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Exposure Assessment and Monitoring of Antiblastic Drugs Preparation in Health Care Settings: A Systematic Review

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Summary

Several antiblastic drugs (ADs) are classified as carcinogenic, mutagenic, and/or toxic for reproduction. Despite established guidelines and safe handling technologies, ADs contamination of the work environments could occur in healthcare settings, leading to potential exposure of healthcare staff. This systematic review investigates the main techniques and practices for assessing ADs occupational exposure in healthcare settings. The reviewed studies unveil that workplace contamination by ADs appears to be a still-topical problem in healthcare settings. These issues are linked to difficulties in guaranteeing: (i) the adherence to standardized protocols when dealing with ADs, (ii) the effective use of personal protective equipment by operators involved in the administration or management of ADs, (iii) a comprehensive training of the healthcare personnel, and (iv) a thorough health surveillance of exposed workers. A "multi-parametric" approach emerges as a desirable strategy for exposure assessment. In parallel, exposure assessment should coincide with introducing novel technologies to minimize exposure (i.e., risk management). Assessment must consider various departments and health operators susceptible to ADs contamination, with a focus extended beyond worst-case scenarios, also considering activities like surface cleaning and logistical tasks related to ADs management. A comprehensive approach in ADs risk assessment enables the evaluation of distinct substance behaviors and subsequent exposure routes, affording a more holistic understanding of potential risks.

1. Introduction

Occupational chemical risk in hospitals is a growing concern: both acute and chronic exposures to different substances and compounds used in these environments may, in fact, occur. Among these, exposure to formaldehyde, organic solvents, anesthetic gases, hazardous drugs (HDs), and antiblastic drugs (ADs) can have negative effects on the health of exposed workers [1, 2]. Based on the definitions provided by the American Society of Hospital Pharmacists in 1990 and by the National Institute for Occupational Safety and Health (NIOSH) in 2004, it can be stated that HDs are the greatest chemical

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hazard present in the healthcare field and one of the most dangerous chemical agents ever developed [3]. Among these hazardous agents, ADs (also known as cytotoxic drugs, antineoplastic drugs, anticancer drugs, or anticancer chemotherapy) are used to treat cancer [4, 5]. These drugs, depending on their mechanism of action, can be classified as carcinogenic, mutagenic, and/or reprotoxic [2, 4, 6, 7]; for this reason, the occupational exposure of healthcare personnel to these substances should be carefully evaluated, as exposure to ADs could be associated with potential health risks among healthcare workers [8].

The effects of both long and short-term exposure to ADs on healthcare workers are indeed well reported in the literature, ranging from nausea, vomiting, and diarrhea to eye and throat irritation, menstrual irregularities, skin reactions and skin rashes, hair loss, headache, and dizziness. ADs can also eventually lead to cancer, infertility, miscarriage, malformation, and genotoxicity [4, 9]. Exposure to ADs may occur mainly through skin absorption, followed by inhalation of drug aerosols and droplets, eye contact through a splash of liquids, ingestion, and sharps stick injury [5, 9].

In particular, occupational exposure to ADs (and related waste) can occur during various activities performed by healthcare personnel, such as (i) preparation, (ii) administration, (iii) transportation, (iv) storing of drugs, in addition to their waste treatment, which includes (v) transporting and disposing of waste and (vi) cleaning up spills [4, 5]. Despite the numerous guidelines in place regarding the use and handling of ADs, and the adoption of safe handling technologies (e.g., isolators and closed systems), the environment of the anticancer drug circuit can remain contaminated [2]. For example, in their study, Forges and collaborators [9] report how the entire circuit of the drugs could be contaminated: this can include (i) external surfaces of vials, (ii) storage rooms, (iii) gloves of the pharmacy technicians or nurse during handling and administration of drugs, (iv) infusion bags, (v) carts of care and even (vi) the patients' rooms.

The International Agency for Research on Cancer (IARC) has currently listed several ADs and two combination therapies as having an association with cancer in patients who are treated with them. In particular, eleven agents and two combined therapies have been classified as Group 1 (human carcinogens), twelve as Group 2A (probable human carcinogens), and eleven as Group 2B (possible human carcinogens) [10, 11]. It is also recognized how the use and administration of ADs are highly regulated issues in many countries. The Food and Drug Administration (FDA) in the United States and the European Medicines Agency (EMA) in Europe regulate the approval, labeling, and monitoring of the adverse effects of ADs. In addition to the legislation related to the use of ADs, it is important to evaluate the regulations related to the occupational exposure of workers who can be exposed to ADs. Several workers (e.g., oncologists, nurses, pharmacists, laboratory technicians, healthcare assistants, support staff, etc.) can be potentially exposed to these drugs during their jobs in hospitals, clinics, and pharmacies. In addition, cleaning and waste management personnel in healthcare facilities and workers in the pharmaceutical industry must also be considered to be potentially exposed [12].

For the reasons reported before, Professional Practice Organizations and Government Agencies published guidelines and other documents to protect workers who may be occupationally exposed during the (i) preparation, (ii) administration, (iii) cleaning of waste management of these drugs, (Table S1; supplementary materials). In particular, available guidelines generally respect the primary prevention measures and the hierarchy of control to mitigate workplace hazards throughout all their life cycle: referring to ADs that cannot be eliminated or substituted by another less toxic substance, exposure controls should be systematically implemented in the following hierarchical order of efficacy: (i) engineering controls; (ii) administrative controls; (iii) work practice controls; (iv) use of personal protective equipment (PPE). An issue referring to the management of occupational risk of ADs is that no Occupational Exposure Limit Values (such as RELs (NIOSH Recommended Exposure Limits), PELs (OSHA Permissible Exposure Limits), TLVs® (ACGIH - American Conference of Governmental Industrial Hygienists - Threshold Limit Values) or OELVs (European Union Occupational Exposure Limit Values) have been established for ADs in occupational and non-occupational fields [1, 2,

13]. Many manufacturers have internal occupational exposure limits, which are not generally available to regulatory agencies [12]. Therefore, only guidance values have been independently determined in different Countries such as Germany [14], the Netherlands [15], and the USA [16]. Guidelines for preventing ADs occupational exposure in Italy were published in 1999 [17].

Even though good practices have been defined and could be adopted during the use and handling of antiblastic agents, several studies reported how healthcare personnel could be exposed to antiblastic drugs: hospital staff handling ADs may indeed be exposed chronically to low doses of these drugs. Many studies have found the presence of these drugs in the urine of technicians, pharmacists, or nurses [18]. Available studies on exposure assessment are generally based on biological monitoring [18] and administering a questionnaire to workers (qualitative exposure assessment). In contrast, measuring ADs contamination (typically superficial contamination) for environmental exposure monitoring seems less common. Therefore, this study aims to investigate the main techniques and practices currently used for assessing exposure to ADs, highlighting the critical issues related to this topic. Since a comprehensive systematic review of biological monitoring data was recently published by Leso et al. [18], the present study is focused only on environmental monitoring and qualitative assessment techniques (i.e., administering questionnaires to potentially exposed workers) for occupational exposure assessment to ADs. After (i) a general overview of the studies considered in this review (Paragraph 3.1), the main results are presented subdivided by investigation methodology: (ii) questionnaire (Paragraph 3.2) and (iii) environmental monitoring (Paragraph 3.3). For both, the details of the application of the experimental method and the critical issues that emerged from the investigated articles are presented.

2. Methods

The results outcomes from three different databases (Scopus, Web of Science, and PubMed) are considered in this review. A list of keywords is arranged for each database in a search query, as reported in Table S2 (Supplementary materials): 835 papers were found (747, 26, and 62 papers in Scopus Web of Science and PubMed, respectively). Duplicates (n=66) were removed from the total number of papers. The articles have been, therefore, screened by (i) title (511 papers removed), (ii) abstract (143 papers removed), and (iii) publication year (36 papers removed). The remaining papers (full-text reading) are then selected following the inclusion and exclusion criteria chosen *a priori*. In particular, only scientific papers written in English are considered in this review, excluding conference papers and review articles. Further, articles are then selected based on consistency with the aims of this study. Thus, studies concerning occupational exposure to ADs published in 2010 that (a) performed environmental monitoring, (b) reported a risk assessment section, and (c) reported a risk management section. Only the articles that meet the above-mentioned inclusion criteria and aims of the review are examined. After that, 48 papers are finally included in this review (Table S3; Supplemental materials). Phases i-iii, as well as the screening process of article summaries, are conducted separately (and double-checked) by different authors (FB, CZ, AZ, AS), to reduce operator-related errors. The papers to be reviewed were selected following the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) criteria guidelines [19, 20]. A flowchart of the literature research and review process is reported in Figure 1.

3. Results

3.1. General Description of the Considered Studies

The supplementary materials report a general description of the reviewed articles, focusing on the period (Table S4) and geographical distribution (Table S5) of the study and of the investigated structures (Table S6).

3.1.1. Exposure and Risk Assessment Methods

The methods used in the reviewed studies for occupational exposure to ADs and risk assessment are

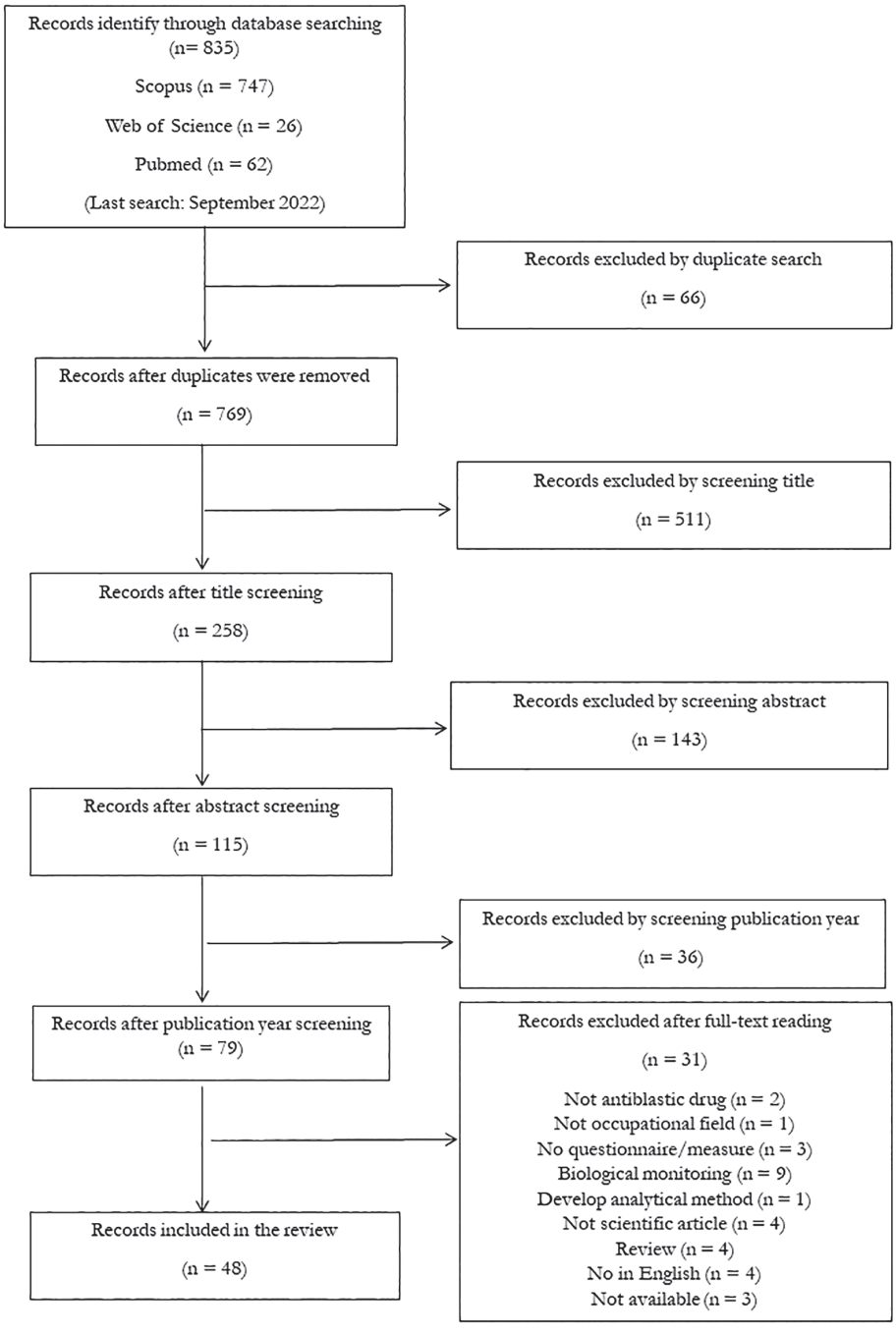

Figure 1. Flowchart of the literature research.

divided into two groups. The first group is "questionnaire and survey", which includes survey investigation methods intended to collect information about a group of workers under study and the statistical monitoring of consequences on health conditions due to exposure to ADs and other external variables that influence the cytotoxic consequences. The second group of methods is called "environmental monitoring" studies, which include sampling procedures for assessing environmental contamination, especially on working surfaces and tools. On a database of 48 selected articles (Table 1), 26 (54%)

show evidence of environmental monitoring study techniques. Of these, 23% of the studies also provide a questionnaire submitted to the workers involved (strictly restricted to healthcare workers) and the working conditions. The remaining 11 articles (23%) are only on a questionnaire submitted to involved workers, investigating risk perception among healthcare workers, knowledge of the guidelines by medical personnel, and compliance to guidelines while performing the daily job tasks (workers' self-assessment). Two of the questionnaire-based studies are dedicated to the use and knowledge of modern technologies for the management of risk posed by ADs in the medical field, which are Hyperthermic intraperitoneal chemotherapy and Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) [21, 22].

3.1.2. Investigated Population

In most (56%) of the reviewed studies (considering both environmental contamination monitoring studies and survey investigations), the healthcare workers involved in the studies are nurses (anyhow, several studies investigated more than one professional figure): in fact, the nursing staff typically manages the ADs in each step of their administration to the patient, making this category of healthcare workers a precious source of information both in relation to the medical skills that require exposure to ADs and about information of a demographic nature.

The second most abundant group of investigated workers in the reviewed studies (31%) is the one that included pharmacists and pharmacy technicians responsible for the preparation of drugs (Table 2). As regards the role of pharmacists, it is understandable that almost a third of the personnel involved in the studies investigated fall into this professional category, given that the pharmaceutical department is the one most afflicted by environmental drug contamination.

Table 1. Number (and percentage of the total - 48 studies) of reviewed articles divided according to the adopted exposure and risk assessment method.

Type of Study	N (%)	References
Measurement-based	26 (54%)	[6, 8, 9, 15, 23-44]
Questionnaire-based	11 (23%)	[3, 5, 22, 45-52]
Both measurement- and questionnaire-based	11 (23%)	[13, 21, 53-61]

3.1.3. Work Task

The results relating to the activities and procedures undertaken by the employees (Table 3) confirm those previously obtained about the professional classification of the healthcare workers (Table 2). The administration of medications, which includes dosage, intravenous injection, and patient care, comprehends more than half (54%) of the study activities described in the articles, closely followed by the preparation of drugs (40%), which includes all the pharmaceutical procedures. The same study often assessed the exposure to ADs for more than one work task or procedure. Only a few studies consider other peculiar activities, such as cleaning

Table 2. The number (and percentage of the total 48 studies) of reviewed articles was divided according to the classification of healthcare workers in study groups. n.a.: information not available and/or details not further described in the reviewed articles.

Medical Professionals and Healthcare Workers	N (%)	References
Nurses	27 (56%)	[3, 5, 8, 9, 13, 21, 29-32, 39, 42, 44-48, 50-53, 55, 56, 58-61]
Pharmacy technicians (and/or pharmacists and/or employees involved in the preparation of drugs)	15 (31%)	[3, 6, 13, 28, 29, 36, 39, 40, 43, 44, 46, 53, 58, 59, 61]
Other healthcare workers (e.g., medical staff (surgeons, doctors, anesthetists, etc.))	21 (44%)	[3, 21, 22, 25, 29, 30, 32, 33, 35, 40-42, 45, 47-50, 54, 57-59]
n.a.	7 (15%)	[15, 23, 24, 26, 34, 37, 38]

Table 3. Number (and percentage of the total - 48 studies) of reviewed articles, divided according to the classification of the assessed work tasks. n.a.: information not available and/or details not further described in the reviewed articles.

Work Tasks	N (%)	References
ADs administration	26 (54%)	[13, 21, 27-31, 33, 35, 38, 40, 41, 43-49, 51, 53-56, 58, 59]
ADs preparation	19 (40%)	[13, 23, 24, 28, 29, 31, 35-37, 39-44, 49, 53, 58, 59]
Cleaning	5 (10%)	[23, 33, 48, 59, 60]
Other activities	9 (17%)	[8, 15, 22, 23, 25-27, 59, 61]
n.a.	9 (17%)	[3, 5, 6, 9, 32, 34, 50, 52, 57]

Table 4. Number (and percentage of the total - 48 studies) of reviewed articles, divided according the antiblastic drugs analyzed in studies under review. n.a.: information not available and/or details not further described in the reviewed articles.

Antiblastic Drugs	N (%)	References
Cyclophosphamide	24 (50%)	[6, 9, 13, 15, 23, 24, 26-30, 33, 34, 37-39, 41-44, 53, 54, 56, 57]
Ifosfamide	11 (23%)	[6, 9, 13, 15, 26, 34, 37, 39, 53, 54, 57]
5-flourouracil	17 (35%)	[6, 15, 24, 30, 35, 37, 38, 40, 42-44, 53-55, 57-59]
Methotrexate	5 (10%)	[15, 28, 40, 54, 57]
Cytarbine	3 (6%)	[25, 53, 59]
Paclitaxel	8 (17%)	[6, 9, 25, 43, 44, 53, 54, 57]
Platinum	3 (6%)	[21, 30, 54]
Gemcitabine	7 (15%)	[6, 13, 25, 38, 40, 54, 58]
Other	19 (40%)	[3, 6, 8, 9, 13, 15, 21, 22, 24, 26, 32, 35, 36, 40, 46-48, 51, 54]
n.a.	8 (17%)	[5, 31, 45, 49, 50, 52, 60, 61]

surfaces and medical tools and logistic activities (e.g., packing, storage, and transportation of drugs), taken into consideration in 10% and 17% of the studies, respectively. It is noteworthy that personnel assigned to these tasks have not been consulted or questioned. This could be due, on the one hand, to the fact that some categories of potentially exposed workers (for example, cleaning workers) were not included in the studies, but on the other hand, that cleaning and logistical activities could be delegated to medical staff (increasing their probable routes of exposure).

3.1.4. Antiblastic Drugs

Most studies provide an extended knowledge about the evaluated hazardous compounds (Table 4). Cyclophosphamide (CP; Formula: $C_7H_{15}Cl_2N_2O_2P$; CAS Number: 50-18-0), is used in most of the reviewed studies (52%) as an indicator of workplace contamination. However, most of the reviewed studies do not rely on one drug acting as an indicator of contamination but rather consider different ADs, thus allowing to cover a greater number of case studies. The set of contamination indicator substances identified in the reviewed articles is narrowed down to 8 major known drugs, described below, among the hundreds of available ADs. IARC has taken steps to group and evaluate these medicines capable of inhibiting cell division and growth; some of these substances fall into Group 1 of human carcinogens [2, 58]. The availability of various contamination indicators allows the investigation of the different behaviors of substances and, consequently, the different ways of contamination to which medical personnel may be exposed [6]. After CP, the other most common ADs considered in the reviewed studies are: (i) 5-fluorouracil (Formula: $C_4H_3FN_2O_2$; CAS Number: 51-21-8) (35% of the reviewed studies);

(ii) Ifosfamide (Formula: $C_7H_{15}Cl_2N_2O_2P$; CAS number: 377873-2) (23%); (iii) Paclitaxel (Formula: $C_{47}H_{51}NO_{14}$; CAS Number: 33069-62-4) (17%); (iv) Gemcitabine (Formula: $C_9H_{11}F_2N_3O_4$; CAS Number: 95058-81-4) (15%); (v) Methotrexate (Formula: $C_{20}H_{22}N_8O_5$; CAS Number: 59-05-2) (10%); (vi) Cytarabine (Formula: $C_9H_{13}N_3O_5$; CAS Number: 147-94-4) (6%). A small percentage of the reviewed studies (6%) use platinum as an indicator of the presence of ADs, as this element is present in the molecular structure of cisplatin (cis-diamminedichloroplatinum (II); Formula: $Pt(NH_3)_2Cl_2$; CAS Number 15663-27-1). Finally, a limited percentage of articles (17%) do not provide detailed information regarding the specific ADs considered indicators of environmental contamination. Still, it is understandable to classify these articles as descriptive of statistical surveys focused on training, occupational risk, and demographic information relating to healthcare personnel. Therefore, they are not oriented toward surface measurements and sampling (Table 4).

3.2. Questionnaire-Based Risk Assessment

As previously stated, 22 (46%) of the reviewed studies (Table 1) rely on questionnaire-based methods of investigation for what concerns both cytotoxic and non-cytotoxic variables that may influence the evaluation of occupational risk rates among healthcare workers. 9 out of these 22 articles add the survey investigation to the antiblastic drugs-detection campaign, considering, therefore, the questionnaire complementary to the study of contamination in the working environment. The entirety of the articles carries enough information to classify them into four non-mutually excludable categories: (i) interview or oral examination (5%); (ii) survey (50%); (iii) standardized questionnaire or demographic study (45%); (iv) other (such as daily diaries kept by the employees, or other forms of questionnaire, 15%) (Table 1). Often, when the questionnaire plays an additional role in the measurement study design, this investigative method is focused more on the demographic aspects of the study groups (e.g., age, sex, nature of occupation, work experience, years of service, job, etc.) rather than the elements which may affect the results on occupational risk rates and/or the employees' exposure to ADs. Each study's average number of involved subjects (described as "medical professionals") is 266, calculated based on various cases. Ranking the articles based on participation, i.e., the number of subjects involved in the reviewed studies, 5 classes of numerousness can be defined. Only 5 % of the reviewed studies involved (i) over 1000 subjects or (ii) from 500 to 1000 subjects.

Most of the reviewed studies (35%) involved between 100 and 500 interviewed healthcare workers, followed on an equal footing by survey groups formed by (iii) 50 to 100 (20%) and (iv) 10 to 50 workers (20%). For what concern the contents of the questionnaires (Table 5), 6 out of 20 articles do not provide specific information about cytotoxic variables and/or previous health conditions capable of influencing – and further increasing – the probability of contracting tumors and/or other health problems; 4 of these studies are focused on the specific training of personnel in the administration of Ads.

In their article, Asefa and collaborators [5] illustrate a questionnaire-based study on three major sectors: demographic characterization of involved subjects, knowledge and practice on safe handling of drugs, and use of personal protective equipment. Further, 2 out of 6 articles [22,45] are survey-based studies revolving around the practice of HIPEC procedures (as in, the administration of a hyperthermic solution with a high concentration of chemotherapy directly into the peritoneal cavity); questions about the training and knowledge of specialized personnel and the availability of PPE. One of these also takes into consideration the PIPAC therapy, as in a locoregional therapy for peritoneal carcinomatosis. Another study [57] mainly focuses on the compliance of healthcare personnel to the correct use of PPE. The other three studies investigate risk perception and management after implementing control programs for ADs. Of the remaining 14 articles, six do not detect, among the study groups, any relevant variables known to have cytotoxic consequences on the exposed subjects. These mentioned variables concern the exposure to first- and second-hand smoke, to radiations (specifically, those common in the healthcare environment, such as ultraviolet and X radiation), the consumption of alcohol and other drugs, and previous health conditions.

Table 5. Number (and percentage of the total- 20 studies) of reviewed articles, divided according to the characteristics of questionnaires. PPE: Personal Protective Equipment**.**

Descriptive table of questionnaires	N (%)	References
Type of questionnaire		
Interview (oral examination of subjects)	1 (5%)	[48]
Survey and/or study population	10 (50%)	[22, 45, 46, 50-54, 56, 57]
Standardized questionnaire on general information	9 (45%)	[3, 5, 45, 47, 53, 55, 56, 58, 59]
Other	3 (15%)	[48, 53, 58, 60, 61]
Information on variables known to influence cytotoxic risk		
Smoking and/or second-hand smoke exposure	5 (25%)	[53, 55, 56, 58, 59]
Alcohol and drug consumption	3 (15%)	[55, 56, 59]
Exposure to radiation and chemical	6 (30%)	[47, 51, 53, 55, 56, 58]
Previous health conditions and medical history	5 (25%)	[53, 55, 56, 59]
Information on training and/or use of PPE		
Information on training and/or use of PPE provided in the study	11 (55%)	[3, 45-48, 51-54, 56, 57, 60, 61]
Information on training and/or use of PPE not provided in the study	9 (45%)	[5, 21, 22, 39, 49, 50, 55, 58, 59]

Among the 8 studies focused on exposure to cytotoxic risks, it is consistent that the element that most contributes to the increase in the probability of cytotoxic and carcinogenic risk in the medical field is radiation, used as a diagnostic tool. It is also interesting to note how the previous health conditions of the workers have equal weight to the exposure to tobacco smoke (25% of studies confirm both the presence of smokers among the subjects and previous pathologies among those same groups); this confirms the influence of external and subjective factors in the development of pathologies – in this case, linked to exposure to Ads – and the incidence of active and passive smoking on health conditions.

Regarding the information on the training of employees and their knowledge and use of PPE, most questionnaire-based studies (55%) deemed it necessary to explore this aspect of the medical profession. One of these studies not only relies on a questionnaire but also explores in depth the handling practices and events related to the manner of use of Ads and the specific use of PPE during the preparation and administration of drugs through a 6-week diary per subject [53]. This led to a detailed study description, a defined stratification of the personnel involved, and a deep knowledge of the techniques, guidelines, and materials used.

3.2.2. Overall Comment and Critical Issues

The analysis of the information summarized in the questionnaires provides an overview of some critical issues concerning the correlation between guidelines and/or training provided to staff and widespread contamination in hospital working environments. Of the 20 articles, 9 do not give evidence of the supply and use by personnel of PPE [5, 21, 22, 39, 49, 50, 55, 58, 59], and 4 of these [21, 55, 58, 59] describe the evidence of widespread contamination in the workplace due precisely to the lack of training and the incorrect or non-existent use of PPE. Of the 4 studies that highlight a widespread problem of surface contamination, 2 of these [21, 58] delve into the question relating to the lack of guidelines and/or specific training of medical personnel: the administration of drugs in oncological departments appears to be the area where it occurs most risky contact with medicines, reaching situations of exposure by dermal contact, by hand-to-mouth contact or inhalation of vapors. A particular case [56], however, provides evidence of how, while implementing incentive programs for the use of PPE and adopting international guidelines for the management of occupational risk provided by the American Society of Health-System Pharmacists

(ASHP), the NIOSH and the US OSHA (Occupational Safety and Health Administration), there remains a detectable residual genotoxic risk; therefore, there is a definable probability of contracting tumors following exposure to this family of drugs.

The lack of a staff training and education program on the risks of managing ADs is also reflected in the recurrence of cases of occupational accidents, such as accidental drug spills and injections. It should be noted that health surveillance must be arranged for workers exposed to ADs for whom the risk assessment results reveal a risk to health (and the health surveillance program should be specific to the type of exposure defined based on the risk assessment results).

Generally speaking, health surveillance can include detecting early and reversible signs of occupational diseases and contribute to promoting a safe and healthy working environment. To this end, it may be useful to collect as much relevant information as necessary for this purpose [2]. Anyhow, specific medical surveillance for personnel involved in managing and administering antiblastic agents is completely lacking (or, rather, is not documented) in the reviewed studies. Even when included, employee health monitoring programs appear to be insufficient.

3.3. Environmental Monitoring of Exposure to ADs

As said, environmental monitoring of contamination from ADs is one of the policies recommended by the authorities, especially in the European context. European Policy Recommendations underline the importance of defining procedures for detecting workplace AD contamination to identify the vehicles and routes of exposure and improve the efficiency of prevention and protection of the medical personnel [2]. As previously stated, 37 (77%) studies considered in this systematic review are based on the sampling of surfaces to determine the environmental contamination by ADs drugs in a hospital setting (Table 5). The sampling techniques adopted in the reviewed articles pertain exclusively to environmental sampling methods; therefore, biological sampling methods will be excluded, although sometimes cited within the considered sources, even if previous publications face the issue of contamination by cytotoxic drugs, focusing their method on the biological tracking and monitoring of drugs through the occupational process of preparation and administration of said drugs. The undeniable impact on subjects exposed to ADs is highlighted in numerous previous studies. Indeed, several studies demonstrate that remarkable portions of healthcare workers may have traces of these substances or their metabolites in biological fluids [18]. The biological monitoring helped to show the correlation between the detected presence of drugs in bodily fluids of medical workers (such as urine and blood) and relevant consequences on health conditions, commonly related to skin rashes, chromosomal aberrations, and, in female subjects, to infertility and miscarriage [9].

3.3.1. Sampling Techniques

Overall, analyzing the methods for the study of spread contamination, the reviewed studies can be sorted into three main categories: (i) those based on surface wipe sampling techniques, (ii) those that rely on dermal and pad samples, and (iii) those based on air sampling methods (comprehensive of personal samples) (Table 6). Around 64% of the 37 articles report using wipe sampling techniques to detect workplace contamination. For most of these studies, information on the numerical quantity of the samplings is provided. The process is useful and inexpensive; the required materials and samples-analysis-technologies are easily accessible and imply the possibility of numerous specimens to track the contamination pattern. It is a direct consequence that the greatest amount of information regarding materials and analysis techniques was available for studies based on environmental sampling of surfaces. The reviewed articles have provided detailed data regarding the number of samplings conducted through surface sampling: most wipe-samples-based studies (around 37%) collected between 100 and 500 samples, 17% of the studies collected between 10 to 50 samples, 10% collected between 50 and 10, and between 1 and 10 samples. Few studies have sampled between 500 and 1000 surfaces (3%) and more than 1000 surfaces (3%).

Table 6. Number (and percentage of the total - 37 studies) of reviewed articles, divided according to the characteristics of measurement techniques. n.a.: information not available and/or details not further described in the reviewed articles.

Descriptive table of measurements and sampling	N (%)	References
Type of samples		
Surface Wipe Sample	24 (65%)	[13, 15, 24, 26, 28, 29, 33-35, 37, 38, 40-44, 53-59, 61]
Air and/or Personal Sample	1 (3%)	[53]
Dermal and/or Pads Samples	6 (16%)	[28, 36, 56-59]
Other	2 (5%)	[25, 31]
Support used for Surface Wipe Samples (in 24 studies in which Surface Wipe Sampling was perfomed)		
Kleenex	1 (4%)	[13]
Gauze	2 (8%)	[44, 55]
Nonwoven	9 (38%)	[24, 26, 28, 37, 38, 42, 43, 53, 59]
Other	1 (4%)	[31]
n.a.	12 (50%)	[15, 29, 33-35, 40, 41, 54, 56-58, 61]
Sampling areas (in 37 studies in which environmental sampling was performed)		
Biological Safety Cabinets	9 (24%)	[13, 29, 35, 37, 41, 42, 44, 53, 57]
Surfaces in working areas and floors	18 (49%)	[13, 15, 24, 29, 34, 35, 38, 40, 41, 43, 44, 53-57, 59, 61]
Medical tools and/or clothes/fabrics	12 (32%)	[24, 26, 28, 31, 32, 36, 38, 55-59]
Everyday activities-related surfaces and commonly used objects	7 (19%)	[32, 34, 41-44, 55]
n.a.	4 (11%)	[8, 25, 33, 60]
Analytical procedures (in 37 studies in which environmental sampling was performed)		
HPLC-MS/MS	11 (30%)	[6, 9, 13, 23, 28, 29, 34 39, 40, 53, 54]
HPLC-MS	2 (5%)	[24, 26]
HPLC-UV-Vis	3 (8%)	[37, 58, 59]
HPLC-DAD	4 (11%)	[25, 43, 44, 55]
UPLC-MS/MS	1 (3%)	[35]
GC-MS	4 (11%)	[15, 41, 42, 54]
GC-MS/MS	4 (11%)	[30, 37, 38 56]
Voltammetry	2 (5%)	[30, 54]
Other *(semi-quantitative method for tracing (UV) and for exposure assessment (modeling))*	3 (8%)	[27, 31, 36]
n.a.	4 (11%)	[8, 57, 60, 61]

Only 1 out of the considered publications [53] describe a study based on air and personal sample techniques. The study was focused on evaluating the antiblastic drug exposure of healthcare workers at 3 university-based US cancer centers, which proved to be one of the most complete and thorough studies among those considered in this review.

A more relevant percentage (16%) of the 37 articles evaluated dermal exposure and/or pad samples. This method implies the evaluation of contamination directly on subjects whose skin has been potentially exposed to ADs. Only half of them provide precise information about the collected quantity of samples. [53]

3.3.2. Methods and Techniques of Surface Wipe Sampling of ADs

Delving into the surface wipe sampling materials and techniques (Table 6), 38% of the surface-sampling-based studies rely on nonwoven fabric. Diverse types of papers and pads are quoted in the articles, showing how similar materials may be used under different circumstances and how the macro-category of non-fabric-based samples may be divided into different methods and materials of analysis. Among these studies, it is interesting to highlight examples of nonwoven tissues, such as Whatman paper wetted with sterilized water – made by acid-hardened cellulose filters – exploited in two French studies (suggesting it may be a technique mostly popular in Europe), Kimtech and Kimwipe tissue – laboratory paper towels, the first wetted with ethyl-acetate ($C_4H_8O_2$) – useful for their high absorbency and chemical passivity to perform delicate tasks of sampling, and glass fiber filter papers, wetted with water, known to be used in one of the considered studies. Two of the 30 (8%) studies conducted in Portugal present a method based on using gauze to sample surfaces. However, tissue fiber (gauze) quickly dries the biological substance. Therefore, it is necessary to ensure the material is sufficiently moistened with ethyl-acetate.

3.3.3. Sampling Areas

Knowing most articles propose a surface sampling technique, the collection of information related on sampling positions is, in the present review, specifically focused on working surfaces and medical tools (Table 6). Indeed, surfaces in working areas, such as worktops, tables, trails, preparation, and drug administration surfaces, are included in 49% of the studies. In comparison, medical tools and/or clothes and fabrics available for medical personnel closely follow with a percentage of 32%. These sampling areas are distributed within the hospital environments involved in the preparation and administration of chemotherapy drugs and the patient care units, where the drugs are administered to patients via injection or other specific chemotherapy administration techniques. As reported by Hon and collaborators [29], the stages for the sampling activities can be divided into areas to recognize the most common areas of evaluation of contamination rates: (i) the delivery of ADs through the logistic department, (ii) the drug preparation in the specific isolated room in the pharmacy department equipped with biological safety cabinets (BSCs), (iii) the transportation within the wards and through different hospital environments, (iv) the administration of drug within the patient care units and (v) the waste disposal (which represent a further biological risk of contamination and a route for occupational exposure). Particularly, since BSCs are a recurring risk management measure, it is worth noting that 24% of the studies report having practiced samplings of BSC surfaces. BSCs prove to be a useful tool to remedy the widespread contamination; in the results subsequently discussed, it will be seen how a high environmental contamination is present only in 2 of the studies in which samplings were conducted on the surfaces of the BSCs. Some "Everyday objects" (such as phones, computer devices, handles and handlebars, and other objects shared by the medical personnel) involved in the medical facilities follow as a recurrent group (19% of the studies) of items considered among the detected surfaces. It is interesting to observe how these generic tools – in the narrow sense unrelated to the healthcare activities of administering antiblastic drugs – are included in the studies almost with the same frequency as BSCs, a specific medical device thought to prevent biohazard.

3.3.4. Analytical Procedures for Analysis of ADs Samples

The analysis of the ADs samples (collected with the previously described methods) can be conducted with different analytical procedures (Table 6). Mass spectrometry (single or tandem) is the most widely used analytical technique (38% of studies are known to use this technology). Of the considered studies, 9 out of the 14 use mass spectrometry reports to couple this technique with liquid chromatography. Further, 7 of the 14 considered studies couple mass spectrometry with gas chromatography. Alternatively, methods based on ultraviolet radiation or

X-rays are relatively frequent. One article also provided specific indications regarding the software used to support analytical techniques specifically created for biomedical research (MedCalc) [31]. Focusing on wipe test sampling analytical techniques (mostly used sampling technique) used in studies of this type, this work does not provide further information regarding these techniques, as they are reported in a recent review of the literature focused precisely on this topic [62].

3.3.5. Overall Comment and Critical Issues

Contamination of the workplace by ADs could be related to incorrect practices and/or a lack of risk management measurements in the investigated workplaces [23, 37, 52, 59]. Nevertheless, it should be noted that environmental contamination is also significantly reduced in the presence of correct training and protection of personnel. Only a few studies report relevant workplace contamination by ADs [6, 23, 25, 33, 40, 41]. Further, some of the reviewed studies, characterized by a critical issue of a general nature about the hospital structure and the healthcare workers involved, focus the attention on the economic impact of risk prevention devices, on the need to make drug monitoring and tracing programs more efficient, on the guidelines to be implemented to reduce exposure and recurrence of accidental events [13, 23, 31, 42, 43, 45, 48, 51, 52, 58, 59]. It is worth noting that for more than half of the reviewed articles, it was not possible to obtain information regarding the availability and/or of correct use personal protective equipment by health professionals [3, 6, 8, 15, 22-26, 29, 32-34, 38, 40-44, 49-53, 55, 57, 58, 61]. Only 11 studies reported the availability of training programs or guidelines and procedures for drugs management and use of protective devices [6, 13, 21, 23, 28, 31, 37, 39,42, 47, 48, 51, 52, 56, 57, 59, 60].

Further, only a few of these studies report and describe the presence of a specific medical surveillance protocol [13, 21, 23, 45-47]. A relevant link could be speculated between the adoption of clear and carefully imparted procedures and guidelines to personnel, the pertinent use of PPE (more useful and efficient in protecting the healthcare worker than in preventing the spread of ADs in the workplace), and the significant decrease in the concentration of contaminating substances in the environment. Concerning the problem of accidental contamination events, it can be stated that a small proportion (approximately 17%) of studies dealing with environmental monitoring report the occurrence of occupational accidents related to drug administration [3, 13, 23, 30, 34, 41, 42, 44-49, 52, 53, 60]. In most cases, these are spills that occurred during the preparation of the equipment for administering the drug to the patient: connection between tubes, syringes, and infusion lines, or contact with previously opened vials and/or vials damaged during transport of the material between hospital wards. It is logically difficult to predict the probability of the occurrence of accidental events of this type. Still, it is possible that the recurrence of these events could be limited by defining effective and efficient work procedures and operator training. Certainly, the degree of risk to which the healthcare worker is exposed increases significantly in the absence of personal protective equipment, especially when the professional accident involves dermal contact or accidental injection following the handling of syringes and infusion systems. Two studies [31, 38] can be particularly significant regarding workplace contamination's impact on healthcare workers' health conditions and the importance of making expensive technologies for prevention and protection from exposure to cytotoxic drugs available to hospital facilities and cancer treatment centers. The first of these two studies [31] effectively highlights how a closed-system drug transfer device can contribute to a significant containment of the diffusion of surface contamination. The second study [38] illustrates the advantage of using a cytotoxic safe infusion system (CSIS, i.e., a disposable sterile infusion system, functioning through a single closed line system by the effect of gravity or exerted pressure) for drug preparation and administration. Its usefulness lies in the ability to eliminate the risk of aerosolization of ADs and to prevent the spreading of substances on surfaces following accidental events in the event of a leak. However, a limit to the dissemination of the application of this technology is its rather expensive

cost and the need of a specific training program for the use of this technology.

4. Discussion

This study investigates the main techniques and practices currently used to assess exposure to ADs. This review focuses, in particular, on the (i) administration of questionnaires to workers and (ii) the environmental sampling techniques for the assessment of workplace contamination (especially on work surfaces) by ADs. As mentioned, this study did not evaluate biological monitoring, as it was considered in a recent systematic literature review [18]. From the studies considered in this work, however, it can be highlighted that only 19% of studies (Table 1) based their exposure assessments on both environmental sampling and the administration of questionnaires. These results indicate that a "multiparametric" approach still seems not to be considered in the majority of cases: for this reason, as mentioned, the authors recommend applying both types of evaluation to conduct an overall evaluation of exposure to ADs as complete as possible.

The following discussion can be drawn from the evaluation of the results reported in the 48 articles included in this review. In general, 23% of the considered studies were based solely on administering questionnaires to workers, while 58% focused only on environmental sampling. According to the authors, using a questionnaire associated with environmental sampling (and, in the best case, biological monitoring) could be the best solution for ADs exposure evaluation and risk management. Therefore, its integrated use is recommended. Evaluation studies of this type should also be performed in association with the introduction of new technologies aimed at minimizing the worker's exposure to ADs (e.g., robotic systems, isolators, HIPEC) to evaluate their effectiveness and to evaluate the application of peculiar procedures/protocols by health professionals. Furthermore, the assessments should be carried out in the various departments affected by a possible ADs contamination and on all the operators involved in their handling and management, and not exclusively in the case that can be considered as the worst-case scenario (e.g., ADs preparation area), to coherently evaluate all the possible exposure situations to ADs. For the same reason, activities conducted by healthcare professionals, such as cleaning surfaces and medical instruments and logistic activities (e.g., packaging, storage, and ADs transport), should be better evaluated (and thus included in the monitoring protocols) in terms of their potential contribution to occupational exposure to ADs. In addition, it can be suggested to evaluate a wide range of ADs in different workplace environments, as (i) hospital facilities tend to manage a wide variety of AD depending on the chemotherapy treatments envisaged and on the technologies available, and (ii) the availability of different contamination indicators allows to investigate the different behavior of the substances and, consequently, the different route of contamination to which medical personnel can be exposed.

More specifically, administering questionnaires (also understood as interviews, oral examinations, surveys, standardized questionnaires, or demographic studies) commonly aim to investigate the worker's knowledge concerning safe managing ADs and using PPE. Specifically, some studies have focused on evaluating the correct application of the procedures indicated for peculiar tools and technologies (e.g., HIPEC). In addition to this information (and to that of a descriptive/demographic type and, although less frequent, on variables known to influence the cytotoxic risk on health), the tendency seems to be to investigate topics such as the operator's perception of the risk and its management. The results of some studies analyzed in this review show how an AD contamination situation can often be correlated with the lack of standardized procedures, the incorrect use of PPE, and an incompletely satisfactory training of healthcare workers. The lack of a staff training and education program on AD management risks is also reflected in the recurrence of workplace accidents (e.g., accidental drug injections and spills). Further, another critical issue that emerged from the evaluation of the studies based on the administration of questionnaires is related to the lack of specific medical surveillance for the personnel involved in the management and administration of antiblastic agents, which in some cases would

appear to be completely lacking. ADs environmental monitoring is one of the policies for ADs risk assessment and management recommended by most of the authorities, especially in the European context. Specifically, European Policy Recommendations underline the importance of defining procedures for the detection of drugs, identifying the routes of contamination, and improving the efficiency of prevention and protection of medical personnel. In general, it can be stated that most of the studies considered in this review focused on (i) sampling based on surface wipe sampling techniques, followed by studies (ii) based on dermal and pad samples and, albeit less numerous, (iii) on air sampling methods (comprehensive of personal sampling campaigns). Studies based on AD environmental monitoring also suggest a correlation between incorrect practices and/or lack of risk management measurements (such as the correct use of PPE) in the investigated workplaces and the widespread contamination of surfaces by ADs. On the contrary, as expected, there is a significant link between the adoption of clear and carefully imparted procedures and guidelines to personnel, the pertinent use of PPE, and the significant decrease in the contaminating substances in the environment. However, in this case, there is still a significant lack of medical surveillance programs for health workers. Nevertheless, it is noted that environmental contamination is significantly reduced in the presence of correct training and personnel protection. Finally, considering the problem related to accidental events, it can be stated that a small proportion of studies report the occurrence of occupational accidents related to drug administration, mainly attributable to the preparation of the equipment for administering the drug to the patient (e.g., the connection between tubes, syringes, and infusion lines, or contact with previously opened vials and/or vials damaged during transport of the material between hospital wards): it is difficult to make predictions regarding the occurrence of these accidental events, but it is important to underline how the recurrence of these events could be limited by defining effective and efficient work procedures.

5. Conclusions

The present review and the studies analyzed in its drafting highlight several critical issues that require particular attention.

Specifically, (i) the correct use of standardized protocols for the management and manipulation of ADs, as well as (ii) the proper use of PPE, (iii) the correct training of all personnel involved in the handling and management of these drugs and (iv) complete health surveillance are essential features for the purpose the assessment and management of occupational risk posed by ADs. Although the critical issues reported above were already well known and recognized, from the analyzed articles, the need to implement these measures still emerges today, as environmental contamination by ADs seems to be a topical problem in hospital-type environments since several healthcare professionals are still exposed to ADs, despite the adoption of protective and preventive measures [18]. In particular, the literature is not yet fully comprehensive regarding assessing exposure to Ads for certain categories of healthcare workers (e.g., workers engaged in the logistics of ADs and individuals involved in cleaning surfaces potentially contaminated by Ads). A potentially critical scenario could arise for workers tasked with cleaning surfaces of pharmaceutical isolators or robotic instruments (or, more generally, work surfaces). While these preventive systems are designed to protect the individual responsible for preparing the ADs, they may not provide optimal protection for the healthcare worker responsible for cleaning them.

Although exposure to ADs is normally kept under control, thanks to the adoption of preventive interventions, the development/improvement of personal protective equipment, and the correct training and information activities for operators, from the studies analyzed in this review still emerge some criticisms that cannot be ignored: a "new" approach, which could be defined as "multiparametric" (which includes analyses of diverse types - from questionnaires to environmental and biological sampling), is therefore necessary. This approach should allow the implementation of optimal strategies that can protect workers while maintaining the clinical efficiency of antiblastic therapy [18].

This "multi-parametric" approach can be very useful since (i) different methodologies (i.e., environmental sampling, biological monitoring, questionnaires, and interviews) obviously and necessarily provide different information, which cannot be directly compared with each other, but which can provide complementary information, thus providing a total understanding of the exposure to ADs; (ii) a certain investigation methodology can be applied when another is not usable (for example, because analytical and procedural limits).

Supplementary Materials: The following are available online, Table S1. List of documents referred to ADs; Table S2. Search query arranged for each database; Table S3. Complete list of papers found suitable and reviewed in this study; Table S4. Number (and percentage of the total - 48 studies) of reviewed articles, divided according to the study period (five-year intervals); Table S5. Number (and percentage of the total - 48 studies) of reviewed articles, divided according to the study location (major geographical areas). Table S6. Number (and percentage of the total - 48 studies) of reviewed articles, divided according to: a) Healthcare facilities considered in the studies under review. b) Departments and wards considered in the studies under review.

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