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Carcinogenic drug exposure among health-sector workers: the need for exposure assessment and surveillance

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ABSTRACT Antineoplastic drugs (ANDs) used for chemotherapy can cause secondary cancers in treated patients and can pose carcinogenic risks to health-sector workers anywhere along these drugs' life cycle in a facility, from production to patient administration. Several PAHO/WHO Collaborating Centers (CCs) have experience addressing these hazards in the health sector. The objectives of this report are four-fold: 1) Provide an overview of longstanding research and prevention efforts, led by PAHO/WHO and its Occupational Health CCs, aimed at reducing the burden of occupational cancer in the Americas; 2) Discuss how robust AND exposure assessment and educational/outreach work by PAHO CCs can form the basis of exposure mitigation efforts among health-sector workers; 3) Through the presentation of original AND exposure assessment data from a pharmaceutical compounding facility in Chile, highlight relatively inexpensive methods by which such data can be generated; and 4) Discuss how effective, periodic environmental surveillance in healthcare facilities results in the identification of AND contamination in the work environment and enables the implementation of low-cost, high-impact interventions to reduce the risk of occupational cancer in health-sector workers, including in limited-resource settings.

The risk of health-sector worker exposure to ANDs and other hazardous drugs is an important issue for inclusion within PAHO/WHO's broader efforts at reducing the impact of occupational cancer in the Americas. This report demonstrates that a wide range of accessible AND-exposure mitigation strategies are feasible at both a facility and a national policy level across the hemisphere.

Keywords Occupational cancer; risk assessments; health personnel; antineoplastic agents.

It is estimated that anywhere from 2–8% of all cancers are, at least in part, caused by occupational exposures (1), with occupational carcinogens responsible for 350,000 deaths and 7.2 million disability-adjusted life years (DALYs) worldwide in 2016 (2). In the Americas, the rate of occupational cancer deaths is estimated at approximately 5–15 per 100,000 (2), but this is likely an underestimate due to a possible lack of accurate attribution to occupational exposures, under-reporting, and absence of robust surveillance systems.

Efforts at reducing the burden of occupational cancer in the Americas must rely on effective surveillance mechanisms in order to both quantify the problem and identify targets for intervention. The challenges inherent in such surveillance are numerous, but, in part through PAHO/WHO-led initiatives, have been overcome in certain areas and led to the implementation of concrete programs to prevent and mitigate risk factors for occupational cancer across different industries and countries. A case in point is the Americas Elimination of Silicosis Initiative, which included an emphasis on the prevention of silica-induced lung cancer (3).

While legacy carcinogens associated with 'dirty industries', such as asbestos and benzene, easily come to mind when

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considering occupational carcinogen exposure, a surprising additional source of risk arises from the unlikely work sector of health care: the hazardous, anti-cancer drugs (also known as antineoplastic drugs, or ANDs) used for chemotherapy. Many of these drugs are both acutely toxic and have chronic side effects, including, counter-intuitively, causing cancer themselves (4). The use of ANDs have already risen more than 30% in certain low- and middle-income countries (LMICs) from 2010-2019 (5). With the increased cancer incidence expected globally, and especially across LMICs in the next two decades (6), the continued increase in the use of these drugs is also anticipated.

With WHO's emphasis on non-communicable diseases (NCDs) in the last decade and a new focus on ensuring access to cancer treatment in LMICs, the risk of such drug exposure to healthcare workers and other health-sector workers (e.g. cleaning/laundry staff, veterinary workers, and those involved in pharmaceutical preparation), operating outside safety frameworks found in well-resourced countries, must be addressed.

The objectives of this report are four-fold: 1) Provide an overview of longstanding research and prevention efforts, led by PAHO/WHO and its Occupational Health Collaborating Centres (CCs), aimed at reducing the burden of occupational cancer in the Americas; 2) Discuss how robust AND exposure assessment and educational/outreach work by PAHO CCs can form the basis of exposure mitigation efforts among health-sector workers; 3) Through the presentation of original AND exposure assessment data from a pharmaceutical compounding facility in Chile, highlight relatively inexpensive methods by which such data can be generated; and 4) Discuss how effective, periodic environmental surveillance in healthcare facilities results in the identification of AND contamination in the work environment and enables the implementation of low-cost, high-impact interventions to reduce the risk of occupational cancer in health-sector workers, including in limited-resource settings.

I. MONITORING AND PREVENTION OF OCCUPATIONAL CANCER IN THE AMERICAS: PAHO'S LEAD ROLE

Accurately estimating the burden of workplace carcinogen exposure is a constantly evolving science, which must account for the dose and duration of workers' exposure, data which are often unfortunately unavailable. Estimating the number of exposed workers in any given industry is especially challenging in LMICs, including many in the Americas, given the large proportion of workers in the informal labor force (7).

These challenges make cross-disciplinary and cross-country collaboration all the more essential. In this, PAHO plays a central role in bringing together and facilitating the exchange of knowledge, expertise, and experience among experts and worker representatives across different institutions and countries. Instrumental in PAHO's efforts has been its extensive network of CCs, comprised of universities, hospitals, research institutes, academies, and ministries designated to carry out certain initiatives in support of PAHO's programs, with 15 such centers comprising the Occupational Health CC network (8).

PAHO's occupational cancer prevention work in the Americas, in close collaboration with its CCs, has accelerated in recent years. As part of WHO's Global Plan of Action on Workers' Health (2008-2017), PAHO prioritized several target areas for occupational and environmental cancer prevention measures, including elimination of asbestos- and silica-related diseases, increasing hepatitis B immunization for health-sector workers, elimination of second-hand tobacco smoke from all indoor workplaces, and the creation of national registries, reporting, and information systems (3). Over the past decade, PAHO has continued its focus on the prevention and control of occupational and environmental cancer, with the adoption of the CARcinogen EXposure (CAREX) model for use in the Americas (9) and through its current Plan of Action on Workers' Health (2015-2025) (10).

Since 2009, the Occupational Health CC at the University of Maryland, Baltimore in the U.S. (UMB) has collaborated with the CC at El Bosque University in Colombia, which shares occupational cancer terms of reference, on several occupational cancer prevention initiatives. One such project was the development, along with experts from the Canadian Occupational Cancer Research Centre and the Latin American Council on Hygiene and Safety, of a Spanish-English webinar "Chemical Substances, Cancer, and Work: Enhancing the sound management of chemicals for cancer prevention" at the 2014 World Day for Safety and Health at Work (11). The UMB and El Bosque University CCs have continued to collaborate on the issue of health-sector worker exposure to ANDs, resulting in two AND exposure assessment publications from a Colombian study, published in 2016-17 (12,13).

II. HEALTH-SECTOR WORKER EXPOSURE TO ANDS: OVERVIEW OF COMMONLY-FOUND CARCINOGENS AND EXPOSURE ASSESSMENT STRATEGIES

Health-sector worker exposure to ANDs is a useful case study in the challenges of adequate exposure assessment to target areas for health interventions, including many that can be readily implemented in limited-resource settings.

II.A. ANDs: Commonly found carcinogens in healthcare settings

It has been known for decades that certain medications pose health risks to workers who handle or otherwise come into contact with them at various stages of the drugs' "life cycle", from production all the way to patient administration and elimination into the waste stream. The U.S. National Institute for Occupational Safety and Health (NIOSH; also a CC) classifies a drug as hazardous if sufficient evidence, from animal and/or human studies, demonstrates that it causes cancer, is mutagenic or genotoxic, causes developmental or reproductive toxicity, and/or is acutely toxic (14).

The WHO's International Agency for Research on Cancer (IARC) Monographs on the Identification of Carcinogenic Hazards to Humans are an authoritative compilation of human carcinogens and contain classifications of many ANDs (Table 1) as Group 1 (carcinogenic to humans) and Group 2A (probably carcinogenic to humans) (15). IARC's list is relied upon by public health organizations and agencies, including PAHO (16), the European Commission's European Code Against Cancer initiative (17) and NIOSH (18).

TABLE 1.[a] ANDs on 1) IARC's Group 1 (carcinogenic to humans); or 2) IARC's Group 2A (probably carcinogenic to humans) List (15,22)

Antineoplastic Drugs (ANDs)[b]	
IARC Group 1 (Carcinogenic to Humans)	IARC Group 2A (Probably Carcinogenic to Humans)
Arsenic trioxide	Azacitidine
Azathioprine	BCNU
Busulfan	CCNU
Chlorambucil	Chlorozotocin
Chlornaphazine	Cisplatin
Cyclophosphamide	Doxorubicin HCl
Etoposide	Mechlorethamine HCl
Etoposide-cisplatin-bleomycin (ECB)	*N*-Ethyl-*N*-nitrosourea
Melphalan	*N*-Methyl-*N*-nitrosourea
Methoxsalen	Procarbazine HCl
Mustargen-oncovin-procarbazine-prednisone (MOPP)	Teniposide
Semustine	
Tamoxifen	
Thiotepa	
Treosulfan	

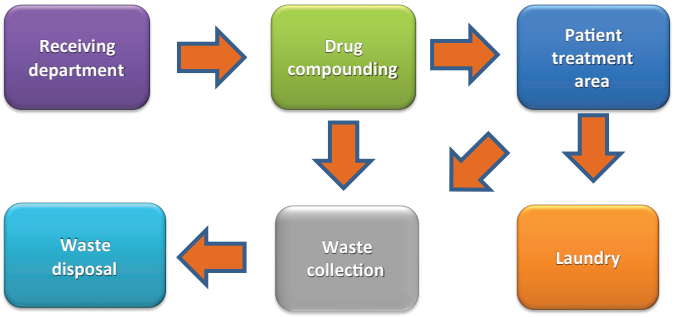
ANDs (antineoplastic drugs)
IARC (International Agency for Research on Cancer)

a. This table was compiled by one of the authors (SA) based on the list presented in PAHO's 2013 Safe Handing Guidance, in addition to cross-checking the list against the original source documents: publicly available, open-access monographs published by IARC. Both sources are cited in the table heading.
b. This list does not include *non-AND* drugs that are classified by NIOSH as hazardous based on their carcinogenicity, or drugs which display other toxicities, such as reproductive, developmental, genotoxic, mutagenic, or direct-organ-toxic effects. For a complete list of drugs hazardous to health-sector workers, including all carcinogenic drugs, see the "NIOSH List of Hazardous Drugs in Healthcare Settings, 2020" (draft) (4).

ANDs comprise the majority of hazardous drug classes in healthcare settings that are known to be carcinogenic (4). In addition to their potentially carcinogenic effects, ANDs can cause a variety of other short-term (e.g. hair loss, nausea, and hypersensitivity) and long-term (e.g. reproductive and developmental) side effects in exposed workers (19). For this reason, studies on the prevalence of, and potential remedies to, occupational exposure to ANDs, have been a significant focus of health-sector worker protection.

Exposure to ANDs can occur at various points within healthcare workflows (Figure 1). Drug compounding (preparation) is a process by which medications are produced from manufactured stock materials, usually drugs in powder form that require liquid diluent to be added to the drug vial which is under pressure. This activity, which optimally should be performed within a biologic safety cabinet or other containment device, in some settings is performed by pharmacists or nurses at the point of care where medications are ultimately administered to patients. As evidenced by the case study below, compounding of ANDs – even in centralized compounding facilities experienced in performing such production techniques – can pose a risk to workers through skin contact, inhalation, or even ingestion of drug aerosols and/or finished product residues. The transport/transfer and administration of drugs within healthcare facilities are other potential points of exposure and are key targets of safe handling guidance. Finally, an often-overlooked process in the realm of AND exposures involves the cleaning of work areas in which any of the aforementioned steps took place and where drug residues may remain.

FIGURE 1.[a] Path of Hazardous Drugs Through a Healthcare Facility (22)



Source: Reproduced from Safe Handling of Hazardous Chemotherapy Drugs in Limited-Resource Settings. Washington, DC : PAHO, 2013. Available from: https://www.paho.org/hq/dmdocuments/2014/safe-handling-chemo-therapy-drugs.pdf

II.B Exposure assessment for ANDs

Surveillance methods of health-sector worker exposure to ANDs comprises environmental monitoring, which detects release of AND residues on work surfaces and in the air, and biological monitoring, which quantifies workers' actual absorption of the hazardous drugs. Exposure monitoring most commonly involves wipe sampling studies of the work environment, recommended by the United States Pharmacopeia (USP) 800 to be performed at baseline and at least every 6 months thereafter (20) and by the International Society of Oncology Pharmacy Practitioners (ISOPP) at least annually (21), and which are an affordable approach in limited-resource settings. Biological monitoring is generally more resource-intensive and may require human subjects' approval due to collection of bodily fluids (12). Regardless of method, such exposure assessment is essential to measure worker exposure to potential carcinogens and increase workers' awareness about the risks of handling ANDs, and periodically to evaluate the effectiveness of safety procedures to mitigate such exposure.

A 1979 urine mutagenicity study was the first to document health-sector worker exposure to ANDs, in nurses who prepared and administered them (22). Numerous environmental and biological monitoring studies have subsequently been published, with most, however, focusing on high-income-country settings (23). UMB has been actively collaborating with Latin American colleagues to quantify health-sector worker exposure to ANDs in limited-resource settings in the Americas. In 2016, researchers at the Universidad de Concepción in Concepción, Chile and UMB demonstrated the effectiveness of a relatively low-cost analytical method, using a High-Performance-Liquid-Chromatography-UV (HPLC-UV) instrument, to detect low levels of AND contamination on work surfaces (12) and, the following year, successfully utilized the technology in a public hospital in Colombia to detect various AND residues on work surfaces in multiple areas of the hospital, including the preparation/compounding and administration areas (13). (This Colombian collaboration was also enabled by the years-long partnership between UMB and the El Bosque CC.) In the study, the IARC Group 1 carcinogen cyclophosphamide (Table 1) was detected even after thorough disinfection/cleaning procedures, in some cases at even higher amounts than before cleaning, and even though the facility had adopted U.S. Occupational Safety and Health Administration and NIOSH safe handling guidelines.

This highlighted the importance of ensuring the effective implementation of both proper handling and cleaning protocols for ANDs and other hazardous drugs in healthcare facilities.

II.C. Exposure assessment in a central pharmacy compounding facility: New data from Chile

Nearly all previous AND-exposure monitoring studies have focused on healthcare facilities, such as clinics and hospitals (23). New data have been compiled by this paper's first author and his colleagues at the Universidad de Concepción, from a wipe sampling study carried out in a centralized compounding facility (CCF) in Concepción, Chile. This pilot study demonstrates the importance of baseline exposure assessment as a means of determining the need for safety controls, in addition to the feasibility of exposure assessment, replicating a relatively low-cost HPLC-UV analytical methodology especially adapted for this purpose (12).

The CCF in Concepción supplies patient-individualized doses of ANDs to an estimated one third of the public and private hospitals in Chile. Key areas of the facility include a clean room where compounding is undertaken, a storage room, and an AND waste area. Local and U.S. Occupational Safety and Health Administration (OSHA) (24) and NIOSH (14) recommendations for the safe handling of hazardous drugs are instituted at the facility. At the time of the study, workers directly involved in handling ANDs included 6 pharmacists, 8 pharmacy technicians, 8 nursing technicians, and 2 housekeeping workers. Among the most frequent tasks performed were AND compounding and transporting, cleaning and decontamination of working surfaces, storing of AND supplies, and waste handling.

The study collected 60 wipe samples looking for contamination with one of three ANDs: Ifosfamide, cyclophosphamide, and paclitaxel. Cyclophosphamide is a carcinogen (IARC Group 1; Table 1), while the molecularly similar ifosfamide is also thought to likely be carcinogenic to humans based on data from animal studies (although IARC has so far deemed it a Group 3 [non-classifiable] substance) (25). According to the U.S. Food and Drug Administration, ifosfamide and paclitaxel are also pregnancy "Category D" drugs known to pose a risk to the fetus based on data from human studies or post-marketing experience (26). Sampling methodology and drugs measured were replicated from previous published work (12).

Of the 60 analyzed wipe samples, 12 (20%) were positive for AND contamination. Table 2 shows the distribution of positive samples according to work areas in the CCF.

TABLE 2.[a] AND surface contamination in work areas at a centralized compounding facility (CCF) in Concepción, Chile

Work area/room	Contamination level value/mean ± SD (ng/cm^2)		
	Ifosfamide	Cyclophosphamide	Paclitaxel
Storage			
Transportation Cart	< LOD	< LOD	< LOD
Shelf	53.9[b]	< LOD	< LOD
Labelling			
Counter	76.6[b]	< LOD	< LOD
Floor in front of counter	71.0 ± 12.7	< LOD	80.1[b]
Anteroom			
Cart	< LOD	< LOD	< LOD
Counter	29.8[b]	< LOD	< LOD
Floor in front of table	< LOD	< LOD	< LOD
Compounding/preparation			
BSC (Isolator)	148.1[b]	< LOD	< LOD
Floor in front of BSC	160.4[b]	< LOD	< LOD
Isolator handle	634.2[b]	< LOD	< LOD
Pass-through window tray	94.2 ± 47.5	< LOD	< LOD
Chemotherapy waste bin	< LOD	< LOD	< LOD
Worker chair	< LOD	< LOD	< LOD
IV bag	< LOD	< LOD	< LOD

N= 60
BSC (Biological Safety Cabinet)
IV (intravenous)
SD (standard deviation)
Limit of Detection (LOD): ifosfamide = 0.02 ng/cm^2; cyclophosphamide = 0.1 ng/cm^2; paclitaxel = 0.03 ng/cm^2 (12)

Source: a. This table was prepared by one of the authors (CMR) based on results obtained from his wipe sampling study described in this report.
b. Based on a single value, no SD.

Ifosfamide was the most common AND found in the wipe samples, with most contamination occurring within the compounding/preparation area. The highest contamination level for ifosfamide was found on the isolator handle, a highly touched surface that can easily be ignored when cleaning and disinfecting work surfaces. The average ifosfamide levels found in this study were comparable to those found in a large study of Canadian hospitals (27) but much higher than those in another study of German pharmacies (28). However, any surface contamination with potentially carcinogenic ANDs is a concern from an occupational safety standpoint.

Several factors were likely responsible for the higher detection rate of ifosfamide. Considerably more ifosfamide was handled relative to the other two analyzed medications during the sampling study (ifosfamide 210 g, cyclophosphamide 122 g, and paclitaxel 53 g). Another factor is that ifosfamide's physical and chemical properties make it more likely to remain on work surfaces for longer periods of time than the other analyzed drugs (29), posing challenges to standard decontamination protocols. Therefore, it is important for health-sector workers, who rightly focus on infection prevention and control strategies when preparing and administering drugs, to also be trained on how to minimize hazardous drug contamination.

To our knowledge, this is the first wipe sampling study to be conducted in Chile and serves as an example of the universal applicability of environmental exposure assessment techniques that can be employed in varied facilities across different PAHO member countries. As with the previously cited studies, the current data highlight that robust environmental surveillance for occupational carcinogen exposure can be undertaken, with comparatively modest HPLC-UV analytical methodology that is more likely available in public health and hospital laboratories and, thus, more accessible than other techniques (e.g. state-of-the-art liquid chromatography mass spectrometry (LCMS)) in limited-resource settings. Such environmental surveillance can immediately identify specific

high-risk work areas and processes that can be targeted for intervention.

III. MITIGATION OF HEALTH-SECTOR WORKER AND EXPOSURE: HIGH-IMPACT, LOW-COST APPROACHES

III.A. Exposure prevention guidance for ANDs

Multiple guidelines exist for the safe handling of hazardous drugs, including ANDs. Authoritative examples include those from the ISOPP, widely utilized in Europe (21); the USP 800 (20); the U.S. OSHA (24); and NIOSH (14) (with an abbreviated, Spanish-language version of NIOSH's guidance available online (30)).

The various guidelines are largely harmonized in their recommendations and emphasize the classical hierarchy of hazard control technologies to address safety hazards of AND handling, which include use of engineering controls, such as biologic safety cabinets to contain aerosol drug exposure during preparation; administrative controls and safe handling practices which minimize drug aerosol generation; and use of PPE, primarily gloves and gowns, during AND handling to minimize skin exposure (31). An additional adjunct to the safety hierarchy, especially in the absence of a biosafety cabinet, includes the use of closed-system transfer devices.

However, in limited-resource settings, the use of engineering control technologies is often limited by their expense. Thus, in these settings, the selection of classical hierarchy control elements may be reordered, starting with work practice and PPE controls, to still achieve some risk reduction (31). For example, during preparation of ANDs, when the engineering control containment of a biologic safety cabinet is not available, applying a work practice of preparing drugs in low-traffic areas, and controlling personnel access to this area can minimize the number of workers potentially exposed to fugitive drug aerosol. Maintaining clean drug preparation areas and work surfaces also minimizes worker exposure. Numerous studies have demonstrated the effectiveness of rigorous decontamination protocols, using readily available materials, such as sodium hypochlorite (also known as "bleach"), quaternary ammonium solutions, and sterile water (32). Respiratory protection may also be worn by the worker if containment cabinets are not available.

To communicate the need more fully for safe handling of these hazardous drugs, even in resource-challenged settings, in 2013, UMB CC staff and other subject matter experts drafted a monograph for PAHO describing safe handling of ANDs in such settings. This document applied the re-ordered hierarchy of exposure control, emphasizing the use of PPE and work practice controls to limit AND exposure in the absence of more costly engineering control devices, as described above (22). The guidance illustrated the rationale for work practice recommendations, such as methods to minimize drug powder or liquid aerosol and common-sense methods to limit personnel exposure using signs to prohibit foot traffic in preparation areas. To further increase the accessibility of safe handling guidance for workers and experts in the Americas, UMB adapted this 2013 PAHO monograph into a concise Spanish-language presentation of the topic available at: https://www.medschool.umaryland.edu/media/SOM/Departments/Medicine/Occupational-and-Environmental-Medicine/Documents/PAHO-Documents/Safe-Handling-of-Hazardous-Drugs-Spanish.pptx.

III.B. Feasibility of, and need to scale-up environmental exposure assessment and mitigation efforts

Several studies, conducted in high-income countries, have demonstrated the ability of hygiene practices to reduce concentrations of ANDs on work surfaces (33). Although some aspects of those studies relied on engineering controls, other less costly work practices also contributed to aerosol control, such as not clipping needles used for drug transfer (when possible) and regular surface cleaning with bleach and sterile water rinse, as described above. Such low-cost approaches are feasible.

Both at a facility and a national policy level, requiring environmental surface wipe sampling on a set schedule, for example every 6 months as recommended by USP 800, would provide feedback on the efficacy of safe handling procedures and thus, presumably increase compliance with work practice controls. At least 12 countries, including Brazil, Chile, and Mexico, and some U.S. states, have instituted mandates requiring compliance with certain hazardous-drug safe handling practices (34). More countries across the Americas could replicate these mandates in order to increase utilization of these practices and reduce health-sector worker AND exposures. Safe handling regulations may be particularly feasible in countries where drug compounding (preparation) is relatively centralized, such as in the Chilean example discussed above.

IV. CONCLUSION

As cancer incidence, and therefore AND use, is expected to increase considerably on a global level, especially across LMICs in the next two decades, heightened attention is needed on the risks posed to health-sector workers handling these medications. PAHO has expanded its occupational cancer prevention work in the Americas in recent years, in close collaboration with its CCs, some of which are active in expanding awareness of AND-exposure risks to health-sector workers. An extensive body of literature, including the new data from Chile presented in this report, demonstrate the feasibility of both AND exposure assessment and strategies to mitigate associated health risks.

The findings from this report provide support for the following recommendations for PAHO and its CCs, national health regulatory authorities, and individual healthcare facilities involved in the production, distribution, or use of ANDs:

- The risk of health-sector worker exposure to ANDs and other hazardous drugs must continue to be included within PAHO/WHO's broader efforts at reducing the impact of NCDs, including occupational cancers.
- PAHO/WHO CCs and their partners should continue to play a leading role in outreach efforts to further knowledge on the safe handling of ANDs and in demonstrating the feasibility of conducting robust exposure assessment studies in limited-resource settings, which provide an evidence base for policy recommendations for preventive action.
- Environmental exposure assessment efforts, such as wipe sampling studies, are a necessary first step in the mitigation of AND work surface contamination in hospitals and other healthcare facilities.
- Once identified, AND contamination should be minimized through robust application of the hierarchy of controls. This includes engineering controls, if available, consisting of biological safety cabinets and closed-system transfer

devices, administrative and work practice controls, such as those outlined in PAHO's 2013 Safe Handling guidance for ANDs, and concerted training of workers in work practice controls and appropriate PPE requirements.
- Ongoing, periodic environmental exposure assessment is essential to gauge the effectiveness of workplace interventions.

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REFERENCES

1. Purdue MP, Hutchings SJ, Rushton L, Silverman DT. The proportion of cancer attributable to occupational exposures. Ann Epidemiol. 2015;25(3):188-92.
2. GBD 2016 Occupational Carcinogens Collaborators. Global and regional burden of cancer in 2016 arising from occupational exposure to selected carcinogens: a systematic analysis for the Global Burden of Disease Study 2016. Occup Environ Med. 2020;77(3):151-159.
3. Tennassee LM, Lavoie MC, Pahwa M; Pan American Health Organization. Regional and Global Policy Frameworks on Workers' Health and Occupational Cancer. International Conference on Occupational and Environmental Cancer; 3 August 2009. Bogota, Colombia: PAHO; 2009. Available from: https://www.paho.org/en/file/22269/download?token=vwHPAmhH. Accessed 27 September 2022.
4. Connor TH, MacKenzie BA, DeBord DG, Trout DB, O'Callaghan JP, Ovesen JL, et al. NIOSH List of Hazardous Drugs in Healthcare Settings, 2020. Cincinnati, OH: NIOSH; 2020. Available from: https://www.cdc.gov/niosh/docket/review/docket233c/pdfs/DRAFT-NIOSH-Hazardous-Drugs-List-2020.pdf. Accessed 27 September 2022.
5. IQVIA Institute for Human Data Science. Global medicine and usage trends: outlook to 2025. Parsippany, NJ: IQVIA; 2015. Available from: https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/global-medicine-spending-and-usage-trends-outlook-for-2025/iqvia-institute-global-medicines-and-usage-trends-to-2025-0421-forweb.pdf?_=1663768871140. Accessed 26 September 2022.
6. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 202;71(3):209-249.
7. European Parliament Think Tank. Latin America's informal economy. Brussels, Belgium: 2016. Available from: https://www.europarl.europa.eu/thinktank/en/document/EPRS_BRI(2016)589783. Accessed 27 September 2022.
8. Pan American Health Organization. WHO Collaborating Centers in Workers´ Health. Washington, DC: PAHO; [cited 27 September 2022]. Available from: https://www3.paho.org/hq/index.php?option=com_content&view=article&id=1526:2009-collaborating-centers&Itemid=1347&lang=en.
9. Technical Guide (Annex) to the Workshop Proceedings: Building Capacity For CAREX Projects In Latin America And The Caribbean. Bogota, Colombia: Members of the Latin American and Caribbean CAREX Steering Committee; September 2016. http://www.occupationalcancer.ca/wp-content/uploads/2014/07/LAC-Guide_English.pdf. Accessed 27 September 2022.
10. Pan American Health Organization/World Health Organization. Plan of Action on Workers' Health (2015-2025) [CD54/10, Rev. 2]. 67th Session of the Regional Committee of WHO for the Americas; 28 September – 2 October 2015. Washington, DC: PAHO/WHO; 2015. Available from: https://iris.paho.org/bitstream/handle/10665.2/33986/CD54_10Rev.1-eng.pdf?sequence=1&isAllowed=y. Accessed 27 September 2022.
11. Pan American Health Organization/World Health Organization. World Day for Safety and Health at Work 2014, PAHO/WHO Workers' Health/ Sustainable Development and Health Equity (SDE) Special Program. Chemical Substances, Cancer and Work: Enhancing the Sound Management of Chemicals for Cancer Prevention. Washington, DC: PAHO/WHO; 2014. Available from: https://www.paho.org/hq/dmdocuments/2014/Webinar-workers-health-april-28-14.pdf. Accessed 27 September 2022.
12. Müller-Ramírez C, Squibb K, McDiarmid M. Accessible analytical methodology for assessing workplace contamination of antineoplastic drugs in limited-resource oncology health-care settings. J Anal Sci Technol. 2016;7(1):1-9.
13. Müller-Ramírez C, Squibb K, McDiarmid M. Measuring extent of surface contamination produced by the handling of antineoplastic drugs in low- to middle-income country oncology health care settings. Arch Environ Occup Health. 2017;72(5):289-298.
14. National Institute for Occupational Safety and Health. NIOSH alert: preventing occupational exposure to antineoplastic and other hazardous drugs in health care settings. Cincinnati, OH; NIOSH; 2004. Available from: https://www.cdc.gov/niosh/docs/2004-165/pdfs/2004-165.pdf?id=10.26616/NIOSHPUB2004165. Accessed 27 September 2022.
15. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Some Antiviral and Antineoplastic Drugs, and Other Pharmaceutical Agents. Lyon (FR): International Agency for Research on Cancer; 2000. (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, No. 76.) Available from: https://www.ncbi.nlm.nih.gov/books/NBK401398/.
16. Pan American Health Organization. Regional cancer experts discuss a new initiative on cancer prevention for Latin America and the Caribbean. Washington, DC: PAHO; [c2017] [cited 27 September 2022]. Available from: https://www3.paho.org/hq/index.php?option=com_content&view=article&id=13203:newinitiative-cancer-prevention-lac&Itemid=42322&lang=en.
17. Schüz J, Espina C, Villain P, Herrero R, Leon ME, Minozzi S, et al; Working groups of scientific experts. European Code against Cancer 4th Edition: 12 ways to reduce your cancer risk. Cancer Epidemiol. 2015;39 Suppl 1:S1-10.
18. Whittaker C, Rice F, McKernan L, Dankovic D, Lentz TJ, MacMahon K, et al. Current intelligence bulletin 68: NIOSH chemical carcinogen policy. Cincinnati, OH: NIOSH; 2016.
19. Connor T, McDiarmid M. Preventing occupational exposures to antineoplastic drugs in health care settings. CA Cancer J Clin. 2006;56:354–365.
20. United States Pharmacopeia. Hazardous Drugs—Handling in Healthcare Settings (General Chapter <800>). USP; 2016. Available from: https://www.usp.org/compounding/general-chapter-hazardousdrugs-handling-healthcare. Accessed 27 September 2022.
21. International Society of Oncology Pharmacy Practitioners Standards Committee. ISOPP Standards for the Safe Handling of Cytotoxics. J Oncol Pharm Pract. 2022;28(3_suppl):S1-S126.
22. Pan American Health Organization. Safe handling of hazardous chemotherapy drugs in limited-resource settings. Washington, DC: PAHO; 2013. Available from: https://iris.paho.org/handle/10665.2/28554. Accessed 27 September 2022.

23. National Toxicology Program. NTP monograph on the systematic review of occupational exposure to cancer chemotherapy agents and adverse health outcomes. NTP Monograph 05. 2019. Available from: https://doi.org/10.22427/NTP-MGRAPH-5. Accessed 27 September 2022.
24. Occupational Safety and Health Administration. Controlling occupational exposure to hazardous drugs. Washington, DC: OSHA [cited 27 September 2022]. Available from: https://www.osha.gov/hazardous-drugs/controlling-occex.
25. Ifosfamide: Evaluation of the carcinogenicity and genotoxicity. The Hague, The Netherlands Health Council of the Netherlands; 2008. Available from: https://www.gezondheidsraad.nl/binaries/gezondheidsraad/documenten/adviezen/2008/04/01/ifosfamide-evaluation-of-the-carcinogenicity-and-genotoxicity/advies-ifosfamide-evaluation-of-thecarcinogenicity-and-genotoxicity.pdf. Accessed 27 September 2022.
26. Connor TH, MacKenzie BA, DeBord DG, Trout DB, O'Callaghan JP. NIOSH list of antineoplastic and other hazardous drugs in healthcare settings, 2016. Cincinnati, OH: NIOSH; 2016. Available from: https://www.cdc.gov/niosh/docs/2016-161/pdfs/2016-161.pdf?id=10.26616/NIOSHPUB2016161. Accessed 27 September 2022.
27. Merger D, Tanguay C, Langlois E, Lefebvre M, Bussières JF. Multicenter study of environmental contamination with antineoplastic drugs in 33 Canadian hospitals. Int Arch Occup Environ Health. 2014;87(3):307-13.
28. Kiffmeyer T, Tuerk J, Hahn M, Stuetzer H, Hadtstein C, Heinemann A, et al. Application and assessment of a regular environmental monitoring of the antineoplastic drug contamination level in pharmacies- The MEWIP project. Ann Occup Hyg. 2013;57(4):444-55.
29. Connor TH, DeBord G, Pretty JR, Oliver MS, Roth TS, Lees PS, et al. 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.
30. National Institute for Occupational Safety and Health. NIOSH alert: prevención de la exposición ocupacional a los antineoplásticos y otras medicinas peligrosas en centros de atención médica. Cincinnati, OH: NIOSH; 2004. Available from: https://www.cdc.gov/spanish/niosh/docs/2004-165_sp/. Accessed 27 September 2022.
31. McDiarmid MA. Hazards of the health care sector: looking beyond infectious disease. Ann Glob Health. 2014;80(4):315-9.
32. National Institute for Occupational Safety and Health. Hazardous drug exposures in healthcare: decontamination and deactivation of antineoplastic agents. Washington, D: NIOSH [cited 27 September 2022]. Availabe from: https://www.cdc.gov/niosh/topics/hazdrug/sampling.html.
33. Kibby T. A review of surface wipe sampling compared to biologic monitoring for occupational exposure to antineoplastic drugs. J Occup Environ Hyg. 2017;14(3):159-174.
34. Mathias PI, MacKenzie BA, Toennis CA, Connor TH. Survey of guidelines and current practices for safe handling of antineoplastic and other hazardous drugs used in 24 countries. J Oncol Pharm Pract. 2019;25(1):148-162.

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Exposición a medicamentos cancerígenos en trabajadores del sector de la salud: necesidad de evaluación y vigilancia de la exposición

RESUMEN

Los medicamentos antineoplásicos empleados en quimioterapia pueden causar distintos tipos de tumores secundarios en pacientes tratados y presentar riesgos cancerígenos para los trabajadores del sector de la salud en cualquier momento del ciclo de vida de estos medicamentos en las instalaciones, desde su producción hasta su administración al paciente. Varios centros colaboradores de la OPS/OMS tienen experiencia en cuanto a cómo abordar estos peligros en el sector de la salud. Este informe persigue cuatro objetivos: 1) ofrecer una visión general de la labor de investigación y prevención de larga data, liderada por la OPS/OMS y sus centros colaboradores de salud ocupacional, encaminada a reducir la carga del cáncer ocupacional en la Región de las Américas; 2) abordar cómo una evaluación sólida de la exposición a los medicamentos antineoplásicos y la labor educativa y divulgativa de los centros colaboradores de la OPS pueden sentar las bases de los esfuerzos de mitigación de la exposición en los trabajadores del sector de la salud; 3) mediante la presentación de datos originales sobre la evaluación de la exposición a los medicamentos antineoplásicos en una instalación de compuestos farmacéuticos en Chile, destacar métodos relativamente asequibles gracias a los cuales se pueden recopilar dichos datos; y 4) examinar cómo la vigilancia ambiental efectiva y periódica en los centros de salud permite detectar casos de contaminación de medicamentos antineoplásicos en el entorno de trabajo y facilita la ejecución de intervenciones de bajo costo y alto impacto para reducir el riesgo de cáncer ocupacional en los trabajadores del sector de la salud, incluso en entornos de recursos limitados.

El riesgo de exposición de los trabajadores del sector de la salud a los medicamentos antineoplásicos y otros medicamentos peligrosos es una cuestión importante para su inclusión en los esfuerzos más amplios de la OPS/OMS para reducir los efectos del cáncer ocupacional en la Región de las Américas. En este informe se demuestra que una amplia gama de estrategias accesibles de mitigación de la exposición a los medicamentos antineoplásicos es factible tanto a nivel de las instalaciones como de las políticas nacionales en toda la Región.

Palabras clave Cáncer profesional; medición de riesgo; personal de salud; antineoplásicos.

Exposição a fármacos carcinogênicos entre profissionais de saúde: necessidade de avaliação e vigilância da exposição

RESUMO Os medicamentos antineoplásicos usados para quimioterapia podem causar cânceres secundários em pacientes tratados e apresentar riscos carcinogênicos aos profissionais de saúde em qualquer momento do ciclo de vida desses fármacos dentro de um estabelecimento, desde sua produção até a administração ao paciente. Vários centros colaboradores da OPAS/OMS têm experiência em lidar com esses riscos no setor de saúde. Este relatório tem quatro objetivos: 1) fornecer uma visão geral dos esforços de longa data em pesquisa e prevenção liderados pela OPAS/OMS e por seus centros colaboradores de saúde ocupacional, cuja meta é reduzir a carga do câncer ocupacional nas Américas; 2) discutir como uma avaliação robusta da exposição aos antineoplásicos e o trabalho de extensão/educacional dos centros colaboradores da OPAS/OMS podem embasar os esforços de mitigação da exposição entre os profissionais de saúde; 3) por meio da apresentação de dados originais de avaliação da exposição a antineoplásicos obtidos de uma central de manipulação de medicamentos no Chile, destacar métodos relativamente econômicos para gerar esse tipo de dados; e 4) discutir como a vigilância ambiental eficaz e periódica em estabelecimentos de saúde resulta na identificação de contaminação por antineoplásicos no ambiente de trabalho e permite a implementação de intervenções de baixo custo e alto impacto para reduzir o risco de câncer ocupacional em profissionais de saúde, inclusive em contextos de recursos limitados.

O risco de exposição dos profissionais de saúde aos medicamentos antineoplásicos e outros fármacos perigosos é uma questão importante a ser incluída nos esforços mais amplos da OPAS/OMS de reduzir o impacto do câncer ocupacional nas Américas. Este relatório demonstra a viabilidade de uma ampla gama de estratégias acessíveis de mitigação da exposição aos antineoplásicos, tanto no nível das instituições quanto no âmbito de políticas nacionais em todo o hemisfério.

Palavras-chave Câncer Ocupacional; medição de risco; pessoal de saúde; antineoplásicos.