Guidelines for safe handling of hazardous drugs: A systematic review

Mari A. Bernabeu-Martínez¹, Mateo Ramos Merino², Juan M. Santos Gago², Luis M. Álvarez Sabucedo², Carmina Wanden-Berghe³, Javier Sanz-Valero¹*

¹ Department of Public Health and History of Science, School of Medicine, Miguel Hernandez University, Elche, Spain, ² Department of Telematics Engineering, Telecommunication Engineering School of the University of Vigo, Vigo, Spain, ³ Health and Biomedical Research Institute of Alicante, University General Hospital of Alicante, Alicante, Spain

* jsanz@umh.es

Abstract

Objective
To review the scientific literature related to the safe handling of hazardous drugs (HDs).

Method
Critical analysis of works retrieved from MEDLINE, the Cochrane Library, Scopus, CINHAL, Web of Science and LILACS using the terms "Hazardous Substances", "Antineoplastic Agents" and "Cytostatic Agents", applying "Humans" and "Guidelines" as filters. Date of search: January 2017.

Results
In total, 1100 references were retrieved, and from those, 61 documents were selected based on the inclusion and exclusion criteria: 24 (39.3%) documents related to recommendations about HDs; 27 (44.3%) about antineoplastic agents, and 10 (33.3%) about other types of substances (monoclonal antibodies, gene medicine and other chemical and biological agents). In 14 (23.3%) guides, all the stages in the manipulation process involving a risk due to exposure were considered. Only one guide addressed all stages of the handling process of HDs (including stages with and without the risk of exposure). The most described stages were drug preparation (41 guides, 67.2%), staff training and/or patient education (38 guides, 62.3%), and administration (37 guides, 60.7%). No standardized informatics system was found that ensured quality management, traceability and minimization of the risks associated with these drugs.

Conclusions
Most of the analysed guidelines limit their recommendations to the manipulation of antineoplastics. The most frequently described activities were preparation, training, and administration. It would be convenient to apply ICTs (Information and Communications Technologies) to manage processes involving HDs in a more complete and simpler fashion.
Introduction

The toxic properties of cytostatic drugs have been well known since the 1940s when they began to be used in the oncological field [1]. However, it took nearly four decades before Falck et al. [2] published the first paper describing an increase in mutagenicity in nurses working with cytostatic drugs, demonstrating for the first time the potential occupational risk involved in the manipulation of these medicines. The publication of a series of subsequent studies [3–6], whose results pointed to the possible relationship between occupational exposure to cytostatics and the increase of various health effects, was key for different government organizations and scientific societies to establish the first guidelines for the safe handling of this type of medication. In 1981, the Society of Hospital Pharmacists of Australia (SHPA) published the first guide for the safe management of cytostatic medicines [7], and four years later, their North American colleagues followed suit [8, 9].

The concept of a “hazardous drug” (HD), which until then was exclusively associated with cytostatic drugs, was introduced in 1990 by the American Society of Hospital Pharmacists (ASHP) [10] and adopted in 2004 by the National Institute for Occupational Safety and Health (NIOSH). This led to the current and internationally accepted definition: any medicinal product that presents in humans one or more of the following hazard criteria: carcinogenicity, teratogenicity or other developmental toxicity, reproductive toxicity, low dose organ toxicity, genotoxicity or drugs with a similar structure or toxicity profile to other dangerous drugs [11].

Later, in 2014, the NIOSH classified HDs into three groups [12]: antineoplastic drugs; non-antineoplastic drugs that meet at least one criterion of danger; and drugs that present a risk to the reproductive process and which may affect men and women who are attempting to conceive actively and to pregnant or lactating women, but do not pose any risk to the rest of the population.

Hazardous drugs, specifically the subgroup of antineoplastic drugs, have been described as the greatest chemical hazard present in the health field and one of the most dangerous chemical agents ever developed [13].

Organizations focused on occupational safety, such as the Joint Commission [14], the Occupational and Safety and Health Administration (OSHA) [15], the Pan American Health Organization (PAHO) [16] and the European Agency for Safety and Health at Work (EU-OSHA) [17], are paying increasing attention to recommendations and strategies for improving safety regarding HDs.

Importantly, given the complexity and interdisciplinary nature of HD manipulation, these processes are particularly error prone. This fact, in addition to the inherent hazards already described, leads us to consider HD as a high-risk therapy that can pose serious risks for both the patient and the involved professionals [18,19].

Therefore, it is essential to standardize these processes because when a protocol correctly implements clinical guidelines, the variability is reduced. This leads to improved quality and minimized risks associated with this type of medication [20].

However, despite efforts made over the past four decades at the international level to establish guidelines to ensure the safe use of HDs, there are currently no globally harmonized standards for the prevention of HD exposure [13], and the ever-worrisome problem is far from being solved [13,21].

For all the reasons abovementioned, it seems mandatory to achieve an updated revision of the main recommendations and/or standards related to the manipulation of HDs. To achieve a standardized model to handling HDs, the main stages involved in proper HD manipulation must be identified, as should preventive measures that can be applied to avoid occupational exposure to HDs. Therefore, the objective of this work was to review the scientific literature on the safe handling of HDs.
Materials and methods

Design
A descriptive cross-sectional study and critical analysis of the works recovered through systematic techniques was conducted.

Sources of data collection
The data were retrieved from direct query and access, on the Internet, from the following bibliographic databases in the field of health sciences: MEDLINE (via PubMed), The Cochrane Library, Scopus, Cumulative Index to Nursing and Allied Health Literature (CINHAL), Web of Science (ISI-Institute for Scientific Information) and LILACS.

Information processing
To define the search terms, the Medical Subject Headings (MeSH), a thesaurus developed by the U.S. National Library of Medicine, was used. The MeSH descriptors "Antineoplastic Agents", "Hazardous Substances" and "Cytostatic Agents" were considered suitable. Likewise, these terms were used to query the database using the title and abstract field (Title/Abstract).

The main search strategy was created for its usage in the MEDLINE database, via PubMed, using the filters "Humans" and "Guidelines", S1 File.

The search was restricted to results from September 2004 (date of the first NIOSH alert, which establishes the current internationally accepted definition of HD) until January 2017 (moment of the last update). This strategy was adapted to the particular features of other databases considered.

Additionally, a search using a complementary strategy was conducted to reduce the possibility of publication bias by searching the reference lists of relevant guidelines. Furthermore, experts in the domain were contacted to avoid issues regarding possible grey literature (materials and research produced by organizations outside of the traditional commercial or academic publishing and distribution channels).

Inclusion and exclusion criteria
The records were subsequently screened according to the a priori inclusion and exclusion criteria shown in Fig 1.

Inclusion criteria (I).
- Articles that dealt with the HD handling process (I1) and were published in English or Spanish (I2). Additionally, the full text of the document should be accessible (I3). Only one version of each document was included (R). The same criterion was applied to those documents that were duplicated (I4).

Exclusion criteria (E).
- Documents whose scope of application was not health (E1) and all those published by local institutions (E2). Moreover, works were excluded that could not be considered guidelines (E3) according to the definition by MeSH (i.e., a set of statements, directions, or principles presenting current or future rules or policies. Guidelines may be developed by government agencies at any level, institutions, organizations such as professional societies or governing boards, or by the convening of expert panels). It must be noted that many guidelines are presented to the reader as recommendations although they fit in the former definition by MeSH.

Final selection of articles
The selection of relevant articles was performed independently by two authors: MBM and JSV. To validate the inclusion of the studies, the assessment of concordance between these authors
(Kappa index) should be higher than 80% [22]. Whenever this condition was not met, the possible discordances were solved by consulting the author CWB and subsequent consensus among all the authors.

**Data extraction**

The continuous control of the validity of the data was ensured using double tables that allowed detection and corrections of errors by means of new queries to the original data. The Burton-Kebler half-period (the median age) and the Price Index (percentage of the articles published in the last 5 years) were calculated to determine the actuality of the articles.

The chosen documents were classified to systematize and facilitate the understanding of the results and were collected in a table showing the most relevant information from each work. In particular, the following variables were included [Table 1]: first author of the bibliographical reference and year of publication, country, institution or organization that developed the guide, type of institution (governmental, non-governmental, or professional), type of hazardous substance being addressed (HD (based on the NIOSH 2004 alert), antineoplastic (refers to...
Table 1. Description of the articles selected for review.

| Article                        | Country | Institution | Institution type | Language | Type of hazardous substance | Scope                                                                 | Control stages                                                                                   |
|-------------------------------|---------|-------------|------------------|----------|-----------------------------|----------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| Neuss et al., 2017 [24]       | USA     | ASCO/ONS    | Professional     | English  | Antineoplastic drugs        | Healthcare centres                                                   | Stage a: receiving and storage, drug preparation, transport, administration, extravasation (as a complication of administration), patient care. Stage b: training, documentation. Stage c: prescription. |
| OSHA, 2016 [15]               | USA     | OSHA        | Governmental     | English  | Hazardous drugs             | Healthcare centres                                                   | Stage a: receiving and storage, transport, drug preparation, administration, waste management, cleaning procedures, accidental exposure and spill control, patient care. stage b: training, medical surveillance, documentation, biological and environmental monitoring. |
| Connor et al., 2016 [25]      | USA     | NIOSH       | Governmental     | English  | Hazardous drugs             | Healthcare centres                                                   | Stage a: receiving and storage, drug preparation, administration, waste management, cleaning procedures, patient care, accidental exposure and spill control. |
| Poveda et al., 2016 [26]      | Spain   | SEFH        | Professional     | Spanish  | Hazardous drugs             | Healthcare centres                                                   | Stage a: receiving and storage, drug preparation, transport, administration, waste management, cleaning procedures, accidental exposure and spill control; stage b: training, medical surveillance, documentation, drug selection. |
| Delgado et al., 2016 [27]     | Spain   | INSHT       | Governmental     | Spanish  | Hazardous drugs             | Healthcare centres                                                   | Stage a: drug preparation, administration.                                                      |
| Lepe et al., 2016 [28]        | Spain   | Conselleria de Sanitat Universal i Salut Pública, GV | Governmental     | Spanish  | Hazardous drugs             | Healthcare centres                                                   | Stage a: drug preparation, transport, waste management, cleaning procedures, accidental exposure and spill control; stage b: training. |
| Lepe et al., 2016 [29]        | Spain   | Conselleria de Sanitat Universal i Salut Pública, Generalitat Valenciana | Governmental     | Spanish  | Hazardous drugs             | Healthcare centres                                                   | Stage a: drug preparation, transport, administration, waste management, cleaning procedures, accidental exposure and spill control; stage b: training. |
| Garcia Salom et al., 2016 [30]| Spain   | Conselleria de Sanitat Universal i Salut Pública, Generalitat Valenciana | Governmental     | Spanish  | Hazardous drugs             | Healthcare centres                                                   | Stage a: receiving and storage and drug preparation (facilities).                               |

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| Article  | Country    | Institution | Institution type | Language | Type of hazardous substance | Scope                      | Control stages                                                                 |
|----------|------------|-------------|------------------|----------|----------------------------|----------------------------|--------------------------------------------------------------------------------|
| USP Convention, 2016 [31] | USA       | USP         | Governmental     | English  | Hazardous drugs            | Healthcare centres         | Stage a: receiving and storage, drug preparation, transport, administration, waste management, cleaning procedures, accidental exposure and spill control; stage b: training, medical surveillance, documentation, biological monitoring. |
| Erce et al., 2016 [13]      | Belgium    | Parlamento Europeo | Governmental     | English  | Antineoplastic drugs and other hazardous drugs | Healthcare centres    | General                                                                     |
| Tomkins, 2015 [32]          | USA        | ONS, ASCO, HOPA | Professional     | English  | Hazardous drugs            | Healthcare centres and home setting | General                                                                     |
| Easty et al., 2015 [33]     | Canada     | CCO         | Governmental     | English  | Antineoplastic drugs       | Healthcare centres and home setting | Stage a: receiving and storage, drug preparation, transport, administration, extravasation (as a complication of administration), waste management, accidental exposure and spill control, patient care; stage b: training, medical surveillance, environmental monitoring, drug selection. |
| Spark et al., 2015 [34]     | United Kingdom | Cardiff and Vale University Health Board, Gales | Governmental | English  | Antineoplastic drugs       | Healthcare centres    | Stage a: receiving and storage, drug preparation, transport, administration, extravasation (as a complication of administration), waste management, accidental exposure and spill control, patient care; stage b: training; stage c: prescription, validation. |
| Guardino, 2015 [35]         | Spain      | INSHT       | Governmental     | Spanish  | Antineoplastic drugs       | Healthcare centres    | Stage a: drug preparation; stage b: training.                                 |
| Poveda et al., 2015 [36]    | Spain      | Grupo español de consenso | Professional     | Spanish  | Hazardous drugs            | Healthcare centres    | General                                                                     |
| Goldspiel et al., 2015 [37] | USA        | ASHP        | Professional     | English  | Antineoplastic drugs and biotherapy agents | Regulatory agencies, manufacturers, healthcare centres and home setting | Stage a: receiving and storage, drug preparation, transport, administration, extravasation (as a complication of administration), accidental exposure and spill control, patient care; stage b: training, documentation, drug selection; stage c: prescription, validation, patient monitoring, manufacturing. |
| USP Convention, 2014 [79]   | USA        | USP         | Governmental     | English  | Non-sterile drug preparations, including hazardous drugs | Healthcare centres    | Stage a: receiving and storage, drug preparation, waste management; stage b: documentation, training; stage c: validation. |

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| Article                                      | Country       | Institution         | Institution type | Language | Type of hazardous substance | Scope                                                                 | Control stages                                                                 |
|---------------------------------------------|---------------|---------------------|------------------|----------|----------------------------|----------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Health and Safety Executive, 2014 [38]      | United Kingdom| HSE                 | Governmental     | English  | Antineoplastic drugs       | Healthcare centres, home setting and veterinary clinics                | Stage a: receiving and storage, drug preparation, transport, administration, waste management, cleaning procedures, accidental exposure and spill control, patient care; stage b: training, medical surveillance, documentation, biological and environmental monitoring. |
| British Columbia Cancer Agency, 2014 [39]  | Canada        | BCCA                | Governmental     | English  | Antineoplastic drugs       | Healthcare centres                                                    | Stage a: receiving and storage, drug preparation, transport, administration, waste management, accidental exposure and spill control, patient care; stage b: training, medical surveillance, documentation. |
| Arce et al., 2014 [40]                     | Spain         | AMMTAS              | Professional     | Spanish  | Antineoplastic drugs       | Healthcare centres                                                    | Stage a: receiving and storage, drug preparation, transport, administration, extravasation (as a complication of administration), waste management, cleaning procedures, accidental exposure and spill control, patient care; stage b: training, medical surveillance, documentation; stage c: validation. |
| Casaus et al., 2014 [41]                   | Spain         | MSSSI               | Governmental     | Spanish  | Drugs coldDounded at the Hospital Pharmacy Services | Healthcare centres                                                    | Stage a: receiving and storage, drug preparation, transport, waste management, cleaning procedures; stage b: training, documentation. |
| INSHT, 2014 [42]                           | Spain         | INSHT               | Governmental     | Spanish  | Biologic agents            | Any workplace in which biological agents are handled, including healthcare centres | General                                                                       |
| ASHP, 2014 [43]                            | USA           | ASHP                | Professional     | English  | Sterile drug preparations, including hazardous drugs | Healthcare centres                                                    | Stage a: receiving and storage, drug preparation, transport, waste management, cleaning procedures, accidental exposure and spill control; stage b: training, medical surveillance, documentation. |
| Alexander et al., 2014 [44]                | Australia     | WCMICS              | Governmental     | English  | Monoclonal antibodies      | Healthcare centres                                                    | Stage a: drug preparation, transport, administration, waste management, accidental exposure and spill control; stage b: training. |
| Siderov, Jim, 2013 [45]                    | Australia     | COSA/CPG            | Professional     | English  | Monoclonal antibodies      | Healthcare centres                                                    | Stage a: drug preparation, administration, waste management, cleaning procedures. |
| Article | Country     | Institution* | Institution type | Language | Type of hazardous substance | Scope                      | Control stages                                                                 |
|---------|-------------|---------------|------------------|----------|-----------------------------|----------------------------|--------------------------------------------------------------------------------|
| PAHO, 2013 [16] | USA | PAHO-WHO | Non-governmental | English | Antineoplastic drugs | Healthcare centres | Stage a: receiving and storage, drug preparation, transport, administration, waste management, cleaning procedures, accidental exposure and spill control, patient care; stage b: training, medical surveillance, documentation. |
| INSHT, 2013 [46] | Spain | INSHT | Governmental | Spanish | Chemical agents | Any workplace in which chemicals are handled, including healthcare centres | General |
| ESOP, 2013 [47] | Germany | ESOP | Professional | English | Antineoplastic drugs | Manufacturers, healthcare centres and home setting | Stage a: receiving and storage, drug preparation, transport, administration, extravasation (as a complication of administration), waste management, cleaning procedures, accidental exposure and spill control, patient care; stage b: training, medical surveillance, documentation, biological monitoring; stage c: manufacturing, prescription, validation, patient monitoring. |
| The Quality Unit, NHS Scotland, 2012 [48] | United Kingdom | The Scottish Government | Governmental | English | SACT** | Healthcare centres and home setting | Stage a: receiving and storage, drug preparation, transport, administration, extravasation (as a complication of administration), waste management, cleaning procedures, accidental exposure and spill control, patient care; stage b: training, medical surveillance, documentation, biological monitoring; stage c: prescription, validation, patient monitoring. |
| INSHT, 2012 [49] | Spain | INSHT | Governmental | Spanish | Hazardous agents | Any workplace in which individual protection is necessary | General |
| Cohen, 2012 [50] | Spain | INSHT | Governmental | Spanish | Chemical agents | Any workplace in which chemicals are handled | General |
| Braun et al., 2012 [14] | USA | The Joint Commission | Non-governmental | English | Hazardous substances | Healthcare centres | General |
| Perez et al., 2012 [51] | Switzerland | ESMO/EONS | Professional | English | Antineoplastic drugs | Healthcare centres | Stage a: extravasation (as a complication of administration); stage b: documentation; stage c: patient monitoring. |
| ASWCS, 2012 [52] | United Kingdom | ASWCS | Governmental | English | Antineoplastic drugs | Healthcare centres | Stage a: extravasation (as a complication of administration); stage b: training, documentation. |

(Continued)
Table 1. (Continued)

| Article                        | Country       | Institution                          | Institution type | Language | Type of hazardous substance       | Scope                                           | Control stages                                                                 |
|--------------------------------|---------------|--------------------------------------|------------------|----------|-----------------------------------|------------------------------------------------|--------------------------------------------------------------------------------|
| Goodin et al., 2011 [53]       | International | Panel Internacional de farmacéuticos | Professional     | English  | Oral antineoplastic drugs        | Manufacturers, distributors, healthcare centres and home setting | Stage a: receiving and storage, drug preparation, transport, administration, waste management, cleaning procedures, accidental exposure and spill control, patient care; stage b: training; stage c: manufacturing, prescription. |
| Huber, 2010 [54]              | USA           | The Pennsylvania Patient Safety Authority | Governmental     | English  | Hazardous drugs                  | Healthcare centres and home setting              | Stage a: receiving and storage, transport, administration, waste management, cleaning procedures, accidental exposure and spill control, patient care. |
| Cercós et al., 2010 [55]      | Spain         | GEDEFO                                | Professional     | Spanish  | Antineoplastic drugs            | Healthcare centres                              | Stage a: accidental exposure and spill control; stage b: documentation. |
| Chaffee et al., 2010 [56]     | USA           | ASHP/UHC Pharmacy Council             | Professional     | English  | Antineoplastic drugs            | Healthcare centres                              | Stage a: receiving and storage, drug preparation, transport, administration, waste management, cleaning procedures, accidental exposure and spill control, patient care; stage b: training, medical surveillance, documentation. |
| ASWCS Network Nurse Group, 2010 [57] | United Kingdom | ASWCS                                | Governmental     | English  | Antineoplastic drugs            | Healthcare centres                              | Stage a: receiving and storage, drug preparation, transport, administration, extravasation (as a complication of administration), waste management, accidental exposure and spill control, patient care; stage b: training, documentation; stage c: prescription, validation. |
| Carrington et al., 2010 [58]  | Australia     | COSA                                  | Professional     | English  | Antineoplastic drugs and targeted therapy | Healthcare centres and home setting              | Stage a: drug preparation, transport, administration, extravasation (as a complication of administration), patient care; stage b: training, documentation; stage c: prescription, validation, patient monitoring. |
| Russi et al., 2009 [59]       | USA           | ACOEM                                 | Professional     | English  | Hazardous drugs                 | Healthcare centres                              | General                                                                 |
| Jacobson et al., 2009 [60]    | USA           | ASCO/ONS                               | Professional     | English  | Antineoplastic drugs            | Home setting                                    | Stage a: drug preparation, administration, extravasation (as a complication of administration); stage b: training, documentation; stage c: prescription, validation, patient monitoring. |

(Continued)
| Article | Country | Institution | Institution type | Language | Type of hazardous substance | Scope | Control stages |
|---------|---------|-------------|-----------------|----------|-----------------------------|-------|-----------------|
| CAPhO, 2009 [61] | Canada | CAPhO | Professional | English | Antineoplastic drugs | Healthcare centres | Stage a: receiving and storage, drug preparation, transport, administration, waste management, cleaning procedures, accidental exposure and spill control; stage b: training, documentation; stage c: validation, patient monitoring. |
| INSHT, 2009 [62] | Spain | INSHT | Governmental | Spanish | Carcinogen or mutagen agents | Any workplace in which carcinogens or mutagens are handled | General |
| Shulman et al., 2008 [63,64] | USA | ASCO | Professional | English | Antineoplastic drugs | Healthcare centres and home setting | Stage a: drug preparation, administration; stage b: documentation; stage c: prescription. |
| Gallant et al., 2008 [65] | Canada | ASSTSAS | Professional | English | Hazardous drugs | Healthcare centres and home setting | Stage a: receiving and storage, drug preparation, transport, administration, extravasation (as a complication of administration), waste management, cleaning procedures, accidental exposure and spill control, patient care; stage b: training, medical surveillance, environmental and biological monitoring. |
| Connor et al., 2008 [66] | USA | NIOSH | Governmental | English | Hazardous drugs | Healthcare centres | General |
| ESOP, 2008 [67] | Germany | ESOP | Professional | English | Highly potent drugs | Healthcare centres and manufacturers | Stage a: transport. |
| Wengström et al., 2008 [68] | Switzerland | EONS | Professional | English | Antineoplastic drugs | Healthcare centres and home setting | Stage a: extravasation (as a complication of administration); stage b: documentation |
| USP, 2008 [69] | USA | USP | Governmental | English | Sterile drug preparations | Healthcare centres | Stage a: receiving and storage, drug preparation, transport, cleaning procedures; stage b: training, documentation, environmental monitoring; stage c: validation, patient monitoring, and sterilization. |
| Ohio Nurses Association, 2008 [70] | USA | ONA | Professional | English | Antineoplastic drugs and biologic agents | Healthcare centres and home setting | Stage a: administration; stage b: documentation. |
| SHPA Committee of Specialty Practice in Cancer Services, 2007 [71] | Australia | SHPA | Professional | English | Antineoplastic drugs | Healthcare centres | Stage a: transport, waste management; stage b: training, documentation. |
| SHPA Committee of Specialty Practice in Cancer Services, 2007 [72] | Australia | SHPA | Professional | English | Oral antineoplastic drugs | Healthcare centres | Stage a: receiving and storage, drug preparation, transport, administration, waste management; stage b: training, documentation; stage c: validation. |

(Continued)
Table 1. (Continued)

| Article                                      | Country    | Institution | Institution type | Language | Type of hazardous substance          | Scope                          | Control stages                                                                 |
|----------------------------------------------|------------|-------------|------------------|----------|--------------------------------------|--------------------------------|--------------------------------------------------------------------------------|
| Vulto et al., 2007 [73]                     | Europe     | EAHP        | Professional     | English  | Gene medicine                       | Healthcare centres             | Stage a: receiving and storage, drug preparation, transport, administration, waste management, cleaning procedures, accidental exposure and spill control, patient care; stage b: training, medical surveillance, documentation. |
| Otero, 2007 [18]                            | Spain      | MSC- USAL   | Governmental     | Spanish  | High-risk medications               | Healthcare centres             | General                                                                        |
| Connor et al., 2007 [74]                    | International | ISOPP      | Professional     | English  | Hazardous drugs                     | Manufacturers, healthcare centres and home setting | Stage a: receiving and storage, drug preparation, transport, administration, extravasation, waste management, cleaning procedures, accidental exposure and spill control, patient care; stage b: training, medical surveillance, documentation; stage c: validation, drug selection. |
| Guardino et al., 2006 [75]                  | Spain      | INSHT       | Governmental     | Spanish  | Antineoplastic drugs                | Healthcare centres             | Stage a: receiving and storage, drug preparation, transport, administration, waste management, accidental exposure and spill control, patient care; stage b: training, medical surveillance. |
| ASHP, 2006 [76]                             | USA        | ASHP        | Professional     | English  | Hazardous drugs                     | Healthcare centres             | Stage a: receiving and storage, drug preparation, transport, waste management, cleaning procedures, accidental exposure and spill control; stage b: training, medical surveillance. |
| Lymm et al., 2005 [77]                      | United Kingdom | NHS Grampian | Governmental     | English  | Antineoplastic drugs                | Healthcare centres             | Stage a: receiving and storage, drug preparation, transport, administration, extravasation, waste management, accidental exposure and spill control, patient care; stage b: training, medical surveillance; stage c: prescription, validation. |
| SHPA Committee of Specialty Practice in Cancer Services, 2005 [78] | Australia | SHPA        | Professional     | English  | Hazardous drugs                     | Healthcare centres             | Stage a: receiving and storage, drug preparation, transport, waste management, cleaning procedures, accidental exposure and spill control; stage b: training, medical surveillance, documentation. |
anticancer drugs) and other substances), scope (institution or place where HD is applied), and stages of the process being controlled:

1. Stages with risk of exposure: reception and storage, drug preparation, transportation and distribution, administration, extravasation, patient care (excreta handling, body fluids, and linen), waste management, procedures in case of spill or accidental exposure, and cleaning procedures.

2. Stages without risk of exposure: selection of medicines and commercial presentations (choice of medicines at the time of purchase, taking into account specific aspects that may affect the safety and health of professionals, patients and the environment, such as robust packaging to prevent breakage, design that minimizes handling, etc.), staff training and/or patient education, documentation, medical surveillance and environmental and/or biological monitoring of hazardous substances, understood as the measurement of chemical substances and their metabolites in exposed workers [23].

3. Complementary stages: prescription, validation, patient monitoring, manufacturing by the industry and sterilization.

Results

Using the search criteria described, 1100 references were retrieved: 735 in MEDLINE, 183 in the Cochrane Library, 137 in Scopus, 3 in CINHAL, 42 in the Web of Science, and 49 provided by experts. No references were obtained from the search performed in the LILACS bibliographic database.

After applying the inclusion and exclusion criteria, reviewing the bibliographic lists, and consulting with experts (Fig 1), 61 documents were selected [11,13–16,18,24–79] (check Table 1).
The Kappa coefficient of the agreement in the selection of articles amongst the evaluators was 98.0% (p < 0.001).

The 61 selected articles received an obsolescence rate, according to the Burton-Kebler Index, equal to 5 years, with a Price index of 45.9%.

The documents had been developed in 13 different countries: the USA (20 guidelines, 32.8%) and Spain (17, 27.9%) were largest producers of guides, followed by the United Kingdom (6, 9.8%), Australia (6, 9.8%), Canada (4, 6.6%), Switzerland (2, 3.3%), Germany (2, 3.3%) and Belgium (1, 1.6%). Likewise, other countries such as Sweden, Austria, Malaysia, France and Italy participated jointly in the elaboration of several documents both in the European scope (1, 1.6%) and at the international level (2, 3.3%).

Fig 2 presents the chronological development in a timeline figure to illustrate the sequence and development of guidelines over years and countries.

Regarding the language, 44 of the 61 (72.1%) references retrieved were written in English and 17 were (27.9%) in Spanish.

In relation to institutional affiliation, 36 different organizations were identified: 15 agencies or governmental institutions authored 30 (49.2%) documents, 19 professional societies developed 29 documents (47.5%), and 2 non-governmental agencies published 2 (3.3%) guides; see Table 1.

Scope
Most of the documents (38, 62.3%) focused their recommendations on the handling of hazardous substances in health centres, and 12 (19.5%) took into account the home setting. In 5 (8.2%) documents [42,46,49,50,62], the scope was general (i.e., the application area of the guidelines is not specific but applies to any sector in which such hazardous substances are handled), and 6 (9.8%) guides included, in addition to the health area, recommendations for other sectors, such as the pharmaceutical industry, regulatory agencies and veterinary clinics [37,38,47,53,67,74].

Type of substance
Twenty-four documents approached HD-related recommendations (39.3%) [11,14,15,25–32,36,43,54,56,59,65–67,69,74,76,78,79], whereas 27 studies (44.3%) focused on antineoplastics (specific for anticancer drugs) [13,16,24,33–35,37–40,47,48,51–53,55,57,58,60,61,63,64,68,70–72,75,77]. In addition, 10 guidelines (16.4%) addressed other types of substances, such as
monoclonal antibodies, gene medicine and other chemical and biological agents [18,41,42,44–46,49,50,62,73].

**Stages in the management process for dangerous drugs**

Amongst all the retrieved guidelines, 14 (23.3%) references considered all the stages of the manipulation process in which there is a risk of exposure (stage a); the extravasation stage was considered a part of the administration stage since it is a complication of this [11,15,16,26,33,38,40,47,48,53,56,65,73,74]. Of these 14 guides, 13 also considered stages in the handling process without risk of exposure: drug selection and commercial presentations [26,33,74], staff training and/or patient education [11,15,16,26,33,38,40,47,48,53,56,65,73,74], documentation [15,16,26,38,40,47,48,56,73,74], medical surveillance [11,15,16,26,33,38,40,47,56,65,73,74] and environmental and/or biological monitoring [15,33,38,47,65,74]. Furthermore, 6 of the 14 references also addressed complementary stages: prescription [47,48,53], validation [40,47,48,61,74], patient monitoring [47,48,61], and manufacturing [47,53,74].

Only one guide, the ISOPP Standards of Practice [74], addressed all stages of the process of handling hazardous substances (stages with and without risk of exposure).

No standardized systems to ensure quality management, traceability of processes, and minimization of risks associated with these drugs were found. There was no mention in the reviewed guidelines of any computerized system to ensure the proper management of the entire HD process.

Twelve (20%) of the selected documents did not include specific stages of the manipulation process. Their content was of a general nature, describing transversal actions that can affect all stages of the process, general prevention measures, and strategies, guidelines or policies to be followed [13,14,18,32,36,42,46,49,50,59,62,66].

The most described stages were elaboration (41 guides, 67.2%), staff training and/or patient education (38 guides, 62.3%), and administration (37 guides, 60.7%). The stages that were less frequently addressed were cleaning and decontamination procedures (26 guidelines, 42.63%), patient care (24 documents, 39.3%), and medical surveillance (18 documents, 29.5%) [Table 2].

**Discussion**

The high number of retrieved guidelines shows the existing concern regarding exposure to HDs and the safe management of these substances. However, unexpectedly, there was only one international consensus document that tackles the entire process of HD manipulation, and there were no computerized systems recommended to guarantee proper management of the HD process.

This study shows that obsolescence is very present. Half of the recovered guidelines were published in the last 5 years, a larger ratio than other previously published papers in the health sciences and hospital pharmacy environments [80,81]. These results support the high interest that the study of HD management is experiencing in recent years.

It is not surprising that the United States is the place of origin of most guidelines since it is the country with the highest scientific production. It must be borne in mind that eight of the top ten universities in the world are in the USA, which continues to be the world leader in science and innovation [82]. However, European countries as a whole are the promoters of the largest scientific production in this context, a phenomenon previously observed by Hon et al. [83].

Although works from both continents have the same validity, it is important to note that the recommendations contained in documents from the US may not be transferable to Europe, mainly due to differences in the regulatory framework of the different countries. Therefore,
given the relevance of the issue to workers’ health, more initiatives at an international level should be performed to harmonize standards and unify the legal framework as far as possible.

The English language was chosen for publication in most articles since a different language could have a negative impact on visibility and citability. In addition, the number of English-language journals contained in the considered databases is currently very high [82,84].

The institutional affiliation reflects the commitment of the agencies involved in the HD process. Despite multiple efforts made worldwide to establish standards in the management of MP, the safety of HD manipulation is an unresolved issue, which concerns governments and professional societies worldwide because there is a wide range of variants amongst the different guidelines. This conclusion has already been highlighted by other authors [85]. Proof of this is shown in the recent publication from the European Parliament [13], which reflects the preoccupation of addressing this issue.

It is important to emphasize that professional societies were linked entirely to the health field. Involved governmental agencies depend as much on health administration as on labour administration.

### Scope of application

More than one-half of the retrieved documents were targeted exclusively at health centres, and only one-fifth addressed the dangers that might occur at home. With the growing number of oral medications being approved in cancer treatment, the potential for the long-term administration of these drugs to cancer patients is expanding. The use of these drugs at home has the potential to expose family members and caregivers to them, either through direct contact with

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**Table 2. Rate of each stage in the selected documents and its classification regarding exposition.**

| Stage                                | n’   | %    | References                                                                 | Stage type |
|--------------------------------------|------|------|---------------------------------------------------------------------------|------------|
| Receiving and storage                | 33   | 54.1 | [11,15,16,24–26,30,31,33,34,37–41,43,47,48,53,54,56,57,61,65,69,72–79]       | a          |
| Drug preparation                     | 41   | 67.2 | [11,15,16,24–31,33–35,37–41,43–45,47,48,53–56–58,60,61,63–65,69,72–79]       | a          |
| Transport                            | 36   | 59.0 | [11,15,16,24,26,28,29,31,33,34,37–41,43,44,47,48,53,54,56–58,61,65,67,69,71–78] | a          |
| Administration                       | 37   | 60.7 | [11,15,16,24–27,29,31,33,34,37–40,44,45,47,48,51–54,56–58,60,61,63–65,68,70,72–75,77] | a          |
| Extravasation                        | 16   | 26.2 | [24,33,34,37,40,47,48,51,52,57,58,60,65,68,74,77]                             | a          |
| Patient care                         | 24   | 39.3 | [11,15,16,24–26,33,34,37–40,47,48,53,54,56–58,65,73–75,77]                 | a          |
| Waste management                     | 34   | 55.7 | [11,15,16,25,26,28,29,31,33,34,38–41,43–45,47,48,53,54,56,57,61,65,71–79]   | a          |
| Exposure and spill control           | 31   | 50.8 | [11,15,16,25,26,28,29,31,33,34,37–40,43,44,47,48,53–57,61,65,73–78]          | a          |
| Cleaning procedures                  | 26   | 42.6 | [11,15,16,25,26,28,29,31,33,38,40,41,43,45,47,48,53,54,56,61,65,69,73,74,76,78] | a          |
| Drug selection                       | 4    | 6.6  | [26,33,37,74]                                                              | b          |
| Personnel training and/or patient education | 38   | 62.3 | [11,15,16,24,26,28,29,31,33–35,37–41,43,44,47,48,52,53,56–58,60,61,65,69,71–79] | b          |
| Documentation                        | 30   | 49.2 | [15,16,24,26,31,37–41,43,47,48,51,52,55,56,58,60,61,63,64,68–74,78,79]       | b          |
| Medical surveillance                 | 18   | 29.5 | [11,15,16,26,31,33,38–40,43,47,56,65,73–76,78]                              | b          |
| Environmental and/or biological monitoring | 8    | 13.1 | [15,31,33,38,47,65,69,74]                                               | b          |
| Prescription                         | 11   | 18.0 | [24,34,37,47,48,53,57,58,60,63,64,77]                                        | c          |
| Validation                           | 14   | 23.0 | [34,37,40,47,48,57,58,60,61,69,72,74,77,79]                                 | c          |
| Patient monitoring                   | 8    | 13.1 | [37,47,48,51,58,60,61,69]                                                | c          |
| Manufacturing                        | 4    | 6.6  | [37,47,53,74]                                                              | c          |
| Sterilization                        | 1    | 1.6  | [69]                                                                        | c          |

(a) Stages with risk of exposure
(b) Stages without risk of exposure
(c) Complementary stages

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the drugs or indirectly by exposure to the parent compounds and/or their active metabolites in contaminated patients’ waste [86]. This is relevant since the manipulation of HD in this context requires an adequate strategic plan of intervention, monitoring and tracking.

It is important to keep in mind that exposure to risks for professionals, patients and their relatives may not only occur during the stay in the hospital; these risks also occur when HDs are used at home, where the precaution of the patients and caregivers can be more relaxed [20]. Although hospital infrastructure is no longer necessary in the Hospital at Home (Hospital Home Care Services), patient care remains complex [87].

Type of substance

The different guidelines use a heterogeneous terminology when referring to the types of substances addressed, mainly due to the evolution of the definition of HD. Therefore, it is not surprising that most of the guidelines limit their recommendations to antineoplastic or cytotoxic drugs (both terms commonly used interchangeably in the literature to refer to drugs used in the treatment of cancer [85]). The main reason for this is linked to the fact that the risks associated with its manipulation are clearly defined because they are usually prepared in centralized pharmacy aseptic units.

However, according to the NIOSH definition [11] in 2004 that includes antineoplastic and other non-antineoplastic drugs, and particularly after the later update in 2014 of the NIOSH document [12], in which HDs are classified into three lists, a growing trend in the publication of guidelines tackling the concept of HDs can be noted. These new guidelines use a broader and more inclusive concept of HDs.

Conversely, guidelines addressing drugs widely used in the oncology field were taken into account (monoclonal anti-blockers [44,45], genes medicines [73]), which were not initially considered by NIOSH as HDs and whose manipulation has generated uncertainty and variability in clinical practice.

Likewise, guidelines covering agents that comprise HDs were contemplated since they deal more generally with the handling of dangerous substances (chemical agents [46,50], carcinogenic and/or mutagenic [62], biological agents [42], drugs prepared in pharmacy services [41] and high-risk medications [18]).

Stages in the management process of hazardous drugs

The guidelines were very heterogeneous regarding the stages described, likely because there is no international consensus on the phases that comprise the HD manipulation process. To illustrate this feature, we can note that although European authors consider actions such as staff training and/or patient education, medical surveillance and environmental and/or biological monitoring as stages of the process [26,65,74], their American colleagues consider these actions as administrative controls [88].

In general terms, the most frequently mentioned stages were those classified by the authors as stages with a risk of exposure. This is reasonable because elaboration and administration, along with waste management, are considered by NIOSH as the riskiest phases of the process for staff [11].

Special mention should be made about the stages regarding staff training and/or patient education and documentation, both of which are transversal stages affecting all phases of the process. Even without the risk of exposure, these stages were considered more profusely than other stages without risk of exposure, such as the stages of procedures for cleaning and care of the patient. This shows that both stages are fundamental to guarantee the quality of the HD handling process, in which all steps must be performed by qualified staff [89], following
standard protocols and recording all the operations performed throughout the entire life of the HD. Through this recording, the full traceability of the process and the supervision of all the involved stages is facilitated. In this way, it will be possible to evaluate the system as a whole and to establish to which extent the actions comply with the established standards to indicate the points with a margin for improvement and to prevent hazards.

The verification procedures are necessary to evaluate the efficiency of a process and to ensure that there is an adequate control of all the possibilities of risk [90].

A benefit derived from computer-based systems is the support of repositories for the generated records that allow linking, verifying and evaluating data at any time, guaranteeing excellence in management control and traceability [91, 92]

Just one guide [74] covering all the stages of the HD handling process could be identified. This may have occurred because most recovered guides do not include one or several stages in which there is no risk of exposure. Nevertheless, these stages are not of lesser relevance and should also be addressed.

There was a general lack of environmental and/or biological monitoring in the guidelines. This may be due to the limited existence of analytical methods for the quantification of most HDs, both in biological and environmental samples. Currently, there are standardized methods to measure the concentration of just some anticancer drugs, whereas many others are available only in a research setting [65]. Conversely, in most cases, there are no reference standards for environmental exposure, so the interpretation of the results must be performed with caution, and measures must be taken to reduce exposure "as low as reasonably achievable" (ALARA) [65, 93].

Limitations

This work only took into consideration documents provided in English or in Spanish. This set of languages provides a joint coverage of more than 90% of the existing literature in this area [80–82] and includes coverage of many countries (organizations from many countries publish their documents in both English and their official language). Nevertheless, to ensure the best possible identification of main stages, guides in other languages were also consulted. Thus, guides in French [94,95], German [96] or Italian [97–99] were considered, but, as the reader may note in Table 1, no new stages were identified.

The high rate of non-relevant articles in relation to the final selection made can be considered a possible limitation of this review. This may be due to the lack of descriptors (MeSH) specific to the "hazardous drug" concept. The lack of a specific MeSH term forced us to conduct the MEDLINE search in text format using the title and abstract fields. Moreover, the Web of Science and Scopus databases do not have a thesaurus, so the query must be performed in text format using the title, abstract and keywords field, preventing the use of descriptors. This disturbing "noise" from the retrieval point of view has been previously observed in other systematic reviews [100,101]. Likewise, there was publication bias because most references are part of the grey literature since they are reports produced by institutions of different natures and therefore are not indexed in bibliographic databases with scientific content [102].

Conclusions

Based on the above findings, we can conclude that no standardized informatics system was found to ensure quality management, traceability of processes and minimization of risks associated with these drugs. In the considered guidelines, no mention of computerized systems that guarantee the correct management of the HD process was identified.
From the authors’ point of view, it would be convenient to be at the disposal of ICT-based tools that allow a simple and complete configuration of management systems to tackle the prevention of risks associated with HDs. Moreover, further works and specific developments regarding the management and traceability of HDs that allow for their monitoring and evaluation must be generated.

**Supporting information**

S1 Checklist. PRISMA checklist.
(PDF)

S1 File. MEDLINE (via PubMed) search strategy.
(DOCX)

S1 Certificate. Certificate AMJ.
(PDF)

**Author Contributions**

**Conceptualization:** Mari A. Bernabeu-Martínez, Mateo Ramos Merino, Juan M. Santos Gago, Luis M. Álvarez Sabucedo, Carmina Wanden-Berghe, Javier Sanz-Valero.

**Data curation:** Mari A. Bernabeu-Martínez, Carmina Wanden-Berghe, Javier Sanz-Valero.

**Formal analysis:** Carmina Wanden-Berghe, Javier Sanz-Valero.

**Funding acquisition:** Carmina Wanden-Berghe.

**Investigation:** Mari A. Bernabeu-Martínez, Mateo Ramos Merino, Luis M. Álvarez Sabucedo, Carmina Wanden-Berghe, Javier Sanz-Valero.

**Methodology:** Mari A. Bernabeu-Martínez, Mateo Ramos Merino, Juan M. Santos Gago, Luis M. Álvarez Sabucedo, Carmina Wanden-Berghe, Javier Sanz-Valero.

**Project administration:** Luis M. Álvarez Sabucedo.

**Supervision:** Juan M. Santos Gago, Carmina Wanden-Berghe, Javier Sanz-Valero.

**Validation:** Mari A. Bernabeu-Martínez, Mateo Ramos Merino, Juan M. Santos Gago, Luis M. Álvarez Sabucedo, Carmina Wanden-Berghe, Javier Sanz-Valero.

**Writing – original draft:** Mari A. Bernabeu-Martínez, Mateo Ramos Merino, Juan M. Santos Gago, Luis M. Álvarez Sabucedo, Carmina Wanden-Berghe, Javier Sanz-Valero.

**Writing – review & editing:** Mari A. Bernabeu-Martínez, Juan M. Santos Gago, Luis M. Álvarez Sabucedo, Carmina Wanden-Berghe, Javier Sanz-Valero.

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