to mustard gas during Second World War, which led to the use of nitrogen mustards for Hodgkin's disease treatment[1].

The International Agency for Research on Cancer (IARC) has classified many of these drugs as carcinogenic, mutagenic and/or toxic for reproduction. In Monographs 26[2] and 76[3], both available at the IARC website, there is a list of the cytostatic agents included and their classification, shown here in table 1.

Currently, eleven drugs and certain combination therapies are included in Group 1 (azathioprine, busulfan, cyclophosphamide, chlorambucil, chlornaphazine, diethylstilbestrol, melphalan, semustine, tamoxifen, thiotepa, treosulfan, and MOPP), twelve drugs are included in Group 2A (adriamycin, azacitidine, carmustine, cyclosporine, cisplatin, chlorozotocin, etoposide, lomustine, mechlorethamine, procarbazine, teniposide, and testosterone), and eleven drugs are included in Group 2B.

In 1979, the first publication about occupational exposure to cytostatic agents and its association with health risks appeared in the study by Falck *et al.*[4]. In this study, through Ames test, the mutagen activity was analyzed in the urine of nurses who prepared and administered cytostatic agents without protection measures. The existence of risks for health was demonstrated in cases of chronic exposure to some of these drugs in small amounts.

Table 1. *Classification of carcinogenic substances according to the IARC*

Group	Definition
1	The agent is carcinogenic to humans.
2A	The agent is probably carcinogenic to humans.
2B	The agent is possibly carcinogenic to humans.
3	The agent is not classifiable as to its carcinogenicity to humans.
4	The agent is probably not carcinogenic to humans.

Subsequent studies have shown the likelihood of damage for workers exposed to cytostatic agents, with impact on pregnancy[5,6,7,8,9,10] (miscarriages, birth defects), chronic effects[11,12] and acute effects[13,14,15,16].

Based on occupational exposure, different authors studied the potential association with oncogenic effects[17,18,19,20,21]. Though the relationship between prolonged exposure at low levels (the case of occupational activity) and oncogenic effect has not been clearly established, it is considered a potential factor of risk, and therefore all measures available should be implemented in order to minimize the risk of exposure.

Those workers who come into contact with cytostatic agents could be exposed to a risk for their health. This exposure could occur at any point during the drug cycle, from its manufacturing and distribution to its preparation, administration, and waste disposal. Therefore, the workers exposed could be both from the pharmaceutical industry and healthcare staff (physicians, pharmacists, nursing staff, healthcare technicians, and hospital attendants) in charge of preparation, administration, transportation, and waste disposal.

The concern around cytostatic handling has led different countries and organizations to prepare Guidelines for their correct handling. Table 2 shows some of the significant and recent Guidelines[22-40] that have been published.

One way of exposure to cytostatic agents could be through workplace contamination. Therefore, it is very important to determine the presence of cytostatic substances in work surfaces and, most of all, to be aware of the potential measures that should be implemented in order to eliminate or reduce said contamination.

The objective of this bibliographic review is to provide the most updated evidence about exposure to cytostatic agents in the work setting, and to learn about the potential preventive measures that can be implemented to prevent occupational exposure to cytostatic agents.

Material and methods

A bibliographic review was conducted using as information sources the following databases: MEDLINE, COCHRANE PLUS and WEB OF SCIENCE.

Table 2. *Guidelines for safe handling of cytostatic drugs, in alphabetical order*

Title	Author/s
American Society of Clinical Oncology/Oncology Nursing Society chemotherapy administration safety standards[22]	Jacobson JO, Polovich M, McNiff KK, LeFebvre KB, Cummings C, Galioto M, Bonelli KR and McCorkle MR
ASHP Guidelines on Handling Hazardous Drugs[23]	American Society of Health-System Pharmacists
Australian consensus guidelines for the safe handling of monoclonal antibodies for cancer treatment by healthcare personnel[24]	Alexander M *et al.*
Chemotherapy and biotherapy guidelines and recommendations for practice[25]	Brown KA, Esper P, Kelleher LO, O'Neill JEB, Polovich M and White JM
Controlling occupational exposure to hazardous drugs[26]	OSHA
Guidelines for the Safe handling of Cytotoxic drugs And related waste[27]	Occupational Safety and Health Service. Department of Labour. Wellington. New Zealand
Guidelines for the safe handling of hazardous drugs: consensus recommendations[28]	Chaffee BW, Armistead JA, Benjamin BE, Cotugno MC, Forrey RA, Hintzen BL, Pfeiffenberger T and Stevenson JG
Improving Patient and Worker Safety: Opportunities for Synergy, Collaboration and Innovation[29]	TheJointCommission
ISOPP Standards of Practice[30]	ISOPP
Medicamentos citostaticos[31]	Gamundi MC *et al.*
Preventing Occupational Exposure to Antineoplastic and Other Hazardous Drugs in Health Care Settings[32]	NIOSH
Safe handling and administration of antineoplastic chemotherapy[33]	Eisenberg, S
Safe handling of cytotoxic drugs[34]	HSE (Health and Safety Executive)-UK
Safe handling of hazardous chemotherapy drugs in limited-resource settings[35]	PAHO/WHO
Safe handling of hazardous drugs[36]	Polovich M, Bolton DL, Eisenberg S, Glynn-Tucker EM, Howard-Ruben J, McDiarmid MA, Power LA and Smith CA
Safe handling of hazardous drugs: reviewing standards for worker protection[37,38]	Power LA and Polovich M
Safe handling of oral chemotherapeutic agents in clinical practice: recommendations from an international pharmacy panel[39]	Goodin S, Griffith N, Chen B, Chuk K, Daouphars M, Doreau C, Patel RA, Schwartz R, Tames MJ, Terkola R, Vadnais B, Wright D and Meier K
Standards of Practice: Safe Handling of Cytotoxics[40]	International Society of Oncology Pharmacy Practitioners

The period of study was established as the past 5 years.

The search was conducted based on the following key words: surface contamination, cytostatic drug, hazardous drug, drug preparation, occupational exposure, safe handling, closed-system transfer device. Afterwards, a combination of these key words was also used (for example: surface contamination AND hazardous drug, safe handling AND cytostatic, surface contamination AND cytostatic) in the different databases, defining the search according to the following criteria:

Inclusion Criteria

1. Studies describing the association between cytostatic handling and occupational exposure.
2. Human.
3. Publication date: Between 2010 and 2015.
4. Articles published in English and in Spanish.

Exclusion Criteria

1. Redundant articles.
2. Not original or reviews (for example: letters to the editor, editorials).

Ninety-one (91) articles were collected; duplicates or redundant articles were eliminated, and a relevance analysis was conducted by reviewing the article titles and abstracts, leading to a final selection of 13 articles, which are the basis for this study.

Results

Table 3 shows the main characteristics of the 13 articles that form the study, such as: authors, title, year, aspect studied, and main outcomes of the study.

Table 3. *Summary of the articles included in the review*

Authors	Title	Year	Aspects studied	Outcomes
Sessink PJ, Trahan J, Coyne JW	Reduction in Surface Contamination With Cyclophosphamide in 30 US Hospital Pharmacies Following Implementation of a Closed-System Drug Transfer Device	2013	Superficial contamination	Contamination in all the surfaces studied. 86% reduction in contamination levels by cyclophosphamide with the use of the closed system.
Sessink PJ, Connor TH, Jorgenson JA, Tyler TG	Reduction in surface contamination with antineoplastic drugs in 22 hospital pharmacies in the US following implementation of a closed-system drug transfer device	2010	Superficial contamination	Superficial contamination by cyclophosphamide, ifosfamide, and 5-fluoroacil. Statistically significant reduction in the contamination levels with the use of the closed system.
Berruyer M, Tanguay C, Caron NJ, Lefebvre M, Bussières JF	Multicenter study of environmental contamination with antineoplastic drugs in 36 Canadian hospitals: a 2013 follow-up study	2014	Superficial contamination	Superficial contamination in 47% of cases by cyclophosphamide, 18% by ifosfamide and 3% by methotrexate.
Merger D, Tanguay C, Langlois E, Lefebvre M, Bussières JF	Multicenter study of environmental contamination with antineoplastic drugs in 33 Canadian hospitals	2014	Superficial contamination	Superficial contamination in 40% of cases by cyclophosphamide, in 18% by ifosfamide and 5% by methotrexate.
Bussières JF, Tanguay C, Touzin K, Langlois E, Lefebvre M	Environmental contamination with hazardous drugs in Quebec hospitals	2012	Superficial contamination	Superficial contamination in 52% of cases by cyclophosphamide, 20% by ifosfamide, and 3% by methotrexate.
González Álvarez A, López-Montenegro Soria M.A., Albert Marí A., Martínez Gómez M.A., Porta Oltra B., Jiménez Torres N.V	Exposición a fármacos citotóxicos en el personal sanitario	2012	Superficial contamination	Contamination of surfaces by 5-fluoroacil, gemcitabine and cyclophosphamide in the 90 percentile of the superficial concentration. The same outcome for the 75 percentile, with the exception of one surface with cyclophosphamide.
Viegas S, Pádua M, Veiga AC, Carolino E, Gomes M	Antineoplastic drugs contamination of workplace surfaces in two Portuguese hospitals	2014	Superficial contamination	Superficial contamination in 72.8% of cases with one or various drugs.
Miyake T, Iwamoto T, Tanimura M, Okuda M	Impact of closed-system drug transfer device on exposure of environment and healthcare provider to cyclophosphamide in Japanese hospital	2013	Superficial contamination Biological monitoring	Presence of cytostatics in surfaces and urine. Reduction in contamination at the introduction of a closed system.
Sugiura S, Asano M, Kinoshita K, Tanimura M, Nabeshima T	Risks to health professionals from hazardous drugs in Japan: a pilot study of environmental and biological monitoring of occupational exposure to cyclophosphamide	2011	Superficial contamination Biological monitoring	Presence of cytostatics in surfaces (93.75%) and urine (17.7%).
Siderov J, Kirsa S, McLauchlan R	Reducing workplace cytotoxic surface contamination using a closed-system drug transfer device	2010	Superficial contamination	Contamination in all surfaces studied. Reduction in contamination with a closed system, by 24% at 5 months and 68% at 12 months.
Hon C-Y, Barzan C, Astrakianakis G	Identification of Knowledge Gaps Regarding Healthcare Workers' Exposure to Antineoplastic Drugs: Review of Literature, North America versus Europe	2014	Literature review	Superficial contamination studies on 50 of the 71 articles selected for review.
Kopp B, Schierl R, Nowak D	Evaluation of working practices and surface contamination with antineoplastic drugs in outpatient oncology health care settings	2012	Superficial contamination	Superficial contamination in 60.9% of cases by one or various drugs.
Sessink PJ, Leclercq GM, Wouters DM, Halbardier L, Hammad C, Kassoul N	Environmental contamination, product contamination and workers exposure using a robotic system for antineoplastic drug preparation	2015	Superficial contamination Biological monitoring	Superficial contamination inside the cabinet, vials, bags and gloves. Negative samples for urine.

The main outcomes of each article selected are described below; articles have been grouped by geographical area.

Sessink PJ *et al.*[41] (2013) published a study where they measured superficial contamination by cyclophosphamide in 30 Hospital Pharmacies in the United States from 2004 to 2010, and compared the outcomes when using standard techniques for cytostatic preparation (use of Class II biological safety cabinets, gloves, disposable lab coats, negative pressure techniques with vent filters) vs. the use of a closed system (PhaSeal®). Samples were taken from the inner surfaces of the biological safety cabinet, and floors and tables in the preparation room.

Among their outcomes, they found contamination in all the surfaces studied, both when using standard techniques and when the closed system was used. There was an 86% reduction in the levels of contamination with cyclophosphamide with the use of the closed system, compared with the standard preparation techniques (a mean difference from 0.22 to 0.03 ng/cm^2, $p<0.001$).

Previously, **Sessink PJ** *et al.*[42] (2010) published the outcomes of another study with a similar design, measuring superficial contamination in 22 Hospital Pharmacies in the United States (from 2000 to 2005), caused by cyclophosphamide, ifosfamide and 5-fluorouracil. Initially, samples were taken from all surfaces, with workers using standard techniques. Afterwards, a closed system (PhaSeal®) was introduced for cytostatic preparation, and some months afterwards, samples were taken from the same surfaces again.

The results showed that 78%, 54% and 33% of samples tested positive for cyclophosphamide, ifosfamide and 5-fluorouracil. Subsequently, 68%, 45% and 20% of samples tested positive again for the same drugs. Once again, a statistically significant reduction was obtained in the concentrations of cyclophosphamide ($p<0.001$), ifosfamide ($p<0.001$) and 5-fluorouracil ($p<0.01$), of 95%, 90% and 65% respectively.

There is a series of studies in Canada about contamination, involving an important number of hospitals. The first of these studies was the one by **Bussières** *et al.*[43] (2012), including 25 hospitals out of the 68 hospitals that had been invited to participate. The same 12 zones and the same drugs were determined, and 147 pharmacy samples were obtained in total from the 25 hospitals, as well as 112 samples from the patient care areas of 24 hospitals. The outcomes showed 52% positive samples for cyclophosphamide, 20% for ifosfamide, and 3% for methotrexate. This first study was the one that suggested conducting periodical measurements in order to ensure an adequate practice that reduced the exposure to cytostatic agents.

The most recent is the study by **Berruyer M** *et al.*[44] (2014), which studied contamination in 36 hospitals, determining 6 pharmacy areas and 6 patient care areas. The drugs studied were cyclophosphamide, ifosfamide and methotrexate. There was an analysis of 422 samples; 47% of these samples tested positive for cyclophosphamide, 18% for ifosfamide, and 3% for methotrexate.

The study by **Merger D** *et al.*[45] (2014) involved 33 hospitals in Canada. Samples were taken from the same 12 areas (6 from the pharmacy and 6 from patient care areas), and with the same drugs, during 2012. In this case, 363 samples were analyzed, with positive results in 40% of cases for cyclophosphamide, 18% for ifosfamide, and 5% for methotrexate.

In these studies conducted in Canada, no closed systems were used for preparation or administration, and the contamination outcomes in both settings showed higher percentages for preparation. In all cases, the Heads of Pharmacy in hospitals with at lest 50 beds were contacted and invited to participate in the study, and there was an increasingly higher level of participation, applying the same methodology.

In Spain, **González Álvarez A** *et al.*[46] (2012) measured the contamination by 5-fluorouracil, gemcitabine and cyclophosphamide in the surfaces of the biological safety cabinet, the table for treatment preparation in the waiting room, and the table in the administration ward at Day Hospital, by taking 30 samples from each surface. The outcomes showed higher concentrations in the biological safety cabinet, and the drug with the highest concentration was gemcitabine, even though less preparations were conducted per day (1.75) vs. 5-fluorouracil (6.5). The lowest concentrations were found at the table in the administration ward at Day Hospital.

In Portugal, **Viegas S** *et al.*[47] (2014) analyzed the superficial concentration in 2 hospitals during 2013; for this aim, there was a selection of 5 places associated with preparation and 5 places of administration, and 327 samples were taken, in order to analyze the presence of cyclophosphamide (CP), 5-fluorouracil (5FU) and paclitaxel (PTX). Both hospitals used standard preparation techniques in Class II biological safety cabinets, and personal protection equipment. The outcomes showed that 37% of samples exceeded the limit of quantification, and tested positive for one or more drugs. An additional 35.8% tested positive for one or more drugs, exceeding the limit of detection (LOD) but not the limit of quantification (LOD CP = 0.10 µg/cm^2; 5FU = 3.30 ng/cm^2 and PTX = 0.167 ng/cm^2). It was observed that in the two hospitals, the highest levels of concentration appeared in administration settings, because preparation is highly controlled by the Portuguese Health Authorities.

Kopp B *et al.*[48] (2012) initially sent questionnaires to 137 Day Hospitals in Germany; 39 of these were public and 98 were private. Answers were received from 96 Day Hospitals. From these, only 28 were interested in participating in a test of surface samples in order to detect the presence of 5-fluorouracil, cisplatin, gemcitabine, cyclophosphamide, ifosfamide, methotrexate, docetaxel and paclitaxel. A 60.9% of samples tested po-

sitive (153 for 5-fluorouracil, 172 for cisplatin and 73 for the rest of drugs); the drugs most frequently found were 5-fluorouracil (93.5%) and cisplatin (88.4%), and the least frequent were methotrexate (6.8%) and ifosfamide (26%). No association was found between the amount of drug handled and the level of contamination; but they observed that certain work practices, such as the use of multi-channel closed systems for infusion, and administration systems purged and connected in the Pharmacy Unit, led to a lower number of positive samples.

Miyake T *et al.*[49] (2013) conducted a study at the Ise Red Cross Hospital in Japan, in order to assess the impact on superficial contamination and occupational exposure of using a closed system (PhaSeal®) for cytostatic preparation. For this aim, they selected 6 places to take samples in the preparation area, and they took 24-hour urine samples from 4 pharmacists. The outcomes showed that 4 out of the 6 surfaces tested positive for cyclophosphamide before the introduction of the closed system, and 7 months after implementing it, only 1 of the 6 surfaces tested positive. Regarding urine, 34 samples were taken, and 26 tested positive for cyclophosphamide (77.9% of samples) before using the closed system; again, 31 samples were taken after 7 months, and only 2 tested positive (6.3% of cases).

Sugiura S *et al.*[50] (2011) evaluated the presence of cyclophosphamide at the University Hospital in Nagoya, also in Japan, in 2 departments, Paediatric Haematology and Oncology, which had a biological safety cabinet; and in Haematology and Oncology for adults, which did not have a biological safety cabinet. Surface and urine samples were taken; all superficial samples but one tested positive for cyclophosphamide (93.75% of cases), and concentrations were higher in the department without a biological safety cabinet. In the case of urine samples, only 11 out of 62 samples tested positive (17.7% of cases). The values obtained were higher for those workers that administered than for those who prepared, probably due to the fact that no gloves were used for administration, thus favouring dermal absorption.

Siderov J *et al.*[51] (2010) studied superficial contamination by cyclophosphamide in 2 public hospitals in Australia. Twelve (12) places were selected for taking samples in the preparation area, and this was conducted before the introduction of the closed system (PhaSeal®), as well as at 5 months and 12 months after its introduction; however, one of the hospitals withdrew from the study after the first five months. The outcomes showed that at 5 months the contamination by cyclophosphamide was reduced in 24% (from 82.28 to 62.55 ng/cm^2), and at 12 months, the reduction was of 68% (80.65 to 25.98 ng/cm^2).

The article by **Hon C-Y** *et al.*[52] (2014) conducted a comparative literature review for Europe and North America during the 2004-2012 period. They selected 71 articles in total, with 55 for Europe and 16 for North America; "superficial contamination" was the most frequent term, appearing in 50 of the 71 articles. The authors stated that the majority of the outcomes of European articles could not be extrapolated to North America, due to the different regulations and work practices. They also reached the conclusion that there is a lack of publications in North America studying the occupational exposure to cytostatic agents in biologic samples.

Considering the new technological developments, **Sessink PJ** *et al.*[53] (2015) measured contamination when medication was prepared in bags through a robotic system (CytoCare) by sampling cyclophosphamide; contamination was found inside the robot before and after preparation. Specifically, contamination was found in the reconstituted vials and in the bags after preparation (but not before preparation), as well as in the connections. There was also contamination in the gloves used for preparation and cleaning. On the contrary, no contamination was found in the vials with powder, the environmental samples, and the urine of the staff.

Discussion

Studies before 2010 showed the presence of contamination in different surfaces from the areas of cytostatic preparation and administration. In 1992, Sessink *et al.*[54] had already published an article about the presence of cytostatics in work surfaces and staff urine when measuring the presence of various drugs (4 in total). Many more studies have been published since then, taking measurements in hospital pharmacies and administration areas in all continents, and the vast majority have indicated the existence of different types of contamination.

The more recent studies continue demonstrating the presence of different drugs both in surfaces and in the urine and those handling them. Our analysis suggests that, regardless of the numerous guidelines edited in many countries, and the more or less general use of protection measures, there is still an external release of cytostatic substances when these are reconstituted, prepared and administered in many Hospital Pharmacies, onco-haematological hospitalization wards, and Day Hospitals in many hospitals throughout the 5 continents.

Regarding the surfaces tested, we should highlight that Sessink[41,42], in their 2 studies, took samples from the cabinet surfaces and profiles, the floor in front of the cabinet, and the counter where medication is placed. Berruyer[44], Merger[45] and Bussières[43] increased the number of surfaces to be sampled, including the counter for delivery reception, the shelves for drug storage, the inner front grille of the hood, the floor in front of the cabinet, the counter where medication is placed, and the tray used for transporting the drug to the administration area. Besides, they included 6 surfaces in the administration areas, such as the storage shelves, the counter where saline bags are purged, the arm of the administra-

tion armchair, bedside tables in patient rooms, the drug reception table, and the exterior of administration bags or syringes.

González Álvarez *et al.*[46] measured the surfaces in the biological safety cabinet, the treatment preparation table in the waiting room, and the table at the administration ward in the Day Hospital. Viegas[47] selected 4 preparation areas for sampling: door handles and shelves in the service area; countertops, trays and handles in the clean room; countertops and trays in the waiting room, and shelves and knobs of the storage cupboard. Samples were also taken from countertops, infusion pumps, and the reception counter in the administration areas. Though Kopp[48] provides a less accurate description of the places from which samples were taken, there is a reference to selecting the settings so that the whole work circuit was represented, from drug unpacking, preparation and administration, to waste disposal. It is explained that samples were taken from the floor of the rooms, therapy wards, and toilets. Besides, samples were taken from those work areas where drugs are received and verified, and where the system is purged. It is worth highlighting that samples were taken from IV poles, infusion pumps, treatment chair armrests, and the lids of waste containers.

Siderov[51] defined 12 preparation settings in the Oncology Pharmacy, where samples were taken from: the cabinet workspace, the HEPA filter grille, the front grille, around the cabinet air collector, under the work area, the floor in front of the cabin, the floor of the clean room closer to the waiting room, in the middle of the waiting room, verification areas, mixing device, and preparation and storage trays. In this study, samples were also taken from vials.

Reviewed as a whole, these studies show the important variety of settings and materials where contamination has been looked for and found, both in preparation and in administration.

There are a much lower number of studies testing for the presence of cytostatic substances in urine, if compared with those where samples were taken from surfaces. Only the studies by Miyake[49], Sugiura[50] and Sessink[53], the latter with a robotic system, tested the presence of cyclophosphamide in urine, which was positive in the two Japanese studies, and negative with the robotic system. This could be due to the joint action of using a double pair of gloves and lab coat, together with less handling of the drug, because this was conducted by the robot. It is important to point out that, from the perspective of legal consequences, the presence of contamination in surfaces implies the likelihood of drug exposure for the staff member, while the presence in urine implies that the staff member came into contact with the drug, metabolized it and finally excreted it.

Regarding the drugs determined by sampling, the most usual was cyclophosphamide, because it appears in all articles studied. Besides cyclophosphamide, other drugs determined were ifosfamide[42,43,44,45,51], 5-fluorouracil[42,46,51], methotrexate[43,44,45,51], paclitaxel[46,51], cisplatin[51], gemcitabine[46] and docetaxel[51]. The systems used for sampling were those described by Schamus *et al.*[55] and by Larson *et al.*[56], as well as the Cyto Wipe Kit (Exposure Control Sweden AB, Bohus-Björkö, Sweden), which was the most frequently used, but with a lower variety of drugs. The advantage of this system is that all materials are included in a kit, and cold samples can be sent to a predetermined lab.

In the majority of the studies, except for González Álvarez *et al.*[46], the dosing used or the doses handled were not defined, or the volume of work conducted. This means that no conclusions can be made when testing the concentrations observed in different studies. Only as an example: if we observe the most frequent drug (cyclophosphamide), we find the highest values inside the cabinets (3.86 ng/cm^2 in Sessink[41]) and outside the cabinets (60.5 ng/cm^2 and 7.18 ng/cm^2 in administration counters in Viegas[47] and Sugiura[50] respectively). The robotic system also showed significant levels of contamination in vials and preparation bags (4.78 µg/cm^2 and 1.1 µg/cm^2 respectively).

When analyzing the proportion of samples that tested positive for superficial contamination, it is observed that there were very high proportions for the majority of the drugs studied, such as cyclophosphamide (93.75%, 78% and 52%), 5-fluorouracil (93.5% and 33%), ifosfamide (54%, 26% and 20%) or cisplatin (88.4%). These proportions demonstrated that the work procedures used in the different hospitals studied around the world led to contamination by different drugs of the places where these were handled, both in the Pharmacy and in the administration areas, with the risk entailed for the health of the staff and even for those people accompanying patients.

Some of the articles reviewed[41,42,49,51] valued the use of closed systems to reduce the contamination in surfaces and/or biological fluids of handlers. Both articles by Sessink in American hospitals, excluding his article about robots, showed a reduction in contamination. In 2010, the reduction obtained was of 95%, 90% and 65% for cyclophosphamide, ifosfamide and 5-fluorouracil, respectively, while in 2013 the reduction in contamination levels was of 86% for cyclophosphamide, after 6 months of using the closed system. The article by Miyake achieved a 91.9% reduction in the number of positive results in the urine samples of staff members exposed to cyclophosphamide, after 7 months of using closed systems. The outcomes of the study by Siderov showed a 24% reduction at 5 months, and a 68% reduction at 12 months for cyclophosphamide. In the study by Kopp, no reduction percentage was established, but a correlation was estimated between the use of closed systems and the reduction in superficial contamination ($p = 0.01$). These outcomes allow to claim that the closed system

reduced significantly, but did not eliminate completely, the contamination in work surfaces.

In the year 2000, the NIOSH (National Institute for Occupational Safety and Health) created a team to review the studies on hazardous drugs. This study resulted in the document from 2004: "Alert: Preventing Occupational Exposure to Antineoplastic and Other Hazardous Drugs in Health Care Settings"[57], where a closed system was defined for the first time. This definition was subsequently modified, and the term CSTD (closed system drug transfer device) was created to define a system of drug transfer that prevents mechanically the entry of contaminants inside the system, and the leak of hazardous drugs or vapour concentrations outside the system. This definition was adopted by the ISOPP[51], establishing the division between microbiological contamination and chemical contamination.

The interpretation of this definition has created a discussion about what is understood by closed system[58]. Fortunately, the FDA (U.S. Food and Drug Administration) established in 2012 a new category for CSTDs under the ONB code[59], defining it as: reconstitution and transfer of cytostatic and other hazardous drugs in the healthcare setting, indicated to reduce the exposure of healthcare staff to chemotherapeutical agents in the healthcare setting. This new ONB code provides an additional specification about closed systems in terms of staff protection.

As a conclusion, we can say that in the most recent literature it has been observed that there is superficial contamination in different settings and by different cytostatic drugs. There are a lower number of studies where the presence of cytostatics has also been detected in the urine of handlers. This contamination has been verified in many hospitals from different countries and in different continents, including Spain; this shows the globalization of the problem.

Work setting contamination appears in numerous and different places, both in preparation and in administration; it is usually higher during preparation. In all the cases studied, contamination has been found in the cabinet, in the floor in front of the cabinet, in different tables where drugs are temporarily placed, in the waiting room, and in the storage areas. Different drugs have also been studied, with cyclophosphamide being the most frequent.

The introduction of a closed system drug transfer device (CSTD)[41,42,49,51] reduced the levels of contamination up to a 95%; these reduction rates increased as the closed systems were used over a longer time.

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Con este artículo se pretende actualizar el nivel de evidencia existente relativo a la presencia de contaminación por fármacos citostáticos en el ámbito hospitalario en general y en la farmacia hospitalaria en particular, lo cual se asocia con un riesgo para la salud de los trabajadores relacionados. Al mismo tiempo se pretende determinar cuáles son las medidas más eficaces que reducen esta contaminación.

Este artículo es un texto original y no se encuentra en proceso de evaluación por otra revista, no se trata de publicación redundante, y no existe ningún tipo de conflicto de intereses ni de de relación económica por parte de ninguno de sus autores.

Introducción

Los fármacos citostáticos son sustancias citotóxicas diseñadas y utilizadas para causar disfunción celular, inhibiendo el crecimiento de las células cancerosas mediante la alteración del metabolismo y el bloqueo de la división y la reproducción celular. Este daño no es selectivo para las células tumorales, sino que afecta a todas las células del organismo, resultando efectos tóxicos adversos principalmente hematopoyéticos, renales, hepáticos, digestivos y dérmicos.

Su uso se inició en la década de los 50 tras la observación de aplasias medulares en militares expuestos a gas mostaza durante la segunda guerra mundial, lo que propició la utilización de mostazas nitrogenadas en el tratamiento de la enfermedad de Hodgkin[1].

La International Agency for Research on Cancer (IARC) ha clasificado a muchos de estos fármacos como cancerígenos, mutagénicos y/o tóxicos para la reproducción. En las Monografías 26[2] y 76[3], ambas disponibles en la web de la IARC, se pueden consultar los citostáticos incluidos y su clasificación, la cual se muestra en la tabla 1.

Tabla 1. *Clasificación de cancerígenos según la IARC*

Categoría	Definición
1	El agente es carcinógeno en humanos
2A	El agente es probablemente carcinógeno en humanos
2B	El agente es posiblemente carcinógeno en humanos
3	El agente no puede ser clasificado respecto a su carcinogenidad en humanos
4	El agente es probablemente no carginógeno en humanos

Actualmente, once fármacos y ciertas terapias combinadas pertenecen al grupo 1 (azatioprina, busulfan, ciclofosfamida, clorambucilo, clornafacina, dietilestilbestrol, melfalán, semustina, tamoxifeno, tiotepa, treosulfán y MOPP), doce fármacos pertenecen al grupo 2A (adriamicina, azacitidina, carmustina, ciclosporina, cisplatino, clorozotocina, etopósido, lomustina, mecloretamina, procarbacina, tenipósido y testosterona) y once fármacos pertenecen al grupo 2B.

En el año 1979 aparece la primera publicación en relación a la exposición laboral a citostáticos y su relación con los riesgos para la salud en el estudio de Falck *et al.*[4]. En dicho estudio, mediante el test de Ames, se analizó la acción mutágena en la orina de enfermeras que preparaban y administraban fármacos citostáticos, sin medidas de protección. Se puso en evidencia la existencia de riesgos para la salud en casos de exposición crónica a algunos de estos fármacos en pequeñas cantidades.

Estudios posteriores han manifestado la posibilidad de daños a los trabajadores expuestos a citostáticos, afectando a la gestación[5,6,7,8,9,10] (abortos, malformaciones), efectos crónicos[11,12] y efectos agudos[13,14,15,16].

A partir de la exposición laboral, diversos autores estudiaron la posible relación con efectos oncogénicos[17,18,19,20,21]. Aunque no se ha podido establecer claramente una relación entre la exposición prolongada a niveles bajos (caso de la actividad laboral) y un efecto oncogénico, se consideran un factor de riesgo potencial, por lo que deben emplearse todas las medidas disponibles para minimizar el riesgo de exposición.

Aquellos trabajadores que entren en contacto con citostáticos podrían estar expuestos a un riesgo para su salud. Esta exposición puede ocurrir durante todo el ciclo del fármaco que va desde su manufacturación y distribución hasta la preparación, administración y eliminación de los residuos. Así pues, los trabajadores expuestos pueden ser tanto de la industria farmacéutica como personal sanitario (médicos, farmacéuticos, personal de enfermería, técnicos sanitarios y celadores) encargados de la preparación, administración, transporte y eliminación de residuos.

La preocupación en torno a la manipulación de citostáticos ha supuesto que diferentes países y organizaciones elaboren Guías para su correcta manipulación. En la tabla 2 se presentan algunas de las Guías significativas[22-40] y recientes que están publicadas.

Una vía de exposición a citostáticos podría producirse a través de la contaminación de los lugares de trabajo. Por lo tanto, es de gran importancia determinar la presencia de citostáticos en superficies de trabajo y, sobre todo, las posibles medidas a aplicar para eliminar o reducir dicha contaminación.

El objetivo de esta revisión bibliográfica es disponer de la evidencia más actual respecto de la exposición a citostáticos en el ámbito laboral y conocer las posibles medidas preventivas que se puedan aplicar para evitar la exposición laboral a citostáticos.

Tabla 2. *Guías para la manipulación segura de fármacos citostáticos ordenadas alfabéticamente*

Título	Autor/es
American Society of Clinical Oncology/Oncology Nursing Society chemotherapy administration safety standards[22]	Jacobson JO, Polovich M, McNiff KK, LeFebvre KB, Cummings C, Galioto M, Bonelli KR and McCorkle MR
ASHP Guidelines on Handling Hazardous Drugs[23]	American Society of Health-System Pharmacists
Australian consensus guidelines for the safe handling of monoclonal antibodies for cancer treatment by healthcare personnel[24]	Alexander M *et al.*
Chemotherapy and biotherapy guidelines and recommendations for practice[25]	Brown KA, Esper P, Kelleher LO, O'Neill JEB, Polovich M and White JM
Controlling occupational exposure to hazardous drugs[26]	OSHA
Guidelines for the Safe handling of Cytotoxic drugs And related waste[27]	Occupational Safety and Health Service. Department of Labour. Wellington. New Zealand
Guidelines for the safe handling of hazardous drugs: consensus recommendations[28]	Chaffee BW, Armistead JA, Benjamin BE, Cotugno MC, Forrey RA, Hintzen BL, Pfeiffenberger T and Stevenson JG
Improving Patient and Worker Safety: Opportunities for Synergy, Collaboration and Innovation[29]	TheJointCommission
ISOPP Standards of Practice[30]	ISOPP
Medicamentos citostaticos[31]	Gamundi MC *et al.*
Preventing Occupational Exposure to Antineoplastic and Other Hazardous Drugs in Health Care Settings[32]	NIOSH
Safe handling and administration of antineoplastic chemotherapy[33]	Eisenberg, S
Safe handling of cytotoxic drugs[34]	HSE (Health and Safety Executive)-UK
Safe handling of hazardous chemotherapy drugs in limited-resource settings[35]	PAHO/WHO
Safe handling of hazardous drugs[36]	Polovich M, Bolton DL, Eisenberg S, Glynn-Tucker EM, Howard-Ruben J, McDiarmid MA, Power LA and Smith CA
Safe handling of hazardous drugs: reviewing standards for worker protection[37,38]	Power LA and Polovich M
Safe handling of oral chemotherapeutic agents in clinical practice: recommendations from an international pharmacy panel[39]	Goodin S, Griffith N, Chen B, Chuk K, Daouphars M, Doreau C, Patel RA, Schwartz R, Tames MJ, Terkola R, Vadnais B, Wright D and Meier K
Standards of Practice: Safe Handling of Cytotoxics[40]	International Society of Oncology Pharmacy Practitioners

Material y métodos

Se realizó una revisión bibliográfica utilizando como fuentes de información las siguientes bases de datos: MEDLINE, COCHRANE PLUS y WEB OF SCIENCE.

Se estableció el periodo de estudio de los últimos 5 años.

La búsqueda se estableció en base a las palabras clave siguientes: surface contamination, antineoplastic drug, hazardous drug, drug preparation, occupational exposure, safe handling, closed-system transfer device. Después se llevó a cabo una combinación de dichas palabras clave (ejemplo: surface contamination AND hazardous drug, safe handling AND antineoplastic, surface contamination AND antineoplastic) en las diferentes bases de datos definiendo la búsqueda según los siguientes criterios:

Criterios de inclusión

1. Estudios que describan la relación entre la manipulación de citostáticos y la exposición laboral.
2. Humanos.
3. Año de publicación: entre 2010 y 2015.
4. Artículos publicados en inglés y español.

Criterios de exclusión

1. Artículos redundantes.
2. No originales o revisiones (ejemp: cartas al director, editoriales).

Se obtuvo una colección de 91 artículos, de la cual se eliminaron los duplicados o redundantes y se procedió a realizar un análisis de pertinencia revisando los títulos y los resúmenes de los artículos, quedando seleccionados

un total de 13 artículos que conforman la base del estudio.

Resultados

En la tabla 3 se presentan las principales características de los 13 artículos que componen el estudio, tales como: autores, título, año, aspecto estudiado y resultados principales del estudio.

A continuación se describen los principales resultados de cada uno de los artículos seleccionados, los cuales se han agrupado geográficamente.

Sessink PJ *et al.*[41] (2013) publicaron un estudio donde midieron la contaminación superficial por ciclofosfamida en 30 farmacias hospitalarias de Estados Unidos durante los años 2004 al 2010 y compararon los resultados cuando se emplean las técnicas estándar de preparación de citostáticos (uso de cabinas de seguridad biológica clase II, guantes, batas desechables, técnicas de presión negativa con filtros de venteo) frente a cuando se utiliza un sistema cerrado (PhaSeal®). Las muestras fueron tomadas en las superficies interiores de la cabina de seguridad biológica, suelos y mesas de la sala de preparación.

Entre sus resultados encontraron contaminación en todas las superficies estudiadas, tanto en los casos de empleo de técnicas estándar como cuando se utilizó el sistema cerrado. Se observó una reducción en los niveles de contaminación con ciclofosfamida del 86% con el uso del sistema cerrado en comparación con las técnicas de preparación estándar (diferencia de medias de 0,22 a 0,03 ng/cm^2, $p<0,001$).

Previamente, **Sessink PJ** *et al.*[42] (2010) publicaron los resultados de otro estudio con un diseño similar donde se midió la contaminación superficial en 22 farmacias hospitalarias de Estados Unidos (del 2000 al 2005) originada por ciclofosfamida, ifosfamida y 5-fluorouracilo. Inicialmente se realizó la toma de muestras en todas las superficies con los trabajadores utilizando técnicas estándar. Después se introdujo un sistema cerrado (PhaSeal®) para la preparación de citostáticos y algunos meses después se volvió a muestrear otra vez las mismas superficies.

Los resultados mostraron que el 78%, 54% y 33% de las muestras dieron positivo para ciclofosfamida, ifosfamida y 5-fluorouracilo. Posteriormente el 68%, 45% y 20% de las muestras volvieron a dar positivo para los mismos fármacos. Nuevamente se obtuvo una reducción estadísticamente significativa en las concentraciones de ciclofosfamida ($p<0,001$), ifosfamida ($p<0,001$) y 5-fluorouracilo ($p<0,01$) del 95%, 90% y 65% respectivamente.

Hay una serie de estudios en Canadá sobre contaminación en los que han participado un número importante de hospitales. El primero de estos estudios fue el de **Bussières** *et al.*[43] (2012) en el que participaron 25 hospitales de 68 que fueron invitados a participar. Se establecieron las mismas 12 zonas y los mismos fármacos obteniéndose un total de 147 muestras de farmacia de los 25 hospitales y 112 muestras de zonas asistenciales de 24 hospitales. Los resultados mostraron un 52% de muestras positivas para ciclofosfamida, 20% para ifosfamida y 3% para metotrexato. Este primer estudio fue el que propuso realizar mediciones periódicas para asegurar una práctica correcta que reduzca la exposición a citostáticos.

El más reciente es el de **Berruyer M** *et al.*[44] (2014) que estudiaron la contaminación en 36 hospitales, estableciendo 6 zonas de la farmacia y 6 zonas de atención a pacientes. Los fármacos estudiados fueron ciclofosfamida, ifosfamida y metotrexato. Se analizaron 422 muestras de las cuales el 47% dieron positivo para ciclofosfamida, 18% para ifosfamida y 3% para metotrexato.

En el estudio de **Merger D** *et al.*[45] (2014) participaron 33 hospitales de Canadá. Se muestreó en las mismas 12 zonas (6 de farmacia y 6 de pacientes) y con los mismos fármacos durante el año 2012. En este caso se analizaron 363 muestras con resultados positivos en el 40% de los casos a ciclofosfamida, 18% para ifosfamida y 5% para metotrexato.

En estos estudios realizados en Canadá no se emplearon sistemas cerrados, tanto en la preparación como en la administración, mostrando resultados de contaminación en ambos lugares con porcentajes mayores para la preparación. En todos los casos, se contactó con la jefatura de Farmacia de hospitales de al menos 50 camas, invitándoles a participar en el estudio, obteniendo cada vez un mayor grado de participación aplicando la misma metodología.

En España, **Gonzalez Alvarez A** *et al.*[46] (2012) midieron la contaminación de 5-fluorouracilo, gemcitabina y ciclofosfamida en las superficies de la cabina de seguridad biológica, mesa de preparación de tratamientos en antecámara y mesa de la sala de administración en hospital de día, tomando 30 muestras por cada superficie. Los resultados muestran las mayores concentraciones en la cabina de seguridad biológica, y el fármaco con mayor concentración fue la gemcitabina a pesar de realizar menos preparaciones por día (1,75) que el 5-fluorouracilo (6,5). Las concentraciones menores correspondieron a la mesa de la sala de administración en hospital de día.

En Portugal, **Viegas S** *et al.*[47] (2014) analizaron la contaminación superficial en 2 hospitales durante el año 2013, para lo que se seleccionaron 5 lugares relacionados con la preparación y 5 lugares de administración, y tomaron 327 muestras en las que analizaron la presencia de ciclofosfamida (CP), 5-fluorouracilo (5FU) y paclitaxel (PTX). En ambos hospitales se empleaban técnicas estándar para la preparación en cabinas de seguridad biológica clase II y equipos de protección personal. Los resultados mostraron que un 37% de las muestras superaron el límite de cuantificación y dieron positivo a uno o varios fármacos. Un 35,8% adicional dieron positivo a

Tabla 3. *Resumen de los artículos incluidos en la revisión*

Autores	Titulo	Año	Aspectos estudiado	Resultados
Sessink PJ, Trahan J, Coyne JW	Reduction in Surface Contamination With Cyclophosphamide in 30 US Hospital Pharmacies Following Implementation of a Closed-System Drug Transfer Device	2013	Contaminación superficial	Contaminación en todas las superficies estudiadas. Reducción en los niveles de contaminación con ciclofosfamida del 86% con el uso del sistema cerrado.
Sessink PJ, Connor TH, Jorgenson JA, Tyler TG	Reduction in surface contamination with antineoplastic drugs in 22 hospital pharmacies in the US following implementation of a closed-system drug transfer device	2010	Contaminación superficial	Contaminación de superficies por ciclofosfamida, ifosfamida y 5-fluoroacilo. Reducción estadísticamente significativa en los niveles de contaminación con el uso del sistema cerrado.
Berruyer M, Tanguay C, Caron NJ, Lefebvre M, Bussières JF	Multicenter study of environmental contamination with antineoplastic drugs in 36 Canadian hospitals: a 2013 follow-up study	2014	Contaminación superficial	Contaminación superficial en el 47% de los casos por ciclofosfamida, 18% por ifosfamida y3% por metrotexato.
Merger D, Tanguay C, Langlois E, Lefebvre M, Bussières JF	Multicenter study of environmental contamination with antineoplastic drugs in 33 Canadian hospitals	2014	Contaminación superficial	Contaminación superficial en el 40% de los casos por ciclofosfamida, 18% por ifosfamida y5% por metrotexato.
Bussières JF, Tanguay C, Touzin K, Langlois E, Lefebvre M	Environmental contamination with hazardous drugs in Quebec hospitals	2012	Contaminación superficial	Contaminación superficial en el 52% de los casos por ciclofosfamida, 20% por ifosfamida y3% por metrotexato.
González Álvarez A, López-Montenegro Soria M.A., Albert Marí A., Martínez Gómez M.A., Porta Oltra B., Jiménez Torres N.V	Exposición a fármacos citotóxicos en el personal sanitario	2012	Contaminación superficial	Contaminación de las superficies por 5-fluoroacilo, gemcitabina y ciclofosfamida en el percentil 90 de la concentración superficial. Igual resultado para el percentil 75 con excepción de una superficie con ciclofosfamida.
Viegas S, Pádua M, Veiga AC, Carolino E, Gomes M	Antineoplastic drugs contamination of workplace surfaces in two Portuguese hospitals	2014	Contaminación superficial	Contaminación superficial en el 72,8% de los casos a uno o varios fámacos.
Miyake T, Iwamoto T, Tanimura M, Okuda M	Impact of closed-system drug transfer device on exposure of environment and healthcare provider to cyclophosphamide in Japanese hospital	2013	Contaminación superficial Monitorización biológica	Presencia de citostáticos en superficies y orina. Reducción de la contaminación al introducir un sistema cerrado.
Sugiura S, Asano M, Kinoshita K, Tanimura M, Nabeshima T	Risks to health professionals from hazardous drugs in Japan: a pilot study of environmental and biological monitoring of occupational exposure to cyclophosphamide	2011	Contaminación superficial Monitorización biológica	Presencia de citostáticos en superficies (93,75%) y orina (17,7%).
Siderov J, Kirsa S, McLauchlan R	Reducing workplace cytotoxic surface contamination using a closed-system drug transfer device	2010	Contaminación superficial	Contaminación en todas las superficies estudiadas. Reducción de la contaminación con sistema cerrado un 24% a los 5 meses y un 68% a los 12 meses.
Hon C-Y, Barzan C, Astrakianakis G	Identification of Knowledge Gaps Regarding Healthcare Workers' Exposure to Antineoplastic Drugs: Review of Literature, North America versus Europe	2014	Revisión de la literatura	Estudios de contaminación superficial en 50 de los 71 artículos seleccionados para su revisión.
Kopp B, Schierl R, Nowak D	Evaluation of working practices and surface contamination with antineoplastic drugs in outpatient oncology health care settings	2012	Contaminación superficial	Contaminación superficial en el 60,9% de los casos a uno o varios fármacos.
Sessink PJ, Leclercq GM, Wouters DM, Halbardier L, Hammad C, Kassoul N	Environmental contamination, product contamination and workers exposure using a robotic system for antineoplastic drug preparation	2015	Contaminación superficial Monitorización biológica	Contaminación superficial en el interior de la cabina, viales, bolsas y guantes. Muestras negativas para orina.

uno o varios fármacos superando el límite de detección (LOD) pero no el de cuantificación (LOD CP = 0,10 µg/cm^2; 5FU = 3,30 ng/cm^2 y PTX = 0,167 ng/cm^2). En los 2 hospitales se observó que los valores más altos de concentración se dieron en los lugares de administración debido a que la preparación está más controlada por parte de las autoridades sanitarias portuguesas.

Kopp B *et al.*[48] (2012) inicialmente enviaron cuestionarios a 137 hospitales de día de Alemania de los cuales 39 eran públicos y 98 privados, respondiendo 96 de ellos. De éstos, sólo 28 estuvieron interesados en participar en un muestreo de superficies para detectar la presencia de 5-fluorouracilo, cisplatino, gemcitabina, ciclofosfamida, ifosfamida, metotrexato, docetaxel y paclitaxel. Un 60,9% de las muestras (153 para 5-fluorouracilo, 172 para cisplatino y 73 para el resto de fármacos) dieron positivas, siendo los fármacos más frecuentemente encontrados el 5-fluorouracilo (93,5%) y el cisplatino (88,4%), y los menos frecuentes el metrotexato (6,8%) y la ifosfamida (26%). No encontraron relación entre la cantidad de fármaco manipulado y el nivel de contaminación, pero sí observaron que determinadas prácticas de trabajo, como el uso de sistemas cerrados multicanal para la infusión y sistemas de administración purgados y conectados en farmacia, dieron un menor número de muestras positivas.

Miyake T *et al.*[49] (2013) llevaron a cabo un estudio en el hospital japonés "Ise Red Cross Hospital" para valorar cuál sería el efecto del empleo de un sistema cerrado (PhaSeal®) en la preparación de citostáticos sobre la contaminación superficial y la exposición laboral. Para ello seleccionaron 6 lugares del área de preparación donde muestrear y tomaron muestras de orina de 24 h a 4 farmacéuticos. Los resultados mostraron que 4 de las 6 superficies dieron positivo a ciclofosfamida antes de la introducción del sistema cerrado y 7 meses después de comenzar a trabajar con él sólo 1 de la 6 superficies dio positivo. En cuanto a la orina, se tomaron 34 muestras de las que 26 dieron positivo a ciclofosfamida (77,9% de las muestras) antes de utilizar el sistema cerrado y nuevamente 7 meses después se tomaron 31 muestras de las que 2 dieron positivo (6,3% de los casos).

Sugiura S *et al.*[50] (2011) evaluaron la presencia de ciclofosfamida en el hospital universitario de Nagoya, también en Japón, en 2 departamentos: hematología y oncología pediátrica, que disponía de cabina de seguridad biológica, y hematología y oncología de adultos, que no disponía de cabina de seguridad biológica. Se tomaron muestras de superficie y de orina, resultando que todas la muestras superficiales dieron positivo a ciclofosfamida menos una (93,75% de los casos), siendo mayores las concentraciones en el departamento sin cabina de seguridad biológica. En el caso de las muestras de orina, de las 62 muestras sólo 11 dieron positivo (17,7% de los casos). Los valores obtenidos fueron más altos para aquellos trabajadores que administraban que los que preparaban, probablemente debido a que la administración se realizó sin guantes, lo que favoreció la absorción dérmica.

Siderov J *et al.*[51] (2010) estudiaron la contaminación superficial de ciclofosfamida en 2 hospitales públicos de Australia. Se determinaron 12 lugares de la zona de preparación donde realizar los muestreos y éstos se llevaron a cabo antes de la introducción del sistema cerrado (PhaSeal®), así como a los 5 meses y a los 12 meses después de su introducción, aunque uno de los hospitales abandonó el ensayo después de los 5 primeros meses. Los resultados muestran que a los 5 meses la contaminación por ciclofosfamida se redujo un 24% (de 82,28 a 62,55 ng/cm^2) y a los 12 meses la reducción fue del 68% (80,65 a 25,98 ng/cm^2).

El artículo de **Hon C-Y** *et al.*[52] (2014) lleva a cabo una revisión de la literatura a modo comparativo entre Europa y América del Norte para el periodo 2004-2012. Seleccionaron un total de 71 artículos de los que 55 correspondieron a Europa y 16 a América del Norte, siendo el término "contaminación superficial" el que más veces apareció (50 de los 71 artículos). Los autores establecen que la mayoría de los resultados de los artículos europeos no serían extrapolables a América del Norte debido a la diferente normativa y prácticas de trabajo. También concluyen que en América del Norte existe un déficit de publicaciones donde se estudie la exposición laboral a citostáticos en muestras biológicas.

Contemplando las nuevas posibilidades tecnológicas, **Sessink PJ** *et al.*[53] (2015) midieron la contaminación cuando se prepara la medicación en bolsas mediante un sistema robótico (CytoCare) muestreando ciclofosfamida, hallándose contaminación en el interior del robot antes y después de la preparación. Concretamente se encontró contaminación en los viales reconstituidos y en las bolsas después de la preparación (pero no antes de la preparación), al igual que en las conexiones. Hubo también contaminación en los guantes usados para la preparación y la limpieza. Por el contrario no se detectó contaminación en los viales con polvo, en las muestras ambientales y en las orinas de los trabajadores.

Discusión

Estudios anteriores a 2010 mostraron la existencia de contaminación en distintas superficies del área de preparación y administración de citostáticos. Sessink *et al.*[54]. En el año 1992 ya publicaron sobre la presencia de citostáticos en superficies de trabajo y en orina de trabajadores al medir la presencia de varios fármacos (4 en total). Muchos más estudios han sido publicados desde entonces midiendo en farmacias y áreas de administración de hospitales de todos los continentes y la gran mayoría han indicado la existencia de contaminación de diversos tipos.

Los estudios más recientes siguen demostrando la presencia de diferentes fármacos tanto en superficies

como en orina de manipuladores. Nuestro análisis sugiere que, a pesar de las numerosas Guías editadas en numerosos países, y el uso más o menos general de medidas de protección, se sigue produciendo una liberación de citostáticos al exterior cuando se reconstituyen, se preparan y se administran citostáticos en muchas farmacias hospitalarias, plantas de hospitalización onco-hematológicas y hospitales de día de numerosos hospitales de los 5 continentes.

En relación a las superficies analizadas indicar que Sessink[41,42], en sus 2 estudios, muestreó las superficies y perfiles de la cabina, el suelo frente a la cabina y el mostrador donde se deposita la medicación. Berruyer[44], Merger[45] y Bussières[43] ampliaron el número de superficies a muestrear incluyendo el mostrador de recepción de envíos, los estantes de almacenamiento de fármacos, la rejilla delantera interior de la campana, el suelo frente a la cabina, el mostrador donde se deposita la medicación y la bandeja utilizada para el transporte del fármaco a la zona de administración. Además incluyeron 6 superficies de áreas de administración, como estantes de almacenamiento, el mostrador donde se purgan los sueros, el brazo del sillón de administración, las mesillas de las habitaciones de los pacientes, la mesa de recepción de fármacos y el exterior de las bolsas o jeringas de administración.

González Álvarez *et al.*[46] midieron en las superficies de la cabina de seguridad biológica, mesa de preparación de tratamientos en antecámara y mesa de la sala de administración en hospital de día. Viegas[47] eligió para muestrear 4 zonas de la preparación: manillas de puertas y estanterías de la zona de servicio; encimeras, bandejas y manillas de la sala blanca; encimeras y bandejas de la antesala y estanterías y pomos del armario de almacenamiento. Muestreó también las encimeras, bombas de infusión y mostrador de recepción de las áreas de administración. Aunque Kopp[48] hace una definición menos exacta de los lugares donde muestreó, hace referencia a que se seleccionaron las ubicaciones de manera que todo el circuito de trabajo quedase representado, desde el desembalaje de los fármacos, las preparaciones, la administración hasta la eliminación de los residuos. Explica que se recogieron muestras de suelo de las habitaciones, salas de terapia y aseos. Además, se muestrearon las áreas de trabajo, donde se reciben los fármacos y verifican, y donde se realiza la purga del sistema. También hay que señalar que fueron muestreados los porta sueros, las bombas de infusión, los apoyabrazos de las sillas de tratamiento y las tapas de los contenedores de residuos.

Siderov[51] definió 12 lugares de la preparación en farmacia oncológica donde muestreó: el espacio de trabajo de la cabina, la rejilla del filtro HEPA, la rejilla delantera, alrededor del colector de aire de la cabina, por debajo de la zona de trabajo, suelo frente a la cabina, suelo de la sala blanca pegado a la antecámara, en el centro de la antecámara, zonas de verificación, dispositivo de mezcla y bandejas de preparación y almacenamiento. En este estudio también se muestrearon los viales.

El conjunto de los estudios revisados nos muestra la importante diversidad de lugares y material donde se ha buscado y encontrado contaminación, tanto en preparación como administración.

Los estudios donde se determina la presencia de citostáticos en orina son mucho menores si los comparamos con aquellos donde se muestrean superficies. Tan solo los estudios de Miyake[49], Sugiura[50] y Sessink[53], éste último con sistema robótico, estudiaron la presencia de ciclofosfamida en orina, siendo positivo en los dos estudios de Japón y no así con el sistema robótico. Esto podría deberse a la acción conjunta de la utilización de doble par de guantes y bata junto con la menor manipulación del fármaco, ya que lo realiza el robot. Es importante señalar que desde un punto de vista de consecuencias legales, la presencia de contaminación en superficies supone la probabilidad de que el trabajador se exponga al fármaco mientras que la presencia en orina supone que el trabajador entró en contacto con el fármaco, lo metabolizó y finalmente lo excretó.

En relación con los fármacos determinados por el muestreo, el más habitual es la ciclofosfamida ya que está presente en todos los artículos estudiados. Además de la ciclofosfamida también se determinaron la ifosfamida[42,43,44,45,51], el 5-fluorouracilo[42,46,51], metotrexato[43,44,45,51], paclitaxel[46,51], cisplatino[51], gemcitabina[46] y docetaxel[51]. Los sistemas para el muestreo empleados fueron los descritos por Schamus *et al.*[55] y por Larson *et al.*[56], así como el Cyto Wipe Kit (Exposure Control Sweden AB, Bohus-Björkö, Sweden), siendo este último el que se usó con más frecuencia pero con una menor variedad de fármacos. Este sistema dispone de la ventaja de poder disponer de todo el material en un kit y enviar las muestras en frío a un laboratorio predeterminado.

La mayoría de los estudios, salvo González Álvarez *et al.*[46], no definen las dosificaciones empleadas ni las dosis manipuladas ni tampoco el volumen de trabajo realizado. Esto implica que al analizar las concentraciones observadas en distintos estudios no se puedan extraer conclusiones. Sólo a modo de ejemplo si observamos el fármaco más frecuente (ciclofosfamida) encontramos los valores más altos en el interior de las cabinas (3,86 ng/cm^2 en Sessink[41]) y fuera de ellas (60,5 ng/cm^2 y 7,18 ng/cm^2 en mostradores de administración en Viegas[47] y Sugiura[50] respectivamente). El sistema robótico también mostró niveles de contaminación significativos en los viales y bolsas de preparación (4,78 µg/cm^2 y 1,1 µg/cm^2 respectivamente).

Analizando el porcentaje de muestras que dan positivo a contaminación superficial, se observa que la mayoría de fármacos estudiados dan porcentajes muy altos como la ciclofosfamida (93,75%, 78% y 52%), el 5-fluorouracilo (93,5% y 33%), ifosfamida (54%, 26% y 20%) o cisplatino (88,4%). Tales porcentajes eviden-

cian que los procedimientos de trabajo empleados en los distintos hospitales estudiados por todo el mundo suponen la contaminación por diversos fármacos de los lugares donde se manipulan, tanto en la farmacia como en las áreas donde se administra, con el riesgo que esto conlleva para la salud de los trabajadores e incluso los acompañantes de los pacientes.

Algunos de los trabajados revisados[41,42,49,51] valoran el uso de sistemas cerrados para reducir la contaminación superficial y/o en fluidos biológicos de manipuladores. Los 2 trabajos de Sessink, sin contar su trabajo sobre los robots, en hospitales estadounidenses muestran una reducción de la contaminación. En el año 2010 la reducción obtenida fue del 95%, 90% y 65% para ciclofosfamida, ifosfamida y 5-fluorouracilo respectivamente, mientras que en 2013 la reducción en los niveles de contaminación fue del 86% para ciclofosfamida después de 6 meses de emplear el sistema cerrado. El trabajo de Miyake obtiene una reducción del 91,9% de positivos en las muestras de orina de los trabajadores expuestos a ciclofosfamida después de 7 meses de uso de sistemas cerrados. Los resultados del trabajo de Siderov muestran una reducción de un 24% a los 5 meses y del 68% a los 12 meses para ciclofosfamida. En el trabajo se Kopp no se establece un porcentaje de reducción aunque si se calcula una correlación entre el empleo de sistemas cerrados y la reducción de la contaminación superficial ($p = 0,01$). Estos resultados permiten decir que el sistema cerrado redujo significativamente, pero no eliminó totalmente, la contaminación de las superficies de trabajo.

En el año 2000, la NIOSH (National Institute for Occupational Safety and Health) creó un equipo que revisase los estudios sobre fármacos peligrosos. Este trabajo dio como resultado el documento del 2004 "Alert: Preventing Occupational Exposure to Antineoplastic and Other Hazardous Drugs in Health Care Settings"[57] donde se define por primera vez un sistema cerrado (closed system). Esta definición fue posteriormente modificada creándose el término CSTD (closed system drug transfer device) como un sistema de transferencia de fármacos que prohíbe mecánicamente el paso de contaminantes al interior del sistema y la fuga de fármacos peligrosos o concentraciones de vapor fuera del sistema. Esta definición fue adaptada por la ISOPP[51], estableciendo la división entre contaminación microbiológica y contaminación química.

La interpretación que se ha hecho de esta definición ha generado discusión sobre qué se entiende por sistema cerrado[58]. Afortunadamente, la FDA (U.S. Food and Drug Administration) estableció en el año 2012 una nueva categoría para los CSTD bajo el código ONB[59], definiéndolo como: reconstituir y transferir citostáticos y otros fármacos peligrosos en el ámbito sanitario, estando indicado para reducir la exposición del personal sanitario a los agentes quimioterápicos del ámbito sanitario. Este nuevo código ONB nos da una especificación adicional sobre los sistemas cerrados en relación con la protección de los trabajadores.

A modo de conclusión podemos decir que se observa en la literatura más reciente la existencia de contaminación superficial en diferentes espacios y por diferentes fármacos citostáticos. Existen un número menor de estudios dónde también se ha hallado presencia de citostáticos en orina de manipuladores. Esta contaminación se ha verificado en muchos hospitales de diferentes países y en diferentes continentes, incluido España, mostrando la globalidad del problema.

La contaminación de los espacios de trabajo se produce en numerosos y diferentes sitios, tanto en la preparación como en la administración, siendo habitualmente mayor en la preparación. En todos los casos estudiados se ha encontrado contaminación en la cabina, en el suelo frente a la cabina, en diferentes mesas donde se depositan temporalmente los fármacos, en la antecámara y en las zonas de almacén. También se han estudiado diferentes fármacos, siendo el más frecuente la ciclofosfamida.

La introducción de un sistema cerrado de transferencia[41,42,49,51] (CSTD) disminuyó los niveles de contaminación, con reducciones de hasta el 95%, aumentando estos porcentajes de reducción conforme más tiempo se usa el sistema cerrado.

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