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Estimating National-Level Exposure to Antineoplastic Agents in the Workplace: CAREX Canada Findings and Future Research Needs

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Abstract

Objectives: Occupational exposure to antineoplastic agents occurs in various environments and is associated with increased cancer risk and adverse reproductive outcomes. National-level information describing the location and extent of occupational exposure to antineoplastic agents is unavailable in Canada and most other countries. CAREX Canada aimed to estimate the prevalence and relative levels of occupational exposures to antineoplastic agents across work setting, occupation, and sex.

Methods: 'Exposure' was defined as any potential for worker contact with antineoplastic agents. Baseline numbers of licensed workers were obtained from their respective professional bodies. For unlicensed workers, Census data or data extrapolated from human resources reports (e.g., staffing ratios) were used. Prevalence was estimated by combining population estimates with exposure proportions from peer-reviewed and grey literature. Exposure levels (classified as low, moderate, and high) by occupation and work setting were estimated qualitatively by combining estimates of contact frequency and exposure control practices.

Results: Approximately 75 000 Canadians (0.42% of the total workforce) are estimated as occupationally exposed to antineoplastic agents; over 75% are female. The largest occupational group exposed to antineoplastic agents is community pharmacy workers, with 30 200 exposed. By work setting, 39 000 workers (52% of all exposed) are located in non-hospital settings; the remaining 48% are exposed in hospitals. The majority (75%) of workers are in the moderate exposure category.

Conclusions: These estimates of the prevalence and location of occupational exposures to antineoplastic agents could be used to identify high-risk groups, estimate disease burden, and target new research and prevention activities. The limited secondary data available for developing these estimates highlights the need for increased quantitative measurement and documentation of antineoplastic agent contamination and exposure, particularly in work environments where use is emerging.

Keywords: antineoplastic agents; CAREX; cytotoxic drugs; disease burden; exposure assessment; exposure surveillance; occupational exposure

Introduction

Cancer is a leading contributor to global disease burden, with nearly 15 million new cases diagnosed annually (Fitzmaurice *et al.*, 2015). Cancer patients often receive a combination of treatments involving surgery, radiation, and/or systemic drug therapy (Shah, 2008). Antineoplastic agents, also referred to as chemotherapy agents, are the most common type of systemic drug therapy (Pham and Holle, 2015). These drugs interfere with cancer cell proliferation through various mechanisms of action (Shah, 2008), and are administered as curative treatment for chemo-sensitive cancers, adjuvant therapy (i.e., in conjunction with surgery or radiation), maintenance therapy (i.e., to prevent relapse and improve survival), or palliative treatment (i.e., to reduce symptoms and improve quality of life) (Pham and Holle, 2015).

Over 100 antineoplastic agents are currently in use (National Institute for Occupational Safety and Health, 2016), many of which are mutagenic and either known or probable human carcinogens (International Agency for Research on Cancer, 2016). Toxic effects are well documented in patients receiving antineoplastic agent treatments (Pham and Holle, 2015). For individuals who contact antineoplastic agents at work, exposure confers no benefit and is likely to occur chronically at low levels relative to therapeutic doses. Increased cancer risks have been noted in workers employed in oncology departments (Dimich-Ward *et al.*, 2007; Ratner *et al.*, 2010), and occupational exposures to antineoplastic agents have been associated with adverse reproductive outcomes (Fransman, Roeleveld *et al.*, 2007; Ratner *et al.*, 2010; Connor *et al.*, 2014) and dermal, allergic, and other genotoxic effects (National Institute for Occupational Safety and Health, 2015).

Occupational exposure to antineoplastic agents may occur directly via dermal contact, inhalation, ingestion, or accidental injection, or indirectly via contact with contaminated surfaces and objects (National Institute for Occupational Safety and Health, 2015). This can occur in hospitals, where antineoplastic agents are handled in shipping and receiving areas, prepared in pharmacies, administered in wards, and contacted through sanitary services such as laundry, cleaning, and waste handling (Hon *et al.*, 2013). Exposure can also occur in non-hospital settings such as community pharmacies, veterinary care facilities, and home care settings (Meijster *et al.*, 2006).

Similar to other countries, occupational exposure to antineoplastic agents is not monitored for regulatory purposes in Canada. Centralized information describing the location and extent of antineoplastic agent use is unavailable at national and provincial/territorial levels, and few data are available to describe occupational exposures, particularly outside of hospitals. The ubiquity of contamination in occupational environments where antineoplastic agents are used (Hon *et al.*, 2013), and their emerging use in non-hospital environments (e.g., community pharmacies, veterinary clinics, and home care settings) are additional challenges to assessing the locations and numbers of workers exposed. These knowledge gaps are noteworthy, since information on the numbers and locations of workers potentially exposed to antineoplastic agents may be used to identify high-risk groups, estimate burden of disease (e.g., cancer and reproductive outcomes), set priorities for prevention, and monitor exposure trends over time. CAREX Canada is a national surveillance project that draws from existing data sources to estimate the number of Canadians exposed to known and suspected carcinogens, and where possible, to estimate levels of exposure (Peters *et al.*, 2015). Our objectives for this paper were to:

1. Estimate the prevalence of Canadian workers exposed to antineoplastic agents, across work setting, occupation, and sex
2. Estimate levels of exposure across work setting and occupation
3. Discuss implications for future research and prevention activities

Methods

CAREX Canada's approach to selecting and prioritizing known and suspected carcinogens for evaluation

is described elsewhere (Peters *et al.*, 2015). In brief, agents are identified from the International Agency for Research on Cancer (IARC)'s list of Group 1 (known human carcinogens), Group 2A (probable carcinogens), and Group 2B (possible carcinogens). These agents are then evaluated based on their toxicity, prevalence in Canadian settings, and feasibility of evaluation based on available data. In cases where agents are likely to be encountered together, separate IARC agents are grouped for exposure assessment (Peters *et al.*, 2015).

Using this approach, CAREX Canada identified five antineoplastic agents as 'high priority' for assessment based on their IARC classification and likelihood of use in Canadian settings: Chlorambucil, Cyclophosphamide and Melphalan (IARC Group 1), and Adriamycin and Cisplatin (IARC Group 2A) (International Agency for Research on Cancer, 2016). Cancer treatments often incorporate combinations of antineoplastic agents with different modes of action (Shah, 2008), producing a variety of occupational exposure scenarios where co-exposures to multiple agents are likely. To address this complexity, CAREX assessed exposure to antineoplastic agents as a group rather than investigating individual substances.

Similar to other large scale exposure estimation projects (Kauppinen, 2000) 'exposure' was broadly defined as the potential for worker contact with antineoplastic agents, either by working with the drugs directly or via contact with patients receiving the drugs or contaminated surfaces or bodily fluids. This included contact via different routes (e.g., dermal contact, inhalation, ingestion, or injection), and via different drug formulations (e.g., oral, parenteral).

Due to differences in data availability, exposure prevalence across work environments and occupations was estimated by combining a variety of data sources using expert assessment. For each occupation, the most comprehensive source of information available was used to obtain baseline worker numbers; this included provincial/territorial data compiled by the Canadian Institute for Health Information, registrar reports compiled by professional bodies, and information from the Canadian Census. For occupations where information on baseline numbers was not well defined by these sources (e.g., veterinary technicians and pharmacy technicians), extrapolations were conducted by applying information from staffing composition reports to baseline numbers of well-defined staff (e.g., veterinarians and pharmacists). Prevalence for each occupation was then estimated by combining baseline worker numbers with an estimate of exposure prevalence, the latter chosen based on similar exposure scenarios described in the peer-reviewed and/or grey literature. Supplementary Figure 1 (available at *Annals of Work Exposures and Health*) provides a full summary of exposure definitions, baseline population descriptions and data sources, methods and exclusions for each occupation.

CAREX also developed exposure level estimates using an ordinal scale (low, medium, and high) to provide general characterizations of differences in exposure within occupations and across work settings. Peer-reviewed and grey literature sources were used to develop measures of *contact frequency* (characterizing relative differences in contact frequency within occupations) and *control* (characterizing the general extent of exposure control practices typical for a given work environment). Contact frequency was assessed on an occupation-by-occupation basis. In cases where secondary data sources provided sufficient information to describe exposure differences within occupations, a dichotomous ranking ('low' or 'high') was applied. For control, where there was no evidence to indicate the consistent presence of control measures (e.g., workplace policies to guide the use of engineering controls, exposure control plans, and personal protective equipment) in Canada, or where there was some evidence to indicate a general lack of control measures in a given workplace type, *control* was defined as 'low.' Where there was some evidence to indicate the consistent presence of hazard recognition/control measures across Canada in a given workplace type, *control* was defined as 'high.'

'Low exposure' was defined as a combination of *low contact frequency* and *high control*. 'Moderate exposure' was defined as either a combination of *low contact frequency* and *low control*, or of *high contact frequency* and *high control*. 'High exposure' was defined as a combination of *high contact frequency* and *low control*.

To locate peer-reviewed literature describing occupational exposure, use, and controls generally, as well as for specific occupations, Pubmed searches were conducted using the following terms:

1. General search

   (occupation* OR work* OR job*) AND (antineoplastic* OR chemotherap* OR hazardous drug* OR cytotoxic*) AND (exposure* OR monitoring OR awareness OR use OR usage OR control*)

2. Occupation-specific search (using nurses as an example):

   (nurs* OR RN OR LPN) AND (antineoplastic* OR chemotherap* OR hazardous drug* OR cytotoxic*) AND (exposure* OR monitoring OR awareness OR use OR usage OR control*)

Due to a lack of coverage for many occupations and work environments, detailed information from indi-

vidual jurisdictions was frequently applied to produce national estimates of exposure.

For grey literature, the Canadian Health Research Collection, the Canadian Agency for Drugs and Technologies in Health (CADTH) Grey Matters database, and the University of British Columbia library's search engine were used. These searches were performed using combinations of terms as listed above. Websites of provincial/territorial professional and membership groups (where these existed for the occupation in question) were also searched for membership data and technical reports.

Results

Prevalence estimates

Prevalence results are presented in Table 1. Approximately 75 000 Canadians (0.42% of the total workforce) are estimated as occupationally exposed to antineoplastic agents; over 75% are female. The largest occupational group exposed to antineoplastic agents is community pharmacy workers (pharmacists and technicians), with 30 200 workers exposed. When examining exposure by work setting, 39 000 workers (0.22% of the Canadian workforce) are located in non-hospital settings (community pharmacies, veterinary practices, home care settings, geriatric/long term care settings, and sub-contracted laundry facilities); the remaining 36 000 are exposed in hospitals. Exposure prevalence estimates for each occupational group are summarized below; Supplementary Figure 1 (available at *Annals of Work Exposures and Health*) provides a summary of information sources, methods, and exclusions.

Pharmacy workers (pharmacists and pharmacy technicians)

In the most recent publication of a national survey of hospital pharmacies in Canada, 89% (144/161) of hospital site respondents reported preparation of IV cytotoxic drugs (a general term for drugs including antineoplastic agents) in their pharmacy department ('Hospital Pharmacy in Canada 2013/2014 Report,' 2015). CAREX estimates used an exposure prevalence of 85% for pharmacy workers employed in hospital pharmacy departments, given the high likelihood of surface contamination in pharmacies that prepare antineoplastic agents (Hon *et al.*, 2013).

Peer-reviewed literature describing antineoplastic agent dispensations in American and Canadian settings (O'Bryant and Crandell, 2008; Abbott *et al.*, 2014) was consulted to estimate the proportion of community pharmacies handling antineoplastic agents. These sources consistently noted that ~60% of pharmacies reported a dispensation rate of one or more chemotherapy prescriptions per week. CAREX estimates used an exposure prevalence of 60% for all pharmacists and pharmacy technicians in community settings.

Nurses (Registered Nurses and Licensed Practical Nurses) in hospitals and geriatric/long term care

In hospitals, the most detailed description of exposure prevalence was located in Ward *et al.*'s study (Ward *et al.*, 2006; Dimich-Ward *et al.*, 2007) that assessed nurses' likelihood of exposure to antineoplastic drugs across clinical areas in the Canadian province of British Columbia. In this study, 'exposure' referred to being in the same room or working with antineoplastic drugs directly; possible exposure categories were 'no', 'unlikely', 'possible', and 'probable'. CAREX estimates included clinical areas where Ward *et al.* deemed the likelihood of exposure to antineoplastic drugs to be 'unlikely', 'possible', or 'probable' for at least 5% of all direct care nurses. An exposure prevalence similar to that estimated by Ward *et al.* for each clinical area: 75% for Registered Nurses and Licensed Practical Nurses in Oncology, 27% in ambulatory care, 18% in medical/surgical care, and 6% in paediatrics [Personal Communication: Y. Chow, University of British Columbia, July 23, 2009] was then applied to the total numbers of nurses currently employed in these areas across Canada (Canadian Institute for Health Information (CIHI), 2015c).

In Geriatric and Long Term Care settings, 2014–2015 data from the Canadian Institute for Health Information was used to estimate frequency of potential exposure (Canadian Institute for Health Information (CIHI), 2015a). These data describe residents who received services in 1307 residential care facilities and in 119 hospital-based complex continuing care facilities across Canadian jurisdictions. The percentage of cancer diagnoses in continuing care/residential care residents varied by jurisdiction and care setting (residential versus hospital-based continuing care), ranging from 6.9 to 26.7%. In the same time period, chemotherapy treatments were administered to 1.8% of individuals in hospital-based continuing care and <1% of all individuals in residential care (Canadian Institute for Health Information (CIHI), 2015a). CAREX estimates used an exposure prevalence of 1% for direct care Registered Nurses and Licensed Practical Nurses in geriatric and long-term care settings.

Veterinary workers

In veterinary practice, antineoplastic agents are most commonly used to treat companion animals (dogs and cats;

Table 1. Prevalence of exposure[a] to antineoplastic agents by occupation and setting

	Baseline population (*n*)	Exposure prevalence applied (%)	Total exposed (*n*)	Female (%)
Pharmacists				>60
Hospital	6800	85	5800	
Community	23700	60	14200	
Pharmacy technicians[b]				>80
Hospital	8100	85	6900	
Community	26600	60	16000	
Registered Nurses				>90
Hospital				
Oncology	6600	75	5000	
Ambulatory	9300	27	2500	
Medical/Surgical	45000	18	8100	
Paediatrics	6200	6	400	
Geriatric/Long term care	25400	1	300	
Home Care	11100	5	600	
Licensed Practical Nurses				>90
Hospital				
Oncology	400	75	300	
Ambulatory	1000	27	300	
Medical/Surgical	14000	18	2500	
Paediatrics	1000	6	100	
Geriatric/Long term care	39600	1	400	
Home Care	3100	5	200	
Veterinarians				>50
Small animal practice	6900	40	2800	
Mixed (small and large) animal practice	1000	20	200	
Veterinary Technicians[b]				>90
Small animal practice	5500	40	2200	
Mixed (small and large) animal practice	800	20	200	
Cleaning Workers				>60
Hospital	19600	15	2900	
Geriatric/Long term care	14800	1	100	
Home Care Workers				>90
Nurse aides	3600	5	200	
Home support workers	26300	5	1300	
Laundry Workers				>60
Hospital	2700	20	500	
Geriatric/Long term care	2400	2	100	
Sub-contractor facilities	11000	2	200	
Physician Specialists				>40
Oncology (medical and gynaecologic)	500	75	400	
Haematology (adult and paediatric)	500	25	100	
Total exposed			74800	>75

[a]'Exposure' refers to any potential for contact with antineoplastic agents

[b]Total numbers based on staffing extrapolations

Elliot and Mayer, 2009). Peer-reviewed literature was used to estimate the expected prevalence of antineoplastic agent use in veterinary practice. One survey conducted in Western Canada reported cytotoxic drug use in 46% of companion (small) animal practices and mixed (small and large) animal practices (Epp and Waldner, 2012). A similar usage prevalence (46%) was reported by veterinary nurses in an Australian study (Soest and Fritschi,

2004) and a higher prevalence (70.8%) was reported by veterinary practices in the United Kingdom (Cave *et al.*, 2007).

CAREX estimates used an exposure prevalence of 40% in companion animal practices and 20% in mixed animal practices (that treat both companion and large animals). This was done to account for variations across practices and a lower rate of antineoplastic administration expected in mixed animal practice (Elliot and Mayer, 2009; Epp and Waldner, 2012). A detailed summary of these veterinary worker exposure estimates is reported elsewhere (Hall *et al.*, 2013).

Cleaning workers

The prevalence and extent of antineoplastic agent exposure in health care cleaning workers (also referred to as 'housekeeping workers') is not well described in the literature. The number of cleaning workers with potential exposure to antineoplastic agents in hospital settings in 2015 was estimated for the province of British Columbia via consultation with its provincial environmental services technical team (Personal Communication: Provincial Environmental Services Technical Team, British Columbia Canada, January 2016). Approximately 250 health care cleaning workers in the province British Columbia (representing 20% of cleaning workers in hospitals reported in the 2006 Census of Population; Statistics Canada, 2006) were assessed as likely to have physical contact with inpatient or outpatient oncology units.

CAREX estimates used an exposure prevalence of 15% in hospitals to account for variations in health care staffing and antineoplastic agent use across Canadian jurisdictions. An exposure prevalence of 1% was applied to cleaning workers in geriatric/long term care settings. Cleaning workers employed by private companies were not counted in these estimates since such individuals could not be clearly identified in the Census; estimation via other means was out of this study's scope, since outsourcing practices differ across Canadian provincial/territorial jurisdictions as well as across health authorities within jurisdictions.

Home care workers

Unlicensed home care workers (support workers and nurse aides) generally assist with activities of daily living (e.g., bathing, dressing, meal preparation) and constitute the largest occupational group in the home care sector (Home Care Sector Study Corporation, 2003). This is followed by licensed nurses (Registered Nurses and Licensed or Registered Practical Nurses) who most frequently report administering medications to home care clients, and are most likely to administer medications intravenously (Home Care Sector Study Corporation, 2003).

While data on occupational exposures in Canadian home care settings could not be located, contamination in home care settings has been noted in Germany (Böhlandt *et al.*, 2017), Japan (Yuki *et al.*, 2014), and The Netherlands (Meijster *et al.*, 2006). In cases where oncology treatments are administered in hospital outpatient settings, precautionary periods of up to 14 days have been recommended for handling excreta following treatment with antineoplastic agents (Allwood *et al.*, 2002). Therefore, regardless of treatment location (at home versus in an outpatient setting), home care workers' close contact with cancer patients at home confers potential exposure.

Data from the Canadian Institute for Health Information indicate that ~10% of home care clients in community settings are living with cancer, with 1% or fewer of all home care clients receiving chemotherapy treatment at a given time (Canadian Institute for Health Information (CIHI), 2015b). CAREX estimates used an exposure prevalence of 5% to account for home care providers attending to multiple clients on a given day, week, or month.

Laundry workers

As reported for pharmacy workers, ~89% of Canadian hospitals prepare IV cytotoxic drugs in their pharmacy department ('Hospital Pharmacy in Canada 2013/2014 Report,' 2015). Since antineoplastic agents are administered in most hospital facilities, and exposure has been shown to be possible via the handling of contaminated bed linens in hospital settings (Fransman *et al.*, 2005), some degree of exposure in laundry workers is likely. In the case of private sub-contracted laundry facilities, contamination of linens with antineoplastic agents has been detected (Meijster *et al.*, 2006; Fransman, Huizer *et al.*, 2007), although potential for worker exposure may be lower in these settings (Fransman, Huizer *et al.*, 2007).

CAREX estimates used an exposure prevalence of 20% for hospital laundry workers. This accounts for antineoplastic agents being administered in most Canadian hospitals ('Hospital Pharmacy in Canada 2013/2014 Report,' 2015), and assumes that workers in soiled laundry sorting areas (~25 to 35% of all laundry workers [Personal Communication: A. Griffiths, Vancouver Island Health Authority, February 2016]), are at risk of exposure. For laundry workers employed off-site by private sub-contractors, an exposure

prevalence of 2% was used, based on Meijster *et al.*'s estimation that 2% of laundry workers in non-hospital facilities are exposed to antineoplastic agents (Meijster *et al.*, 2006). An exposure prevalence of 2% for laundry workers in Geriatric/Long Term Care facilities was used to reflect a lower frequency of antineoplastic administration in these settings (Canadian Institute for Health Information (CIHI), 2015a), as reported for nurses.

Physician specialists

Although physicians are not known to prepare nor administer antineoplastic agents in Canada, some specialties are expected to sustain close contact with patients receiving the drugs and/or contact contaminated surfaces in oncology treatment areas. No literature could be located to describe physicians' typical contact frequency (nor intensity of contact) with antineoplastic agents. CAREX estimates used an exposure prevalence of 75% for all physicians specializing in medical or gynaecologic oncology, reflecting the proportion used for nurses. For other physician specialties with a high likelihood of contacting antineoplastic agents (haematology and paediatric haematology), a lower exposure prevalence of 25% was used, to address uncertainty in location of practice (e.g., oncology versus non-oncology haematology) and exposure frequency.

Exposure level estimates

Results for exposure level estimates are presented in Table 2. The majority (75%) of workers exposed to antineoplastic agents are in the moderate exposure category. 'High contact frequency' was assigned to workers employed in hospital oncology departments (nurses and cleaners) as well as pharmacists employed in hospitals, since relatively frequent contact with antineoplastic agents has been reported in both areas (Ward *et al.*, 2006; 'Hospital Pharmacy in Canada 2013/2014 Report,' 2015). 'High contact frequency' was also applied to workers in community pharmacies that were likely contact antineoplastic agents on a frequent basis (Abbott *et al.*, 2014). All other workers were assigned a 'low' contact frequency. 'High exposure control' was assigned to hospitals (nursing units and pharmacies) due to consistent reports of workplace policies concerning engineering, administrative, and personal protective controls in these settings. Since no evidence

Table 2. Relative levels of exposure[a] to antineoplastic agents by occupation and setting

Occupation	Low exposure (*n*)	Moderate exposure (*n*)	High exposure (*n*)	Total exposed (*n*)
Nurses (Registered Nurses and Licensed Practical Nurses)				
Hospital	13 900[b]	5300[c]		19 200
Geriatric/Long term care		700[d]		700
Home care		800[d]		800
Physician Specialists	500[b]			500
Pharmacy Workers (pharmacists, technicians)				
Hospital		12 700[c]		12 700
Community		25 700[d]	4500[e]	30 200
Veterinary Workers (veterinarians, technicians)		5400[d]		5400
Home Care Workers (nurse aides, home care workers)		1500[d]		1500
Cleaning Workers				
Hospital		2900[c]		2900
Geriatric/Long term care		100[d]		100
Laundry Workers				
Hospital	500[b]			500
Geriatric/Long term care		100[d]		100
Sub-contractor facilities	200[b]			200
Total exposed				74 800

[a]'Exposure' refers to any potential contact with antineoplastic agents
[b]Low contact frequency, high exposure control = low exposure
[c]High contact frequency, high exposure control = moderate exposure
[d]Low contact frequency, low exposure control = moderate exposure
[e]High contact frequency, low exposure control = high exposure

could be located to indicate the consistent application of such policies in non-hospital settings (e.g., community pharmacies, general veterinary practices, home care) across Canada, 'low exposure control' was assigned to workers employed in these areas.

These results highlight varying levels of exposure frequency and exposure controls within and between occupations and work settings. For example, the majority of hospital nurses exposed were placed into the low exposure category (low contact frequency, high exposure control; n = 13 900), due to expected low frequency of exposure (working in non-oncology areas) and relatively high exposure control expected in hospital environments (National Institute for Occupational Safety and Health, 2004; Meijster *et al.*, 2006*)*. Where more frequent exposure was expected (nurses working in oncology areas), exposed workers were placed into the moderate exposure category (high contact frequency, high exposure control; n = 5300).

A second example focuses on community pharmacy workers. Multiple sources indicated inadequate exposure control in Canadian community pharmacies (Abbott *et al.*, 2014; Tanguay, 2014; Abbott *et al.*, 2011). Therefore for CAREX Canada estimates, all community pharmacy workers were assigned low exposure control. Workers were assigned different levels of contact frequency based on reports of antineoplastic agent dispensation in community pharmacy settings. Only one study that described frequencies of antineoplastic agent handling in community pharmacies across Canada was located *(*Abbott *et al.*, 2014); approximately 51% of community pharmacies reported infrequent handling of antineoplastic agents (defined as dispensing chemotherapy prescriptions at least once per week). For CAREX Canada estimates, 51% of all community pharmacists and pharmacy technicians were placed into the 'moderate exposure' category (low contact frequency, low exposure control; n = 25 700). In the same study, ~9% of community pharmacies reported frequent handling of antineoplastic agents (dispensing chemotherapy prescriptions six times or more per week; Abbott *et al.*, 2014). Therefore for CAREX Canada estimates, 9% of all community pharmacists and pharmacy technicians were placed into the 'high exposure' category (high frequency, low control; n = 4500).

It should be noted that exposure categories were assigned on an occupation-by-occupation basis. Therefore, worker numbers presented across exposure level categories are most useful for considering within, but not between, occupation differences. For most occupations, the assignment of exposure frequency sub-categories was infeasible due to limited sources of exposure data.

Discussion

CAREX Canada estimates that ~75 000 Canadians (0.42% of the total workforce) are occupationally exposed to antineoplastic agents; about half are working outside of hospitals. Over 75% of potentially exposed workers are female; this is an important point, since employment in oncology units has been linked to increased risk of breast cancer in nurses (Ratner *et al.*, 2010) and exposure to antineoplastic agents is associated with a range of reproductive health effects (Fransman, Roeleveld, *et al.*, 2007; Ratner *et al.*, 2010; Connor *et al.*, 2014). Prevalence of exposure to antineoplastic agents (as a group) and relative levels were assessed both within hospitals (where antineoplastic agent use and potential for occupational exposure is typically recognized) and in non-hospital settings (where antineoplastic use and potential for occupational exposure is emerging). Infrequently assessed occupations in this area of research, including cleaning, laundry, veterinary, and home care workers, were included in these estimates. CAREX Canada also developed broad qualitative exposure level categories (low, moderate, high) to further characterize exposures where possible. Using this method, the majority of workers were placed in the moderate exposure level category.

These estimates of occupational exposure to antineoplastic agents were developed using secondary data and expert assessment; providing the best evidence to date about the prevalence and location of occupational exposures to antineoplastic agents on a national level. These population level estimates are unique internationally and of relevance to other countries, since they (and similar methods) could be used to assess exposure and identify key targets for research and prevention. Identifying occupations with: (i) workers frequently exposed to antineoplastic agents; (ii) large numbers of workers exposed to antineoplastic agents; (iii) large proportions of females exposed; or (iv) occupations with inconsistently applied exposure controls can be useful in research and prevention efforts to prioritize exposed groups and target resources. Exposure assessment and reduction in the largest occupational group might be a useful strategy, or reducing exposure to those at highest risk of exposure and/or negative health outcomes could be seen as a priority.

Similar to other large-scale exposure estimation projects, CAREX Canada defines 'exposure' as any level of exposure above background, including all workers with the potential for direct or indirect exposure to antineoplastic agents. Our reliance on secondary data sources to assess exposures at a population level does not permit

an in-depth investigation of exposure scenarios and variability sources at an individual or facility level. However, describing exposures at a population level can be useful for disease burden estimation and priority setting for research and intervention. In Canada, for example, CAREX estimates describing national-level numbers and locations of outdoor workers most highly exposed to solar ultraviolet radiation (Peters *et al.*, 2012) were used to inform the development of a multiple case study for developing sun safety and heat protection programs (Kramer *et al.*, 2015). CAREX Canada estimates, such as those for diesel exhaust (Kim *et al.*, 2014), are currently being applied in the development of national burden of cancer estimates. CAREX Canada estimates have also been used to develop region-specific estimates to identify cancer research and intervention priorities (Labrèche *et al.*, 2013). Internationally, the European CAREX system has demonstrated scientific value through its application in surveillance and burden of disease studies (Driscoll *et al.*, 2005; Rushton *et al.*, 2012) and in the International Agency for Research on Cancer's Monograph series (van Tongeren, 2015). CAREX Canada results have been considered alongside those of similar large-scale projects in other countries (Kauppinen, 2000; Carey *et al.*, 2014) to identify targets for reducing work-related cancers worldwide (Takala, 2015).

Few other countries have developed similar national-level estimates of exposure to antineoplastic agents. The United States National Institute for Occupational Safety and Health (NIOSH) has estimated that 8 million health care workers may be exposed to antineoplastic agents (National Institute for Occupational Safety and Health, 2013). This estimate references the US Bureau of Labor Statistics, which reported a total health care workforce of 12 million in 2015 (US Department of Labor Bureau of Labour Statistics, 2016), thus indicating that over 60% of the US health care workforce may be exposed. CAREX Canada's estimates are more conservative (perhaps due to differences in exposure definitions and the specificity of methods used) and compare more closely to estimates from other countries. Although total population exposure estimates could not be located, it was recently estimated that between 5000 and 15 000 non-hospital workers in The Netherlands (0.07–0.21% of the total workforce) were exposed to antineoplastic drugs (Meijster *et al.*, 2006); this is similar to the CAREX estimate of 39 000 non-hospital workers (0.22% of the total workforce) exposed.

The amount of uncertainty present in CAREX Canada's estimates of exposure to antineoplastic agents for poorly characterized occupations (e.g., cleaners, laundry workers) and work environments where antineoplastic agent usage is emerging (e.g., home care and community pharmacy environments) is difficult to pinpoint in the absence of quantitative exposure data to describe these scenarios. In more frequently studied environments (e.g., hospitals), exposure variability is also expected due to jurisdictional- and facility-level differences in control measures applied, as well as individual adherence to these measures. There is reason to believe that the numbers of exposed workers have been underestimated rather than overestimated for most occupations, since CAREX Canada applied conservative exposure proportions based on the literature available. CAREX Canada estimates also focus primarily on antineoplastic agents administered for cancer treatment and exclude workers that could not be distinguished in the data sources available, such as those involved in non-oncology applications (e.g., treatment of rheumatoid arthritis and Crohn's disease) (Pham and Holle, 2015). Furthermore, the 2006 Census of Population was the most recent source of information on employment numbers across occupations and industries when these numbers were unavailable in more recent reports. Given the increased use of antineoplastic agents in both hospital and non-hospital environments over the past decade (Paoloni and Khanna, 2008; Weingart *et al.*, 2008; Abbott *et al.*, 2014; Pham and Holle, 2015; Canadian Institute for Health Information (CIHI), 2015c; Dayer *et al.*, 2016), the numbers of workers estimated using the 2006 Census (home care, cleaning, and laundry workers) are likely underestimated. This is particularly true for cleaning workers, given substantial variation in health care cleaning service privatization within and between Canadian jurisdictions.

Limited information on additional occupations with potential exposure to antineoplastic agents precluded their assessment. These include paraprofessionals (e.g., dieticians, physiotherapists, and social workers) involved in the clinical care of patients actively receiving chemotherapy treatments, other assisting occupations in health care and community work environments, and workers in waste treatment facilities and universities. CAREX estimates also excluded palliative care workers, since across Canada fewer than 5% of cancer patients receive inpatient chemotherapy during end-of-life care (Dudevich *et al.*, 2014).

Similar to the exposure prevalence estimates, CAREX Canada's exposure level categorization of antineoplastic agents is a broadly applied measure that is not intended for application at a fine level. The exposure frequency and exposure control categories are meant to serve a descriptive function, to identify exposure differences that may occur: (i) within occupations (as a function of estimated contact frequency), and (ii) within occupations

across work environments (as a function of estimated exposure controls) at a national level. These estimates are based on secondary data sources; many of which are limited in scope and quantity and do not account for exposure differences that exist within categories (e.g., lack of adherence to established control measures that may produce high exposures). Therefore, these estimates should be viewed as a source of general guidance for further research and intervention studies. For example, CAREX's inability to categorize exposure levels for various occupations due to low data availability (e.g., home care workers, veterinarians, cleaning workers) may be used to justify additional research in these areas. To our knowledge, the only similar categorization of antineoplastic agent exposures was conducted in the Netherlands, where exposure prevalence in non-hospital environments was estimated as 'low', 'equal to', or 'high' relative to typical hospital environment exposures (Meijster *et al.*, 2006). Quantitative exposure assessment is a worthy goal for future studies; but as emphasized in the next section, this will require increased quantitative measurement of occupational exposure to antineoplastic agents.

Future trends in exposure and implications for research and prevention

Cancer incidence is increasing globally (Fitzmaurice *et al.*, 2015) and this is reflected in occupational exposure trends. In Canada for instance, there was a 50% increase in the numbers of regulated nurses working in oncology treatment areas between 2005 and 2014 (Canadian Institute for Health Information (CIHI), 2015c). The rapid development and increasing availability of less invasive treatment options such as oral cancer therapies (Weingart *et al.*, 2008) has also expanded antineoplastic agent use outside of hospitals (Pham and Holle, 2015), particularly in community pharmacies, veterinary practices, and home care environments.

While more accessible and less aggressive treatment approaches outside of hospitals may incur significant benefit to patients, such developments carry implications for occupational exposures. Meijster *et al.* found that occupational exposure to antineoplastic agents occurs in a variety of work environments outside of hospitals in The Netherlands (Meijster *et al.*, 2006), and a small body of research has begun to recognize the potential risks of exposure in community pharmacies (Abbott *et al.*, 2011, 2014) and veterinary practices (Soest and Fritschi, 2004; Cave *et al.*, 2007; Epp and Waldner, 2012). However, quantitative workplace assessments of exposure to antineoplastic agents are surprisingly few in non-hospital settings where anti-neoplastic agent usage is emerging and expected to increase.

In Canada, home care services are administered by a variety of public, private not-for-profit, and private for-profit agencies, with availability and modes of delivery varying among the provinces and territories (The Canadian Healthcare Association, 2009). For example, some jurisdictions permit the administration of chemotherapy in the home by a professional (usually a home care nurse), whereas others do not (Canadian Home Care Association, 2013). Trends towards oral treatments (including oral antineoplastic agents) that are typically administered at home (Pham and Holle, 2015) will continue to support shifts in care from hospital to home care settings, particularly as the population continues to age and disease burden increases (Canadian Home Care Association, 2013). Baseline numbers and types of formal caregivers employed by home care organizations across the country are not well characterized (The Canadian Healthcare Association, 2009), perhaps because the majority of workers at risk of exposure in Canadian home care settings are unlicensed, low-wage earners (Home Care Sector Study Corporation, 2003) who are rarely mentioned in occupational health literature. It should be acknowledged that such workers may also be less likely to receive educational resources on appropriate exposure controls, and could therefore be less protected relative to other occupations.

In community pharmacies, recent increases in oral antineoplastic agent dispensations without commensurate guidance for safe handling and exposure controls have elicited concern within the industry. The majority of community pharmacists surveyed in three North American studies expressed inadequate knowledge of oral chemotherapy practices, with all groups citing a lack of education and training (O'Bryant and Crandell, 2008; Abbott *et al.*, 2014; Dayer *et al.*, 2016). Only 30% of pharmacist respondents in the Canadian study reported wearing personal protective equipment when dispensing oral antineoplastics; 27% used separate counting trays for oral antineoplastic agents; and 17% used hazardous medications labels (Abbott *et al.*, 2014). This suggests that community pharmacists in Canada and elsewhere would benefit from additional support to inform and protect themselves and other pharmacy staff from potential exposure to antineoplastic agents.

In veterinary settings, cancer treatment rates are steadily increasing, supported by newly established comparative oncology programs with implications for human health (Paoloni and Khanna, 2008). Published data characterizing exposure to antineoplastic agents is not available for Canadian veterinary settings, although surface contamination in veterinary practices has been detected in both the United States (Couch *et al.*, 2013) and The Netherlands (Meijster *et al.*, 2006). The latter

study found high levels of contamination on the gloves of workers administering antineoplastic agents 'higher by a factor of 15 than levels found in hospitals' (Meijster *et al.*, 2006). This is perhaps not surprising, since handling and administration safety practices are not enforced to the same extent in veterinary practices compared to hospitals, where certification is typically required to administer cancer treatments (Klahn, 2014). Furthermore, low rates of personal protective equipment use have been observed during the preparation and administration of antineoplastic agents in veterinary settings (Meijster *et al.*, 2006; Couch *et al.*, 2013), perhaps due to this hazard's competition with many other prevalent and acute health and safety priorities (Epp and Waldner, 2012).

No occupational exposure limits exist for antineoplastic agents. The 'As Low As Reasonably Achievable' principle is commonly applied since no safe exposure levels to avoid toxic effects are known. Recommendations, guidelines, and safety standards for safe work with antineoplastic agents have been issued by various bodies and are an important first step toward standardization. Legislation to minimize exposure in all workers who may contact hazardous drugs at work (including requirements for exposure control programs, employee training, and engineering controls) was recently adopted in the US State of Washington (Washington State Department of Labour & Industries, 2016), however such regulatory protections are rare. In large and/or jurisdictionally diverse countries such as Canada, the implementation of standardized occupational practices is challenged by regional variations in occupational regulation and cancer service organization, and practices may vary even within jurisdictions (Ahmad *et al.*, 2015). Importantly, hazard mitigation resources in emerging non-hospital environments are often limited compared to more established procedures and controls in hospitals and cancer centres (Hall *et al.*, 2013; Abbott *et al.*, 2014).

Guidelines and standards for safe work practices and control measures are needed, and can be effective in reducing occupational exposures. However, even where workplace controls have successfully reduced occupational contact with antineoplastic agents, the potential for exposure is typically not eliminated (Fransman, Peelen *et al.*, 2007). Interventions to reduce exposure as much as possible cannot be verified without quantitative evidence concerning environmental contamination and worker uptake (Kromhout, 2016), and exposure measurements are vital to detect and accurately assess disease risk. Greater availability of measurement data from different sources is also expected to increase the validity of exposure estimates used for risk and disease burden estimation (Lißner *et al.*, 2014). Therefore, we strongly emphasize the need for new and ongoing quantitative assessment of occupational exposure to antineoplastic agents, particularly in non-hospital settings where usage is emerging. Such measures are needed to increase the accuracy of exposure estimation and risk assessment, and to appropriately inform targeted interventions for exposure control.

Conclusions

CAREX Canada estimates that 75 000 (mostly female) workers in Canada are exposed to antineoplastic agents; about half are employed in non-hospital environments. These estimates provide a useful first step to characterizing exposure for domestic and international purposes; however, they rely on secondary data sources and expert assessment using a number of assumptions. Increased quantitative assessment of exposure to antineoplastic agents is needed to inform future risk estimation, intervention, and surveillance activities across various occupations and work environments.

Supplementary Data

Supplementary data are available at *Annals of Work Exposures and Health* online.

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Conflict of Interest

The authors have no conflicts of interest to declare.

Contributorship Statement

ALH, CEP, and PAD conceptualized the study. ALH and CBG conducted data gathering. All authors contributed to designing the study, and were involved in critically reviewing and revising the manuscript.

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