



Review Article

Identification of Knowledge Gaps Regarding Healthcare Workers' Exposure to Antineoplastic Drugs: Review of Literature, North America versus Europe



Chun-Yip Hon^{1,2,*}, Cris Barzan^{2,3}, George Astrakianakis²

¹ School of Occupational and Public Health, Ryerson University, Toronto, Ontario, Canada

² School of Population and Public Health, University of British Columbia, Vancouver, British Columbia, Canada

³ Prevention Division, WorkSafeBC, Vancouver, British Columbia, Canada

ARTICLE INFO

Article history:

Received 16 April 2014

Received in revised form

27 May 2014

Accepted 2 June 2014

Available online 11 June 2014

Keywords:

antineoplastic drugs

healthcare workers

knowledge gaps

occupational exposure

ABSTRACT

We have been examining the issue of healthcare workers' exposure to antineoplastic drugs for nearly a decade and have observed that there appears to be more publications on the subject matter originating from Europe than from North America. The concern is that findings from Europe may not be generalizable to North America because of differences in handling practices, regulatory requirements, and training. Our objective was to perform a literature review to confirm our observation and, in turn, identify gaps in knowledge that warrants addressing in North America. Using select keywords, we searched for publications in PubMed and Web of Science. All papers were initially classified according to the originating continent and then categorized into one or more subject categories (analytical methods, biological monitoring, occupational exposure, surface contamination, and probability of risk/exposure). Our review identified 16 papers originating from North America and 55 papers from Europe with surface contamination being the subject matter most often studied overall. Based on our results, we are of the opinion that North American researchers need to further conduct dermal and/or urinary drug contamination studies as well as assess the exposure risk faced by healthcare workers who handle antineoplastic drugs. Trends in exposure levels should also be explored.

© 2014, Occupational Safety and Health Research Institute. Published by Elsevier. All rights reserved.

1. Introduction

A number of health risks associated with healthcare workers' exposure to antineoplastic drugs have been established since the 1970s [1]. Occupational exposure to these agents have led to a range of health outcomes reported in healthcare workers including acute effects [2], cardiotoxicity [3], reproductive toxic effects [4–6], and chromosomal damage—a precursor to cancer development [7,8]. Nearly 40 years after the association between healthcare workers and the adverse effects of antineoplastic drug exposure was established, the matter remains a concern today for a number of reasons. First, the incident rate of cancer is steadily increasing and, in turn, the use of antineoplastic drugs is growing [9]. Second, existing safe drug handling practices may not effectively eliminate the risk potential as drug contamination of surfaces is prevalent in

multiple departments within a hospital [10,11]. Lastly, the number and variety of healthcare workers potentially exposed to antineoplastic drugs has increased because the use of these agents for treating nonmalignant diseases has expanded [1]. Compounding the problem is the fact that occupational exposure limits have not been established for these drugs by any of the recognized agencies that produce such exposure thresholds (e.g., American Conference of Governmental Industrial Hygienists threshold limit values, German maximum workplace concentration).

Our group of researchers at the University of British Columbia in Vancouver, Canada, have been examining the issue of healthcare workers' exposure to antineoplastic drugs for more than a decade. During our review of the literature for background and research purposes, we noticed a peculiar finding that a larger proportion of the publications on this subject matter originate in continental

* Corresponding author. School of Occupational and Public Health, Ryerson University, 350 Victoria Street, POD 247C, Toronto, Ontario, Canada M5B 2K3.
E-mail address: cyhon@ryerson.ca (C.-Y. Hon).

Europe. Connor et al [10] mentioned this phenomenon as well. Although the information from Europe is of value, the findings and conclusions may not necessarily be transferable to North American healthcare facilities due to differences in standards of practice, legislative requirements and education/training protocols between the two continents. Although results from Europe may not necessarily be generalizable to North America, they are of value by initiating meaningful discussions and acting as an impetus for similar research projects to be conducted in North American facilities. (We know that there are publications based in other continents such as Asia and Australia that have examined the issue of healthcare workers' exposure to antineoplastic drugs. However, we have observed that the work focuses primarily on cross-sectional evaluations of current exposure conditions and do not elucidate contributing factors related to the risk of exposure. We are confident that future work from these other continents will offer valuable insight into this subject matter).

The purpose of this paper was to test our observation that more publications regarding healthcare workers' exposure to antineoplastic drugs originate from Europe than in North America. We conducted a review of the published literature for articles that addressed this topic, categorized them according to subject matter, and then tallied the findings to determine where knowledge gaps exist, if any, between the two continents. From the potential knowledge gaps identified, our goal was to identify and prioritize additional research that is worthy of consideration in North American facilities to better our understanding of healthcare workers' exposure to antineoplastic drugs and the underlying risk that these exposures may present.

2. Materials and methods

We sought articles from two common literature databases: PubMed and Web of Science. Select keywords were used to identify articles for the purposes of this review. The keywords were antineoplastic drugs (along with its synonyms antineoplastic agents and cytotoxic drugs), healthcare, occupational exposure, analytical methods, biological monitoring, risk assessment, surface contamination, and exposure monitoring. The keywords were systematically combined together in order to conduct the literature search. For example, "antineoplastic drugs" AND "occupational exposure" AND "healthcare" was one combination. There were a total of 18 combinations of keywords and all combinations were applied to each of the two databases.

We aimed to identify original research articles (i.e., nonreview) using the aforementioned keywords with the following exclusion criteria: (1) not written in English; (2) not published between January 1, 2004 and December 31, 2012. The year 2004 was chosen as this was the release date of the original NIOSH (National Institute for Occupational Safety and Health) Alert regarding antineoplastic and other hazardous drugs [1]; (3) research conducted outside of North America or continental Europe (as defined by worldatlast.com [12]); (4) nonhuman studies; and (5) not full reports (i.e., letters to the editor).

Every full-text article that met the inclusion criteria was initially classified according to the continent of origin of the study (North America or Europe). Next, the paper was reviewed and categorized into one or more of the following five categories based on its subject matter: analytical methods (e.g., development and validation of a novel laboratory analytical method), biological monitoring (e.g., blood or urine samples), occupational exposure, surface contamination, and probability of risk/exposure. For the purposes of this paper, "occupational exposure" was defined as those instances where dermal and/or airborne contamination levels were measured. "Probability of risk/exposure" was defined as

determinants of exposure and/or studies in which comparisons between exposed and nonexposed populations were made. The number of articles was tallied according to the five subject categories, stratified by the continent, using the COUNTIF function in Microsoft Excel (Microsoft, Redman, WA, USA).

3. Results

Our search of the two literature databases resulted in a total of 80 publications that matched our inclusion criteria. Of these, nine were removed because they were deemed irrelevant (i.e., conference proceedings, not concerning occupational health, or not related to healthcare settings). Therefore, 71 papers remained in the study—16 from North America and 55 that originated in continental Europe.

When these 71 papers were categorized according to their subject matter, the topics discussed in order of frequency (from highest to lowest) were surface contamination, probability of risk/exposure, biological monitoring, occupational exposure, and analytical methods. For each of the five topics, there were always more instances of European-based publications than North American, with a minimum 3-fold difference (Table 1).

4. Discussion

Our analysis suggests that European scientists have been more active in researching the area of healthcare workers' exposure to antineoplastic drugs than their North American counterparts. From 2004 until 2012, there were three times as many papers from Europe compared to North America. We therefore believe that there are opportunities in North America to further our understanding of this occupational health issue.

Surface contamination was the topic most commonly examined in the literature. As Connor et al [10] recently indicated, every paper that has examined surface contamination has found at least one instance of drug residual present. Therefore, we suggest that there is likely no need to explore this particular topic any further. However, as no occupational exposure limits have been established, we recommend that North American researchers and/or occupational hygienists consider developing suitable hygienic guidance values based on surface contamination levels that have been recently obtained from Canadian and American healthcare facilities. Such hygienic guidance values have previously been proposed in two European countries—one for Germany [63] and another set of values for Sweden [39]. Given the potential difference in practices and training regimens, the hygienic guidance values developed in Europe may not be practical or suitable to North American facilities.

European researchers have provided leadership in the area of developing methods for quantifying antineoplastic drug contamination in various matrixes. Researchers in North America can simply adopt and refine these analytical methods according to local needs without the need for rigorous validation. However, it would be ideal if a research facility in North America were capable of performing some of these reported analyses because there may be sample stability concerns if these samples were to be shipped overseas. Upon review of the papers that have developed analytical methods, there appears to be a need to find biological markers of exposure that are specific to the different types of antineoplastic drugs [83] as well as address the issues associated with the large interindividual variability of volume output when collecting urine samples [37].

Inhalation, dermal, urine, and blood samples have been collected by various researchers in order to understand healthcare workers' exposure to antineoplastic drugs. Our results suggest that European researchers have examined occupational exposures

Table 1
Summary of literature review findings with tally of articles based on continent of origin and topics addressed

Author and year	Continent		Topical categories				
	North America	Europe	Occupational exposure	Biological monitoring	Analytical methods	Surface contamination	Probability of risk/exposure
Acampora et al 2005 [13]		×				×	×
Barbieri et al 2006 [14]		×			×		
Brouwers et al 2007 [15]		×			×	×	
Bussieres et al 2007 [16]	×					×	
Caciari et al 2012 [17]		×		×			×
Castiglia et al 2008 [18]		×				×	
Cavallo et al 2005 [19]		×		×		×	×
Cavallo et al 2009 [20]		×		×			×
Chappuy et al 2012 [21]		×			×	×	
Chu et al 2012 [22]	×					×	
Connor et al 2005 [23]	×					×	×
Connor et al 2010 [10]	×		×	×		×	×
Constantinidis et al 2011 [24]		×	×				×
Crauste-Manciet et al 2005 [25]		×	×			×	
Fabrizi et al 2012 [26]		×			×	×	
Favier et al 2012 [27]		×				×	
Forges et al 2011 [28]		×				×	
Fransman et al 2004 [29]		×	×			×	
Fransman et al 2005 [30]		×	×			×	×
Fransman et al 2006 [31]		×	×			×	
Fransman et al 2007 [32]		×	×				×
Fransman et al 2007 [33]		×	×	×		×	×
Harrison et al 2006 [34]	×					×	×
Hedmer et al 2004 [35]		×	×		×	×	
Hedmer et al 2005 [36]		×				×	
Hedmer et al 2008 [37]		×		×			
Hedmer et al 2008 [38]		×		×		×	
Hedmer and Wohlfart 2012 [39]		×				×	
Hon et al 2011 [40]	×		×				
Hon et al 2011 [41]	×		×			×	
Konate et al 2011 [42]		×	×	×		×	×
Kopp et al 2012 [43]		×		×		×	×
Kopp et al 2012 [44]		×				×	×
Lalande et al 2012 [45]		×	×				×
Mader et al 2009 [46]		×		×			×
Mason et al 2005 [47]		×	×	×		×	
Massoomi et al 2008 [48]	×		×				×
McDiarmid and Condon 2005 [49]	×						×
Ndaw et al 2010 [50]		×		×	×		
Nussbaumer et al 2010 [51]		×			×	×	
Nussbaumer et al 2012 [52]		×			×	×	
Nygren et al 2005 [53]		×	×		×		
Nygren et al 2008 [54]							
Odraska et al 2011 [55]		×	×			×	
Odraska et al 2012 [56]		×				×	×
Pieri et al 2010 [57]		×		×			×
Pretty et al 2012 [58]	×		×	×	×	×	
Roberts et al 2006 [59]		×				×	×
Rubino et al 2006 [60]		×		×	×		×
Sabatini et al 2005 [61]		×			×	×	
Sabatini et al 2012 [62]		×		×		×	×
Schierl et al 2009 [63]		×				×	×
Schierl et al 2010 [64]		×				×	
Schierl et al 2012 [65]		×	×			×	
Schulz et al 2005 [66]	×					×	
Sessink et al 2011 [67]	×					×	
Sottani et al 2004 [68]		×		×	×		
Sottani et al 2005 [69]		×		×	×		

(continued on next page)

Table 1 (continued)

Author and year	Continent		Topical categories				
	North America	Europe	Occupational exposure	Biological monitoring	Analytical methods	Surface contamination	Probability of risk/exposure
Sottani et al 2007 [70]		×			×	×	
Sottani et al 2008 [71]		×		×	×		
Sottani et al 2010 [72]		×		×		×	
Sottani et al 2012 [73]		×	×	×		×	
Stover and Achutan 2011 [74]	×					×	×
Testa et al 2007 [7]		×		×			×
Touzin et al 2009 [75]	×					×	
Touzin et al 2010 [76]	×					×	×
Tuerk et al 2011 [77]		×			×	×	
Turci et al 2011 [78]		×		×		×	×
Turk et al 2004 [79]		×					×
Ursini et al 2006 [80]		×	×	×		×	
Villarini et al 2011 [81]		×		×			×
Zock et al 2011 [82]	×					×	
North American subtotals	16		5	2	1	13	7
European subtotals		55	16	23	16	37	23
Overall totals		71	21	25	17	50	30

levels more often than North Americans (Table 1). This may be because some researchers consider the collection of surface contamination samples to be sufficient markers of exposure and therefore personal samples do not need to be collected [63]. This is understandable given that surface wipes are more convenient to collect and are not invasive, and one can obtain a larger sample size with less stringent ethical considerations compared with samples taken from individuals. However, this may mask the true extent of exposure as we have recently reported that, although surface contamination is widespread within a healthcare facility, surface contamination levels are not necessarily indicative of the exposure risks faced by healthcare workers [11,84]. As such, it is recommended that surface contamination be used to identify those job categories at risk of exposure but that personal samples, such as dermal wipes or biological samples, be collected from healthcare workers to evaluate their actual level of risk [84]. Not only have our European colleagues conducted more studies on occupational exposure than we have, but they have also looked at trends in exposure levels over time [33,46,72]. This is an important consideration as analysis of trends is a means to evaluate the effectiveness of control measures in reducing the risk of exposure, and we recommend that North American researchers consider initiating this type of study.

Table 1 indicates that 30 papers determined the probability of risk/exposure due to occupational exposure to antineoplastic drugs—more than two-thirds of which ($n = 23$) originated from Europe. One of the means to confirm that workers are at risk of exposure to antineoplastic drugs and their associated health effects is to perform studies comparing workers that are exposed versus those that are not exposed. Our review found seven such studies—six from European researchers [7,17,19,20,60,81] and only one originating in North America [10]. Because there are likely differences in handling practices and training regimens, the findings reported in Europe may not be representative of the conditions in North American facilities. We, therefore, suggest that more North American researchers adopt a mandate to assess the level of risk associated with the antineoplastic drug exposure levels faced by their healthcare workers by conducting exposed versus nonexposed studies.

Limitations regarding this project need to be mentioned. We treated all antineoplastic drugs alike; however, these drugs differ in

their physical and chemical properties that affect their pharmacokinetics as well as their toxicity. This review had a limited scope whereby publications from other continents and gray literature, including dissertations, were not considered. Some of the studies resulted in multiple related publications; however, they were treated as independent papers in our review. When we combined these related publications, the ratio of European to North American publications remained greater than 3:1 and did not change our conclusions (not shown). In addition, the number of search terms used was somewhat limited. We did attempt to use other terms such as “healthcare facilities” and “anticancer drugs”, but this either resulted in no hits or duplicate results.

In conclusion, our review of the literature indicates that since 2004, more publications regarding healthcare workers' exposure to antineoplastic arise from Europe than in North America. We believe there are a number of research initiatives that can be undertaken in North America to better understand this subject matter. This includes occupational exposure studies (i.e., personal samples quantifying antineoplastic drug contamination levels in healthcare workers) and the subsequent assessment of the risk associated with these exposure levels. In addition, an analysis of the trends in exposure levels from North American facilities is also suggested. Given the known health effects of antineoplastic drugs, we need to better understand the occupational exposures to antineoplastic drugs in North American workplaces and, where necessary, implement control measures to protect our healthcare workers to reduce the level of risk.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgments

This project was funded by the Office of the Vice President of Research and Innovation (OVPRI) at Ryerson University as part of its Work Study Research Assistant Program. The authors thank Ms Michelle Nguyen of Ryerson University for her help in performing select parts of the literature review. Dr Astrakianakis' appointment is funded, in part, by the Michael Smith Foundation for Health Research (MSFHR award number is CI-SCH-01909(07-1)). The

OVPRI was not involved in any capacity with respect to this study or the manuscript.

References

- [1] Centers for Disease Control and Prevention - National Institute for Occupational Safety and Health. Preventing occupational exposure to antineoplastic and other hazardous drugs in health care settings 2004 [Internet]. Publication number 2004-165, Cincinnati (OH), 2004 [cited 2011 Nov 30]. Available from: <http://www.cdc.gov/niosh/docs/2004-165/>.
- [2] McDiarmid M, Egan T. Acute occupational exposure to antineoplastic agents. *J Occup Med* 1988;30:984-7.
- [3] Monica Lamberti, Giovane Giancarlo, Garzillo Elpidio M, Avino Franca, Feola Antonia, Porto Stefania, Tombolini Vincenzo, Di Domenico Marina. Animal models in studies of cardiotoxicity side effects from antineoplastic drugs in patients and occupational exposed workers. *Biomed Res Int* 2014;1-8.
- [4] Valanis B, Vollmer W, Labuhn K, Glass A. Occupational exposure to antineoplastic agents and self-reported infertility among nurses and pharmacists. *J Occup Environ Med* 1997;39:574-80.
- [5] Valanis B, Vollmer WM, Steele P. Occupational exposure to antineoplastic agents: self-reported miscarriages and stillbirths among nurses and pharmacists. *J Occup Environ Med* 1999;41:632-8.
- [6] George Dranitsaris, Johnston Mary, Poirier Susan, Schueller Trudi, Milliken Debbie, Green Esther, Zanke Brent. Are health care providers who work with cancer drugs at an increased risk for toxic events? A systematic review and meta-analysis of the literature. *J Oncol Pharm Pract* 2005;11:69-78.
- [7] Antonella Testa, Giachelia Manuela, Palma Selena, Appolloni Massimo, Padua Luca, Tranfo Giovanna, Spagnoli Mariangela, Tirindelli Donatella, Cozzi Renata. Occupational exposure to antineoplastic agents induces a high level of chromosome damage. Lack of an effect of GST polymorphisms. *Toxicol Appl Pharmacol* 2007;223:46-55.
- [8] McDiarmid MA, Oliver MS, Roth TS, Rogers B, Escalante C. Chromosome 5 and 7 abnormalities in oncology personnel handling anticancer drugs. *J Occup Environ Med* 2010;52:1028-34.
- [9] World Cancer Research Fund International. 2012 Cancer Statistics [Internet]. London (UK). 2012 [cited 2014 Mar 7]. Available from: http://www.wcrf.org/cancer_statistics/.
- [10] Connor Thomas H, DeBord Gayle, Pretty Jack R, Oliver Marc S, Roth Tracy S, Lees Peter SJ, Krieg Jr Edward F, Rogers Bonnie, Escalante Carmen P, Toennis Christine A, Clark John C, Johnson Belinda C, McDiarmid Melissa A. Evaluation of antineoplastic drug exposure of health care workers at three university-based US cancer centers. *J Occup Environ Med* 2010;52:1019-27.
- [11] Hon C-Y, Teschke K, Chu W, Demers P, Venners S. Antineoplastic drug contamination of surfaces throughout the hospital medication system in Canadian hospitals. *J Occup Environ Hyg* 2013;10:374-83.
- [12] World Atlas. Countries listed by continent [Internet]. Galveston (TX). [cited 2014 Mar 7]. Available from: <http://www.worldatlas.com/cntycont.htm>.
- [13] Antonio Acampora, Castiglia Loredana, Miraglia Nadia, Pieri Maria, Soave Claudio, Liotti Francesco, Sannolo Nicola. A case study: surface contamination of cyclophosphamide due to working practices and cleaning procedures in two Italian hospitals. *Ann Occup Hyg* 2005;49:611-8.
- [14] Barbieri A, Sabatini L, Indiveri P, Bonfiglioli R, Lodi V, Violante FS. Simultaneous determination of low levels of methotrexate and cyclophosphamide in human urine by micro liquid chromatography/electrospray ionization tandem mass spectrometry. *Rapid Commun Mass Spectrom* 2006;20:1889-93.
- [15] Brouwers EEM, Huitema ADR, Bakker EN, Douma JW, Schimmel KJM, Van Wieringh G, de Wolf PJ, Schellens JHM, Beijnen JH. Monitoring of platinum surface contamination in seven Dutch hospital pharmacies using inductively coupled plasma mass spectrometry. *Int Arch Occup Environ Health* 2007;80:689-99.
- [16] Bussières J-F, Theoret Y, Prot-Labarthe S, Larocque D. Program to monitor surface contamination by methotrexate in a hematology-oncology satellite pharmacy. *Am J Health Syst Pharm* 2007;64:531-5.
- [17] Caciari T, Casale T, Tomei F, Samperi I, Tomei G, Capozzella A, Ripamonti K, Scala B, Andreozzi G, Nardone N, Schifano MP, Rosati MV. Exposure to antineoplastic drugs in health care and blood chemistry parameters. *Clin Ter* 2012;163:e387-92.
- [18] Loredana Castiglia, Miraglia Nadia, Pieri Maria, Simonelli Angela, Basilicata Pascale, Genovese Giuliana, Guadagni Rossella, Acampora Antonio, Sannolo Nicola, Virginia Scafarto Maria. Evaluation of occupational exposure to antineoplastic drugs in an Italian hospital oncological department. *J Occup Health* 2008;50:48-56.
- [19] Delia Cavallo, Lucia Ursini Cinzia, Perniconi Barbara, Di Francesco Arianna, Giglio Margherita, Maria Rubino Federico, Marinaccio Alessandro, Iavicoli Sergio. Evaluation of genotoxic effects induced by exposure to antineoplastic drugs in lymphocytes and exfoliated buccal cells of oncology nurses and pharmacy employees. *Mutat Res* 2005;587:45-51.
- [20] Cavallo D, Ursini CL, Rondinone B, Iavicoli S. Evaluation of a suitable DNA damage biomarker for human biomonitoring of exposed workers. *Environ Mol Mutagen* 2009;50:781-90.
- [21] Chappuy M, Caudron E, Bellanger A, Pradeau D. Determination of platinum traces contamination by graphite furnace atomic absorption spectrometry after preconcentration by cloud point extraction. *J Hazard Mater* 2010;176:207-12.
- [22] Chu WC, Hon C-Y, Danyluk Q, Chua PP, Astrakianakis G. Pilot assessment of the antineoplastic drug contamination levels in British Columbian hospitals pre- and post-cleaning. *J Oncol Pharm Pract* 2011;18:46-51.
- [23] Connor Thomas H, Sessink Paul JM, Harrison Bruce R, Pretty Jack R, Peters Byron G, Alfaro Raul M, Bilos Appie, Beckmann Gwendolyn, Bing Michael R, Anderson Lakisha M, Dechristoforo Robert. Surface contamination of chemotherapy drug vials and evaluation of new vial-cleaning techniques: results of three studies. *Am J Health Syst Pharm* 2005;62:475-84.
- [24] Constantinidis TC, Vagka E, Dallidou P, Basta P, Drakopoulos V, Kakolyris S, Chatzaki E. Occupational health and safety of personnel handling chemotherapeutic agents in Greek hospitals. *Eur J Cancer Care (Engl)* 2011;20:123-31.
- [25] Crauste-Manciet S, Sessink PJ, Ferrari S, Jomier JY, Brossard D. Environmental contamination with cytotoxic drugs in healthcare using positive air pressure isolators. *Ann Occup Hyg* 2005;49:619-28.
- [26] Fabrizi G, Fioretti M, Mainero Rocca L, Curini R. DESI-MS2: a rapid and innovative method for trace analysis of six cytostatic drugs in health care setting. *Anal Bioanal Chem* 2012;403:973-83.
- [27] Favier B, Labrosse H, Gilles-Afchain L, Cropet C, Perol D, Chaumard N, Latour JF, Hild P. The PhaSeal(R) system: impact of its use on workplace contamination and duration of chemotherapy preparation. *J Oncol Pharm Pract* 2011;18:37-45.
- [28] Forges F, Simoens X, Chauvin F. Comparative parallel assessment of a transfer device in reducing 5-fluorouracil environmental contamination inside positive air pressure isolators. *J Oncol Pharm Pract* 2010;17:61-7.
- [29] Fransman W, Vermeulen R, Kromhout H. Occupational dermal exposure to cyclophosphamide in Dutch hospitals: a pilot study. *Ann Occup Hyg* 2004;48:237-44.
- [30] Fransman W, Vermeulen R, Kromhout H. Dermal exposure to cyclophosphamide in hospitals during preparation, nursing and cleaning activities. *Int Arch Occup Environ Health* 2005;78:403-12.
- [31] Fransman W, Huizer D, Tuerk J, Kromhout H. Inhalation and dermal exposure to eight antineoplastic drugs in an industrial laundry facility. *Int Arch Occup Environ Health* 2006;80:396-403.
- [32] Fransman W, Roeleveld N, Peelen S, de Kort W, Kromhout H, Heederik D. Nurses with dermal exposure to antineoplastic drugs: reproductive outcomes. *Epidemiol Camb Mass* 2007;18:112-9.
- [33] Fransman W, Peelen S, Hilhorst S, Roeleveld N, Heederik D, Kromhout H. A pooled analysis to study trends in exposure to antineoplastic drugs among nurses. *Ann Occup Hyg* 2007;51:231-9.
- [34] Harrison BR. Comparison of surface contamination with cyclophosphamide and fluorouracil using a closed-system drug transfer device versus standard preparation techniques. *Am J Health Syst Pharm* 2006;63:1736-44.
- [35] Hedmer M, Jönsson BAG, Nygren O. Development and validation of methods for environmental monitoring of cyclophosphamide in workplaces. *J Environ Monit* 2004;6:979-84.
- [36] Hedmer M, Georgiadi A, Bremberg ER, Jönsson BAG, Eksborg S. Surface contamination of cyclophosphamide packaging and surface contamination with antineoplastic drugs in a hospital pharmacy in Sweden. *Ann Occup Hyg* 2005;49:629-37.
- [37] Hedmer M, Höglund P, Cavallin-Ståhl E, Albin M, Jönsson BAG. Validation of urinary excretion of cyclophosphamide as a biomarker of exposure by studying its renal clearance at high and low plasma concentrations in cancer patients. *Int Arch Occup Environ Health* 2008;81:285-93.
- [38] Hedmer M, Tinnerberg H, Axmon A, Joensuu BAG. Environmental and biological monitoring of antineoplastic drugs in four workplaces in a Swedish hospital. *Int Arch Occup Environ Health* 2008;81:899-911.
- [39] Hedmer M, Wohlfart G. Hygienic guidance values for wipe sampling of antineoplastic drugs in Swedish hospitals. *J Environ Monit* 2012;14:1968.
- [40] Hon C-Y, Astrakianakis G, Danyluk Q, Chu WC. Pilot evaluation of dermal contamination by antineoplastic drugs among hospital pharmacy personnel. *Can J Hosp Pharm* 2011;64:327-32.
- [41] Hon C-Y, Teschke K, Chua P, Venners S, Nakashima L. Occupational Exposure to antineoplastic drugs: identification of job categories potentially exposed throughout the hospital medication system. *Saf Health Work* 2011;2:273-81.
- [42] Armande Konate, Poupon Joël, Villa Antoine, Garnier Robert, Hasni-Pichard Hélène, Mezzaroba Danielle, Fernandez Gabriel, Pocard Marc. Evaluation of environmental contamination by platinum and exposure risks for healthcare workers during a heated intraperitoneal perioperative chemotherapy (HIPEC) procedure. *J Surg Oncol* 2011;103:6-9.
- [43] Bettina Kopp, Crauste-Manciet Sylvie, Guibert Agnès, Mourier Wilhelmine, Guerrault-Moro Marie-Noelle, Ferrari Sylvie, Jomier Jean-Yves, Brossard Denis, Schierl Rudolf. Environmental and biological monitoring of platinum-containing drugs in two hospital pharmacies using positive air pressure isolators. *Ann Occup Hyg* 2012;57:374-83.
- [44] Kopp B, Schierl R, Nowak D. Evaluation of working practices and surface contamination with antineoplastic drugs in outpatient oncology health care settings. *Int Arch Occup Environ Health* 2012;86:47-55.
- [45] Lalande L, Galy G, Dussosoy E, Noyel J-E, Pivot C. Evaluation of safe infusion devices for antineoplastic administration. *J Infus Nurs* 2012;35:321-7.
- [46] Mader RM, Kokalj A, Kratochvil E, Pilger A, Rüdiger HW. Longitudinal biomonitoring of nurses handling antineoplastic drugs. *J Clin Nurs* 2008;18:263-9.

- [47] Mason HJ, Blair S, Sams C, Jones K, Garfitt SJ, Cuschieri MJ, Baxter PJ. Exposure to antineoplastic drugs in two UK hospital pharmacy units. *Ann Occup Hyg* 2005;49:603–10.
- [48] Massoomi FF, Neff B, Pick A, Danekas P. Implementation of a safety program for handling hazardous drugs in a community hospital. *Am J Health Syst Pharm* 2008;65:861–5.
- [49] McDiarmid MA, Condon M. Organizational safety culture/climate and worker compliance with hazardous drug guidelines: lessons from the blood-borne pathogen experience. *J Occup Environ Med* 2005;47:740–9.
- [50] Ndaw S, Denis F, Marsan P, d'Almeida A, Robert A. Biological monitoring of occupational exposure to 5-fluorouracil: urinary α -fluoro- β -alanine assay by high performance liquid chromatography tandem mass spectrometry in health care personnel. *J Chromatogr B* 2010;878:2630–4.
- [51] Susanne Nussbaumer, Fleury-Souverain Sandrine, Antinori Paola, Sadeghipour Farshid, Hochstrasser Denis F, Bonnabry Pascal, Veuthey Jean-Luc, Geiser Laurent. Simultaneous quantification of ten cytotoxic drugs by a validated LC–ESI–MS/MS method. *Anal Bioanal Chem* 2010;398:3033–42.
- [52] Susanne Nussbaumer, Geiser Laurent, Sadeghipour Farshid, Hochstrasser Denis, Bonnabry Pascal, Veuthey Jean-Luc, Fleury-Souverain Sandrine. Wipe sampling procedure coupled to LC–MS/MS analysis for the simultaneous determination of 10 cytotoxic drugs on different surfaces. *Anal Bioanal Chem* 2011;402:2499–509.
- [53] Nygren O, Gustavsson B, Eriksson R. A test method for assessment of spill and leakage from drug preparation systems. *Ann Occup Hyg* 2005;49:711–8.
- [54] Nygren O, Olofsson E, Johansson L. Spill and leakage using a drug preparation system based on double-filter technology. *Ann Occup Hyg* 2008;52:95–8.
- [55] Odraska P, Dolezalova L, Piler P, Oravec M, Blaha L. Utilization of the solid sorbent media in monitoring of airborne cyclophosphamide concentrations and the implications for occupational hygiene. *J Environ Monit* 2011;13:1480.
- [56] Odraska P, Dolezalova L, Kuta J, Oravec M, Piler P, Blaha L. Evaluation of the efficacy of additional measures introduced for the protection of healthcare personnel handling antineoplastic drugs. *Ann Occup Hyg* 2012;57:240–50.
- [57] Pieri M, Castiglia L, Basilicata P, Sannolo N, Acampora A, Miraglia N. Biological monitoring of nurses exposed to doxorubicin and epirubicin by a validated liquid chromatography/fluorescence detection method. *Ann Occup Hyg* 2010;4:368–76.
- [58] Pretty Jack R, Connor Thomas H, Spasojevic Ivan, Kurtz Kristine S, McLaurin Jeffrey L, B'Hymer Clayton, Gayle Debord D. Sampling and mass spectrometric analytical methods for five antineoplastic drugs in the healthcare environment. *J Oncol Pharm Pract* 2010;18:23–36.
- [59] Roberts S, Khammo N, McDonnell G, Sewell GJ. Studies on the decontamination of surfaces exposed to cytotoxic drugs in chemotherapy workstations. *J Oncol Pharm Pract* 2006;12:95–104.
- [60] Federica Maria Rubino, Verduci Cinzia, Buratti Marina, Fustinoni Silvia, Campo Laura, Omodeo-Salè Emanuela, Giglio Margherita, Iavicoli Sergio, Brambilla Gabri, Colombi Antonio. Assay of urinary α -fluoro- β -alanine by gas chromatography–mass spectrometry for the biological monitoring of occupational exposure to 5-fluorouracil in oncology nurses and pharmacy technicians. *Biomed Chromatogr* 2006;20:257–66.
- [61] Sabatini L, Barbieri A, Tosi M, Violante FS. A new high-performance liquid chromatographic/electrospray ionization tandem mass spectrometric method for the simultaneous determination of cyclophosphamide, methotrexate and 5-fluorouracil as markers of surface contamination for occupational exposure monitoring. *J Mass Spectrom* 2005;40:669–74.
- [62] Sabatini L, Barbieri A, Lodi V, Violante FS. Biological monitoring of occupational exposure to antineoplastic drugs in hospital settings. *Med Lav* 2012;103:394–401.
- [63] Schierl R, Böhlandt A, Nowak D. Guidance values for surface monitoring of antineoplastic drugs in German pharmacies. *Ann Occup Hyg* 2009;53:703–11.
- [64] Schierl R, Herwig A, Pfaller A, Groebmair S, Fischer E. Surface contamination of antineoplastic drug vials: comparison of unprotected and protected vials. *Am J Health Syst Pharm* 2010;67:428–9.
- [65] Schierl R, Novotna J, Piso P, Böhlandt A, Nowak D. Low surface contamination by cis/oxaliplatin during hyperthermic intraperitoneal chemotherapy (HIPEC). *Eur J Surg Oncol* 2012;38:88–94.
- [66] Schulz H, Bigelow S, Dobish R, Chambers CR. Antineoplastic agent workplace contamination study: the Alberta Cancer Board Pharmacy perspective. *J Oncol Pharm Pract* 2005;11:101–9.
- [67] Sessink PJ, Connor TH, Jorgenson JA, Tyler TG. Reduction in surface contamination with antineoplastic drugs in 22 hospital pharmacies in the US following implementation of a closed-system drug transfer device. *J Oncol Pharm Pract* 2011;17:39–48.
- [68] Sottani C, Tranfo G, Bettinelli M, Faranda P, Spagnoli M, Minoia C. Trace determination of anthracyclines in urine: a new high-performance liquid chromatography/tandem mass spectrometry method for assessing exposure of hospital personnel. *Rapid Commun Mass Spectrom* 2004;18:2426–36.
- [69] Sottani C, Tranfo G, Faranda P, Minoia C. Highly sensitive high-performance liquid chromatography/selective reaction monitoring mass spectrometry method for the determination of cyclophosphamide and ifosfamide in urine of health care workers exposed to antineoplastic agents. *Rapid Commun Mass Spectrom* 2005;19:2794–800.
- [70] Cristina Sottani, Turci Roberta, Schierl Rudolf, Gaggeri Raffaella, Barbieri Anna, Saverio Violante Francesco, Minoia Claudio. Simultaneous determination of gemcitabine, taxol, cyclophosphamide and ifosfamide in wipe samples by high-performance liquid chromatography/tandem mass spectrometry: protocol of validation and uncertainty of measurement. *Rapid Commun Mass Spectrom* 2007;21:1289–96.
- [71] Cristina Sottani, Rinaldi Paola, Leoni Emanuela, Poggi Guido, Teragni Cristina, Delmonte Angelo, Minoia Claudio. Simultaneous determination of cyclophosphamide, ifosfamide, doxorubicin, epirubicin and daunorubicin in human urine using high-performance liquid chromatography/electrospray ionization tandem mass spectrometry: bioanalytical method validation. *Rapid Commun Mass Spectrom* 2008;22:2645–59.
- [72] Sottani C, Porro B, Comelli M, Imbriani M, Minoia C. An analysis to study trends in occupational exposure to antineoplastic drugs among health care workers. *J Chromatogr B* 2010;878:2593–605.
- [73] Sottani C, Porro B, Imbriani M, Minoia C. Occupational exposure to antineoplastic drugs in four Italian health care settings. *Toxicol Lett* 2011;213:107–15.
- [74] Stover D, Achutan C. Case study: occupational exposures to antineoplastic drugs in an oncology–hematology department. *J Occup Environ Hyg* 2011;8: D1–6.
- [75] Touzin K, Bussières JF, Langlois E, Lefebvre M. Evaluation of surface contamination in a hospital hematology–oncology pharmacy. *J Oncol Pharm Pract* 2009;15:53–61.
- [76] Touzin K, Bussières JF, Langlois E, Lefebvre M, Metra A. Pilot study comparing the efficacy of two cleaning techniques in reducing environmental contamination with cyclophosphamide. *Ann Occup Hyg* 2010;54:351–9.
- [77] Jochen Tuerk, Kiffmeyer Thekla K, Hadtstein Claudia, Heinemann André, Hahn Moritz, Stuetzer Hartmut, Kuss Heinz-Martin, Eickmann Udo. Development and validation of an LC–MS/MS procedure for environmental monitoring of eight cytostatic drugs in pharmacies. *Int J Environ Anal Chem* 2011;91:1178–90.
- [78] Roberta Turci, Minoia Claudio, Sottani Cristina, Coghi Raffaella, Severi Paolo, Castriotta Cecilia, Del Bianco Massimo, Imbriani Marcello. Occupational exposure to antineoplastic drugs in seven Italian hospitals: the effect of quality assurance and adherence to guidelines. *J Oncol Pharm Pract* 2011;17:320–32.
- [79] Turk M, Davas A, Ciceklioglu M, Sacaklioglu F, Mercan T. Knowledge, attitude and safe behaviour of nurses handling cytotoxic anticancer drugs in Ege University Hospital. *Asian Pac J Cancer Prev* 2004;5:164–8.
- [80] Ursini CL, Cavallo D, Colombi A, Giglio M, Marinaccio A, Iavicoli S. Evaluation of early DNA damage in healthcare workers handling antineoplastic drugs. *Int Arch Occup Environ Health* 2006;80:134–40.
- [81] Milena Villarini, Dominici Luca, Piccinini Renza, Fatigoni Cristina, Ambrogio Maura, Curti Gianluca, Morucci Piero, Muzi Giacomo, Monarca Silvano, Moretti Massimo. Assessment of primary, oxidative and excision repaired DNA damage in hospital personnel handling antineoplastic drugs. *Mutagenesis* 2011;26:359–69.
- [82] Zock MD, Soeffje S, Rickabaugh K. Evaluation of surface contamination with cyclophosphamide following simulated hazardous drug preparation activities using two closed-system products. *J Oncol Pharm Pract* 2010;17:49–54.
- [83] Suspiro A, Prista J. Biomarkers of occupational exposure to anticancer agents: a minireview. *Toxicol Lett* 2011;207:42–52.
- [84] Hon C-Y, Teschke K, Demers PA, Venners S. Antineoplastic drug contamination on the hands of employees working throughout the hospital medication system. *Ann Occup Hyg* 2014;58:761–70.