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

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SUPPLEMENTARY MATERIAL

Table S1. List of documents referred to ADs. ADs: antineoplastic drugs; HDs: hazardous drugs. Document type: A: Alert; BC: Chapter of a book; D: Directive; G: Guide; GL: Guideline; LD: List of Drugs; TM: Technical Manual.

Reference	Title	Document type	Note
[1]	Guidelines for Cytotoxic (Antineoplastic) Drugs	GL	The first published guidelines for the management of ADs.
[2]	Controlling Occupational Exposure to Hazardous Drugs	TM	Withdrawn and replaced by the webpage Controlling Occupational Exposure to Hazardous Drugs.
[3]	Preventing occupational exposure to antineoplastic and other drugs in healthcare settings	A	Additional guidelines that address HDs or the equipment in which they are manipulated are reported by the NIOSH Alert.
[4]	ASHP Guidelines on Handling Hazardous Drugs	GL	Based on the NIOSH Alert.
[5]	List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings	LD	The list supersedes the 2004 list in the next NIOSH Alert and the 2014 list of HDs. The current update (2016) adds 34 drugs, five of which have safe-handling recommendations from the manufacturers.
[6]	Hazardous Drugs - Handling in Healthcare Settings	BC	Describes practice and quality standards for the handling of HDs.
[7]	Guidance for the safe management of hazardous medicinal products at work	G	This guide aims to provide an overview of the good practices available and give practical ways to reduce workers' exposure to hazardous medicinal products
[8]	Directive (EU) 2022/431 of the European Parliament and of the Council of 9 March 2022 amending Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens or mutagens at work	D	Directive 2022/431/EU amends Directive 2004/37/EC [9] on the protection of workers from the risks related to exposure to carcinogens or mutagens at work.

Table S2. Search query arranged for each database (last search: September 2022).

Database	Search query
Scopus	ALL ("antiblastic drug*" OR "antineoplastic drug*" OR "cytotoxic drug*" OR chemotherapy OR "hazardous drug*") AND ALL ("occupational exposure") AND ALL ("risk management" OR "risk assessment" OR "risk evaluation" OR "clinical risk") AND ALL ("healthcare*" OR "healthcare worker*" OR "care worker*")
Web of Science	(((ALL=("antiblastic drug*" OR "antineoplastic drug*" OR "cytotoxic drug*" OR chemotherapy OR "hazardous drug*")) AND ALL=("occupational exposure")) AND ALL=("risk management" OR "risk assessment" OR "risk evaluation" OR "clinical risk")) AND ALL=("healthcare*" OR "healthcare worker*" OR "care worker*")
PubMed	((("antiblastic drug*" OR "antineoplastic drug*" OR "cytotoxic drug*" OR chemotherapy OR "hazardous drug*") AND ("occupational exposure")) AND ("risk management" OR "risk assessment" OR "risk evaluation" OR "clinical risk")) AND ("healthcare*" OR "healthcare worker*" OR "care worker*")

Table SM3. Complete list of papers found suitable and reviewed in this study.

Reference	First Author	Publication year	Title	Source	DOI
[10]	Acramel et al.	2022	Application of an Environmental Monitoring to Assess the Practices and Control the Risk of Occupational Exposure to Cyclophosphamide in Two Sites of a French Comprehensive Cancer Center	Ann Work Expo Health. 2022; 66(9):1215-1223	10.1093/annweh/wn.a.ac035
[11]	Altini et al.	2016	Risk management of onco-hematological drugs: How and how fast can we improve?	Tumori. 2016; 102(Suppl 1):15-29.	10.5301/tj.5000540
[12]	Asefa et al.	2021	Knowledge and Practices on the Safe Handling of Cytotoxic Drugs Among Oncology Nurses Working at Tertiary Teaching Hospitals in Addis Ababa, Ethiopia	Drug Healthc Patient Saf. 2021;13:71-80	10.2147/DHPS.S289025
[13]	Azari et al.	2016	Environmental monitoring of occupational exposure to cyclophosphamide drug in two Iranian hospitals	Int J Cancer Manag. 2017;10(1):e7229	10.17795/ijcp-7229
[14]	Benoist et al.	2022	Perception, knowledge and protective practices for surgical staff handling antineoplastic drugs during HIPEC and PIPAC	Pleura Peritoneum. 2022;7(2):77-86	10.1515/pp-2021-0151
[15]	Bernabeu-Martínez et al.	2021	Perception of risk of exposure in the management of hazardous drugs in home hospitalization and hospital units	PLoS One. 2021;16(7):e0253909.	10.1371/journal.pone.0253909
[16]	Bobin-Dubigeon et al.	2013	A new, validated wipe-sampling procedure coupled to LC-MS analysis for the simultaneous determination of 5-fluorouracil, doxorubicin and cyclophosphamide in surface contamination	J Anal Toxicol. 2013 Sep;37(7):433-9	10.1093/jat/bkt045
[17]	Boiano et al.	2014	Adherence to safe handling guidelines by health care workers who administer antineoplastic drugs	J Occup Environ Hyg. 2014;11(11):728-40	10.1080/15459624.2014.916809

[18]	Boiano et al.	2015	Adherence to Precautionary Guidelines for Compounding Antineoplastic Drugs: A Survey of Nurses and Pharmacy Practitioners	J Occup Environ Hyg. 2015;12(9):588-602	10.1080/15459624.2015.1029610
[19]	Claraz et al.	2020	Assessment of efficacy of postinfusion tubing flushing in reducing risk of cytotoxic contamination	Am J Health Syst Pharm. 2020; 77(22):1866-1873	10.1093/ajhp/zxaa357
[20]	Connor et al.	2010	Evaluation of antineoplastic drug exposure of health care workers at three university-based US cancer centers	J Occup Environ Med. 2010;52(10):1019-27	10.1097/JOM.0b013e3181f72b63
[21]	Constantinidis et al.	2011	Occupational health and safety of personnel handling chemotherapeutic agents in Greek hospitals	Eur J Cancer Care (Engl). 2011;20(1):123-31.	10.1111/j.1365-2354.2009.01150.n.a.
[22]	Cotteret et al.	2020	External contamination of antineoplastic drug vials: an occupational risk to consider	Eur J Hosp Pharm. 2022 Sep;29(5):284-286	10.1136/ejhpharm-2020-002440
[23]	Crickman	2016	Chemotherapy Safe Handling: Limiting Nursing Exposure With a Hazardous Drug Control Program.	Clin J Oncol Nurs. 2017;21(1):73-78.	10.1188/17.CJON.73-78
[24]	Crul and Simons-Sanders	2018	Carry-over of antineoplastic drug contamination in Dutch hospital pharmacies	J Oncol Pharm Pract. 2018;24(7):483-489	10.1177/1078155217704990
[25]	Dugheri et al.	2018	A new approach to assessing occupational exposure to antineoplastic drugs in hospital environments	Arh Hig Rada Toksikol. 2018 Sep 1;69(3):226-237.	10.2478/aiht-2018-69-3125
[26]	Fernandes et al.	2016	Workplace Activity in Health Professionals Exposed to Chemotherapy Drugs: An Otoneurological Perspective	Int Arch Otorhinolaryngol. 2016;20(4):331-338.	10.1055/s-0036-1572431.
[27]	Forges et al.	2021	Evaluation of a safe infusion device on reducing occupational exposure of nurses to antineoplastic drugs: a comparative prospective study. Contamoins-1	Int Arch Occup Environ Health. 2021;94(6):1317-1325	10.1007/s00420-021-01679-x.
[28]	Fransman et al.	2014	Leukemia from dermal exposure to CP among nurses in the Netherlands: Quantitative assessment of the risk	Ann Occup Hyg. 2014 Apr;58(3):271-82.	10.1093/annhyg/met077

[29]	Ferron et al.	2015	Professional risks when carrying out cytoreductive surgery for peritoneal malignancy with hyperthermic intraperitoneal chemotherapy (HIPEC): A French multicentric survey	Eur J Surg Oncol. 2015;41(10):1361-7.	10.1016/j.ejso.2015.07.012
[30]	Hon et al.	2011	Pilot evaluation of dermal contamination by antineoplastic drugs among hospital pharmacy personnel	Can J Hosp Pharm. 2011;64(5):327-32	10.4212/cjhp.v64i5.1067
[31]	Hon et al.	2011	Occupational Exposure to Antineoplastic Drugs: Identification of Job Categories Potentially Exposed throughout the Hospital Medication System	Saf Health Work. 2011;2(3):273-81	10.5491/SHAW.2011.2.3.273
[32]	Kieffer et al.	2015	Preventing the contamination of hospital personnel by cytotoxic agents: evaluation and training of the para-professional healthcare workers in oncology units	Eur J Cancer Care (Engl). 2015 (3):404-10	10.1111/ecc.12249
[33]	Kim et al.	2019	Korean nurses' adherence to safety guidelines for chemotherapy administration	Eur J Oncol Nurs. 2019;40:98-103	10.1016/j.ejon.2019.04.002
[34]	Koller et al.	2018	Environmental and biological monitoring on an oncology ward during a complete working week	Toxicol Lett. 2018;298:158-163	10.1016/j.toxlet.2018.05.002.
[35]	Kopp et al.	2013	Evaluation of working practices and surface contamination with antineoplastic drugs in outpatient oncology health care settings	International Archives of Occupational and Enviromental Health	10.1007/s00420-012-0742-z
[36]	Korczowska et al.	2020	Environmental contamination with cytotoxic drugs in 15 hospitals from 11 European countries—results of the MASHA project	Eur J Oncol Pharm 2020; 3(2):p e24	10.1097/OP9.0000000000000024
[37]	Kumari et al.	2017	Potential Health Risks among Oncology Staff Nurses of Selected Hospitals due to Antineoplastic Drug Exposure	Indian J Public Health Res Dev 2017; 8(4): 358-361	10.5958/0976-5506.2017.00369.2
[38]	Ladeira et al.	2014	Assessment of genotoxic effects in nurses handling cytostatic drugs	Toxicol Environ Health A. 2014;77(14-16):879-87.	10.1080/15287394.2014.910158
[39]	Lalande et al.	2012	Evaluation of safe infusion devices for antineoplastic administration	J Infus Nurs. 2015;38 Suppl 6:S29-35	10.1097/NAN.0b013e3182659abd

[40]	Larroque et al.	2021	Evaluation of the environmental contamination and exposure risk in medical/non-medical staff after oxaliplatin-based pressurized intraperitoneal aerosol chemotherapy	Toxicol Appl Pharmacol. 2021;429:115694	10.1016/j.taap.2021.115694
[41]	Leduc-Souville et al.	2013	Risk management of excreta in a cancer unit	Clin J Oncol Nurs. 2013 Jun;17(3):248-52.	10.1188/13.CJON.248-252
[42]	Liu et al.	2022	Nurses' knowledge, perceptions, and behaviors regarding antineoplastic drugs: the mediating role of protective knowledge	Front. Nurs. 202; 29(2), 3922,155-163.	10.2478/fon-2022-0017
[43]	Moretti et al.	2015	Micronuclei and chromosome aberrations in subjects occupationally exposed to antineoplastic drugs: a multicentric approach	Int Arch Occup Environ Health. 2015;88(6):683-95.	10.1007/s00420-014-0993-y
[44]	Mucci et al.	2020	Occupational exposure to antineoplastic drugs in hospital environments: potential risk associated with contact with cyclophosphamide- and ifosfamide-contaminated surfaces	Med Pr. 2020;71(5):519-529.	10.13075/mp.5893.00931
[45]	Ndaw et al.	2018	Occupational exposure to platinum drugs during intraperitoneal chemotherapy. Biomonitoring and surface contamination	Toxicol Lett. 2018;298:171-176.	10.1016/j.ton.a.let.2018.05.031
[46]	Rossignol et al.	2020	A fully validated simple new method for environmental monitoring by surface sampling for cytotoxics	J. Pharmacol Toxicol Methods. 2020;101:106652	10.1016/j.vascn.2019.106652
[47]	Sadeghipour et al.	2013	Chemical contamination during the preparation of cytotoxics: validation protocol for operators in hospital pharmacies	J Oncol Pharm Pract. 2013;19(1):57-64	10.1177/1078155212452764
[48]	Sessink et al.	2011	Reduction in surface contamination with antineoplastic drugs in 22 hospital pharmacies in the US following implementation of a closed-system drug transfer device	J Oncol Pharm Pract. 2011;17(1):39-48	10.1177/1078155210361431

[49]	Siderov et al.	2010	Reducing workplace cytotoxic surface contamination using a closed-system drug transfer device	J Oncol Pharm Pract. 2010 Mar;16(1):19-25	10.1177/1078155209352543
[50]	Sottani et al.	2010	An analysis to study trends in occupational exposure to antineoplastic drugs among health care workers	J Chromatogr B Analyt Technol Biomed Life Sci. 2010;878(27):2593-605	10.1016/j.jchromb.2010.04.030
[51]	Sottani et al.	2012	Occupational exposure to antineoplastic drugs in four Italian health care settings	Toxicol Lett. 2012;213(1):107-15.	10.1016/j.ton.a.let.2011.03.027
[52]	Sugiura, et al.	2011	Multicenter study for environmental and biological monitoring of occupational exposure to cyclophosphamide in Japan	J Oncol Pharm Pract. 2011;17(1):20-8	10.1177/1078155210369851
[53]	Sugiura, et al.	2011	Risks to health professionals from hazardous drugs in Japan: A pilot study of environmental and biological monitoring of occupational exposure to CP	J Oncol Pharm Pract. 2011;17(1):14-9.	10.1177/1078155209358632
[54]	Ursini et al.	2019	Antineoplastic drug occupational exposure: a new integrated approach to evaluate exposure and early genotoxic and cytotoxic effects by no-invasive Buccal Micronucleus Cytome Assay biomarker	Toxicol Lett. 2019 Nov;316:20-26	10.1016/j.toxlet.2019.08.022
[55]	Viegas et al.	2018	Occupational exposure to cytotoxic drugs: the importance of surface cleaning to prevent or minimise exposure	Arh Hig Rada Toksikol. 2018;69(3):238-249.	10.2478/aiht-2018-69-3137
[56]	Viegas et al.	2014	Antineoplastic drugs contamination of workplace surfaces in two Portuguese hospitals	Environ Monit Assess. 2014 Nov;186(11):7807-18.	10.1007/s10661-014-3969-1
[57]	Villarini et al.	2011	Assessment of primary, oxidative and excision repaired DNA damage in hospital personnel handling antineoplastic drugs	Mutagenesis. 2011 May;26(3):359-69.	10.1093/mutage/geq102

Period of the Study

While it is possible to clearly state the publication year for each of the considered studies, it is not possible to provide a trend about the study period - meant as the time span in which the surveys and/or the measurements of interest took place (Table 2). Roughly 48% of the reviewed articles do not provide sufficiently precise information on the time range, in terms of years in which the monitoring campaign took place. Regarding the remaining articles, considering five-year intervals from 1999 to 2022, a higher number of publications took place in the years between 2008 and 2012, showing a percentage of carried-out searches of 19%. It is followed closely by the 17% of studies taking place in the years from 2013 to 2017. Notably, some of the studies reported data from more than one of the identified periods. Based on our evidence, it's safe to affirm that at least 36% of the literature included in this systematic review is based on research performed in the decade from 2008 and 2017. These articles focus on the characterization of occupational exposure to ADs, the assessment of the associated risk and the staff's adherence to the prevention guidelines defined by the hospital. These may be inspired by the HDs lists by NIOSH published in 2004 and subsequently updated in 2010 and 2012.

Table S4. Number (and percentage of the total - 48 studies) of reviewed articles, divided according to the study period (five-year intervals). n.a.: information not available in the reviewed articles.

Study period	N (%)	References
2018 - 2022	5 (10%)	[12, 22, 40, 42, 44]
2013 - 2017	8 (17%)	[23 ,27, 29, 33, 34, 36, 45, 56]
2008 - 2012	9 (19%)	[16-18, 24, 32, 35, 41, 50, 51]
2003 - 2007	5 (10%)	[21, 24, 48, 50, 53]
1999 - 2002	3 (6%)	[24, 48, 50]
n.a.	23 (48%)	[10, 13-15, 19, 20, 25, 26, 28, 30, 31, 37, 38, 43, 46, 47, 49, 52, 54, 55, 57]

Geographical Distribution

Information about the geographical distribution is reported with an in-depth precision (Table 3): 29 of the reviewed studies (60%) are based in Europe, with most of them spread among France and Italy (21% and 17% respectively). It is interesting to see how Europe is the continent most involved in the study of occupational risk from ADs, while North America and Asia, in a first approximation, share the same degree of involvement in this field (12% and 10% respectively). Studies carried out in Europe show a more widespread application of new technologies in the medical field, such as PIPAC (Pressurized Intra Peritoneal Aerosol Chemotherapy) and HIPEC (Hyperthermic Intraperitoneal Chemotherapy) for the administration of ADs. They also suggest a deepening of knowledge among the personnel, following the application of guidelines, and experimentation of methods suitable for monitoring the contamination of places and surfaces in medical departments. The articles published in China, Japan and South Korea suggest the widespread goal of understanding the perception of risk by the medical personnel, and the potential risk influenced by the healthcare workers' knowledge of the guidelines and the application of the risk prevention methods. As for the studies published in North America and Australia, on more than one occasion they focus on the evaluation of risk reduction following the implementation of drug control programs and the use of the closed-system drug transfer device.

Table S5. Number (and percentage of the total - 48 studies) of reviewed articles, divided according to the study location (major geographical areas). n.a.: information not available in the reviewed articles.

Study location	N (%)	References
Australia	1 (2%)	[49]
Brazil	1(2%)	[26]
Canada	2 (4%)	[30,31]
China	1 (2%)	[42]
Ethiopia	1 (2%)	[12]
Europe (multi-center study)	1 (2%)	[36]
France	10 (21%)	[10, 14, 16, 29, 32, 39-41, 45, 46]
Germany	2 (4%)	[34, 35]
Greece	1 (2%)	[21]
India	1 (2%)	[37]
Iran	1 (2%)	[13]
Italy	8 (17%)	[11, 25, 43, 44, 50, 51, 54, 57]
Japan	2 (4%)	[52, 53]
The Netherlands	2 (4%)	[24, 28]
Portugal	3 (6%)	[38, 55, 56]
South Korea	1 (2%)	[33]
Spain	1 (2%)	[15]
Switzerland	1 (2%)	[47]
U.S.A.	4 (8%)	[18, 20, 23, 48]
n.a.	4 (8%)	[17, 19, 22, 27]

Investigated Healthcare Structures

As, understandably, most of the reviewed studies being carried out within general hospital facilities, open for public access and service, three main categories of environments are considered in this study: (i) hospitals and university hospitals (71%), (ii) cancer treatment centres (10%) and other healthcare structures (13%). Notably, some of the study investigate more than one kind of this structure and some (15%) do not report detailed information on the type of healthcare structure in which the study was performed (Table 4.a). More in detail, speaking about these categories of healthcare structure, aware of the consistent lack of detailed description about the specific department investigated in the reviewed studies (around 65% of the studies do not provide clear information about this), most of the measurements within hospital structures involve the pharmacy department/drug-preparation unit (19%). Other main departments considered in studies under review are the administration units (8%), patient care units (4%) and hospital areas specifically used for the treatment of oncological pathologies (2%) (Table 4.b). Regarding the obtained results, it's interesting to observe how the study of environmental contamination is, understandably, mostly relegated to the medicines-preparation areas. However, this could be a limiting element as regards the contamination of shared areas in the hospital structure, with the possibility of putting at risk medical personnel who are not used – and consequently, unprepared – to the management of ADs.

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. n.a.: information not available in the reviewed articles.

Investigated environment		N (%)	Reference
a	Hospital or University Hospital	34 (71%)	[12-14, 19-21, 24-28, 30-39, 42-46, 48-50, 52-54, 56, 57]
	Cancer treatment centre/oncology hospital	5 (10%)	[16, 31, 36, 40, 52]
	Other	6 (13%)	[10, 11, 23, 39, 51, 55]
	n.a.	7 (15%)	[15, 17, 18, 22, 29, 41, 47]
b	Pharmacy and/or preparation units	9 (19%)	[22, 30, 46, 48-51, 54, 56]
	Administration units	4 (8%)	[33, 46, 54, 56]
	Patients care units	2 (4%)	[10, 51]
	Oncologic and/or other surgery units	1 (2%)	[45]
	Other	6 (13%)	[10, 28, 34, 35, 39, 53]
	n.a.	31 (65%)	[11-21, 23-27, 29, 31, 32, 36-38, 40-44, 47, 52, 55, 57]

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