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Original Article

Investigating antineoplastic drug surface contamination in veterinary settings and on canine patients

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Abstract

Antineoplastic drugs can persist on surfaces in human and veterinary oncology clinics where they are administered, resulting in potentially hazardous exposures for healthcare workers and cancer patient caregivers. To assess potential surface contamination in occupational settings, a new liquid chromatography-selected reaction monitoring-mass spectrometry (LC-SRM-MS/MS) method was developed to simultaneously detect six commonly used antineoplastic drugs. A surface wipe and desorption method was optimized for cyclophosphamide, doxorubicin, methotrexate, etoposide, paclitaxel, and 5-fluorouracil with drug desorption recoveries ranging from 49% to 79%. The limit of detection (LOD) and limit of quantitation (LOQ) ranged from 0.01 to 0.12 ng/ml and 0.01 to 1.33 ng/ml, respectively. This method was used to quantify cyclophosphamide and doxorubicin surface contamination from wipe samples collected at a veterinary clinic following drug administration to canine-patients. Specific areas in the oncology treatment room identified as frequently contacted were sampled to determine the antineoplastic drug surface contamination that could lead to worker exposure through dermal contact, with cyclophosphamide and doxorubicin levels ranging from 6.68 to 17.4 pg cm^{-2} and 13.5 to 40.3 pg cm^{-2}. Additionally, cyclophosphamide and doxorubicin wipe samples (n = 50) were obtained from two kennel surfaces and 10 canine-patients after chemotherapy. Samples were collected from the patients' coats before leaving the clinic and day after in the home environment to investigate the potential for dogs to be a source of household contamination. Cyclophosphamide was identified in samples collected at home in 4/5 canine-patients at levels ranging from 2.61 to 368 ng/sample, while doxorubicin was identified on kennel surfaces wiped post-treatment at levels ranging from 3.53 to 1655 pg cm^{-2}. These findings support the ability of this method to detect contamination of these drugs in both occupational clinics and homes. The results set the stage for investigating contamination levels in various settings, such as human and veterinary clinics and home environments, as well as evaluating the effectiveness of decontamination products and protocols toward reducing workplace and environmental exposures.

Key words: capillary mass spectrometry, exposure assessment, healthcare surface contamination; pet-mediated home contamination

What's Important About This Paper?

Dogs treated with antineoplastic drugs in veterinary oncology clinics may result in residual contamination on surfaces and on their fur, leading to dermal exposure among veterinary staff and pet owners. This study employed a novel analytical method to demonstrate an approach for assessing such contamination, thereby improving dermal and surface exposure assessment in occupational and household settings where antineoplastic drugs are administered.

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Introduction

It is estimated that there were more than 1.9 million new human cancer cases in the United States in 2023, increasing over 25% in the last 15 years (Siegel et al. 2023). This corresponds with studies projecting a 40% increase in demand for chemotherapy by 2025 and the growing need for technicians and patient caregivers to administer treatment (Erikson et al. 2007; Yang et al. 2014; Knapp and Ignoffo 2020). These caregivers may come in contact with antineoplastic drugs, as they can persist on surfaces where they are administered, leading to potential exposure from skin contact and subsequent dermal uptake. Chronic, low-level exposure to cytotoxic antineoplastic drugs in occupational settings has been associated with cardiotoxic, genotoxic, reproductive, and other adverse health outcomes (Falck et al. 2003; Baker and Connor 1996; Valanis et al. 1999; Fransman et al. 2007; Ladeira et al. 2014; Focaccetti et al. 2015; NIOSH 2023). Overall, the increasing administration of antineoplastic drugs in oncology clinics may lead to the contamination and exposure of numerous patients, pharmacy, nursing, clerical staff, and family members, resulting in the possible development of adverse health effects. As the settings for this type of chemotherapy change toward home care, there is a growing need for monitoring strategies that can effectively detect contamination and prevent exposure in both clinical and remote (home) environments.

Similar trends of cancer incidence and chemotherapy increases in humans have been observed in companion animals, as cancer chemotherapy for dogs has become more common with new treatments using a variety of antineoplastic drugs as therapy (Fisher et al. 1993; Coiffier et al. 2002; Garrett et al. 2002). Cancer is the leading cause of death in dogs, with 25% to 30% of dogs developing the disease, and antineoplastic drugs, including cyclophosphamide and doxorubicin, are commonly used in veterinary oncology clinics in combination therapies such as CHOP (cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone) (Pang and Argyle 2009; Dobson 2013; Gardner et al. 2016). With the growing canine chemotherapy administration, more than 315,000 veterinarians, technicians, and assistants, students, cleaning and maintenance workers, and administrative staff in the United States may be exposed to these drugs in clinics (BLS, 2023). Similar to the human cancer care workforce, the companion animal cancer care workforce is predominantly female, with women entering the field making up 84% of the profession (Bain 2023). Furthermore, as the dogs continue to metabolize and excrete the antineoplastic drugs post-treatment, they could serve as a source for contamination at home. The magnitude and variability of in-home contamination from canine-patients have not yet been characterized. Following companion animal chemotherapy, veterinary healthcare workers and pet owners may be exposed to antineoplastic drug residues through dermal contact or environmental contamination, posing potential chronic health risks; therefore, monitoring and decontamination strategies are essential to safeguard the health of these populations.

Surface wipe sampling represents an important health and safety surveillance tool to understand the level of antineoplastic drug contamination in different settings. Despite evidence of widespread contamination in human hospitals, there are considerable differences in the magnitude and variability between human healthcare environments, with little data available to characterize veterinary clinic or patient home-based exposures. Previous studies have focused on identifying antineoplastic drug contamination in veterinary settings; however, there is a lack of research quantifying this surface contamination in comparison to human healthcare settings (Meijster et al. 2006; Kandel-Tschiederer et al. 2010; Couch et al. 2013; Janssens et al. 2015; Fung and Seneviratne 2016; Senyk 2021). The primary source for guidelines on the safe handling of antineoplastic drugs derives from the International Society of Oncology Pharmacy Practitioners (ISOPP) with several countries, including Canada, Germany, and Australia, adapting their methods to develop their safety standards with the former having enforceable regulations (NIOSH 2004; BAuA 2014; Connor et al. 2007; Mathias et al. 2019; Olsen et al. 2019). Currently, there are no widespread occupational exposure limits, regulatory standards with explicit surface sampling requirements, or standard methodologies for dermal sampling to assess worker or caregiver exposures within the United States (Ashley et al. 2011; Power et al. 2018; The United States Pharmacopeial Convention 2019; NIOSH 2023). Additional work has focused on guidance for recommended sampling programs and risk assessment for improved occupational safety, but there are no federally regulated limits for antineoplastic drug surface concentrations (Connor and McDiarmid 2006; Broadwater et al. 2022; American Industrial Hygiene Association (AIHA) 2023; Arnold et al. 2023).

The work we present takes advantage of implementing our newly developed and validated capillary liquid chromatography–selected reaction monitoring-mass spectrometry (LC-SRM-MS/MS) method, combining the simultaneous detection of six commonly used antineoplastic drugs: cyclophosphamide, doxorubicin, methotrexate, paclitaxel, etoposide, and 5-fluorouracil for maximum sensitivity. The research goal was to understand the potential dermal exposure of veterinary healthcare workers resulting from contact with contaminated surfaces in

clinical settings following canine-patient treatment, as well as pet owners from canine-patients, who potentially serve as secondary sources of exposure in home environments. To our knowledge, this is the first study sampling surfaces in veterinary oncology clinics in tandem with canine-patients in their homes to quantify antineoplastic drug contamination and sets the stage to improve home healthcare. This research provides an environmental monitoring solution for antineoplastic drug contamination and offers data to support the development of future decontamination strategies and occupational safety guidelines.

Methods

Chromatographic conditions

Chromatographic separation was performed using a Dionex UltiMate 3000 RSLCnano UPLC system coupled to a nanospray ion source. A 1 µL aliquot was injected onto a capillary Zorbax SB C18 column (0.5 × 100 mm, 1.8 µm particle size). The column was heated to 35 °C, and the flow was set to 10 µL/min. The mobile phases consisted of H_2O with 1 mM NH_4HCO_2 and 0.1% HCOOH (A) and CH_3OH (B) used in a linear multi-step gradient starting at 5% B for 4 min, increasing to 30% B over 1.5 min, increasing to 80% B over 1.5 min, increasing to 95% B over 10 min, and remaining constant at 95% B for 2 min before decreasing to starting conditions. The total run time was 26 min.

Mass spectrometry conditions

A TSQ Vantage triple quadrupole mass spectrometer (Thermo Scientific, Waltham, MA) was used for the identification of antineoplastic drugs. Selected reaction monitoring (SRM) was performed with multiple segmented scan events for the transition between negative electrospray ionization (ESI-) and positive electrospray ionization (ESI+) modes in a single MS run. MS parameters for each drug and respective internal standard were individually optimized using direct infusion as well as the identification of fragment ions for both qualitative and quantitative analyses (Supplementary Table 1). Data were analyzed using Thermo Scientific Xcalibur Software (Thermo Scientific, Waltham, MA).

Analytical process

The antineoplastic drugs and internal standards were analyzed at decreasing concentrations to assess the analytical limit of detection (LOD) and limit of quantitation (LOQ). The LOD was set at the lowest concentration each compound could be detected with at least a 3:1 signal-to-noise (SN) ratio evaluated on peak height. The LOQ was set at the lowest concentration each compound could be detected with at least a 10:1 SN ratio evaluated on peak height (FDA 2021). To evaluate and quantify the LOD and LOQ, a calibration curve was prepared using a mixture of increasing antineoplastic drug concentrations, ranging from 0.05 to 100 ng/mL, and a constant amount of their isotopically labeled standard at a concentration of 10 ng/mL (Supplementary Table 1). Daunorubicin, an analog of doxorubicin, was used as its internal standard (Choi et al. 2020). The method detection limit was calculated from the LOD, considering the drug desorption recovery in the wiping sample processing for each sample and surface (Jeronimo et al. 2015; Colombo et al. 2017).

Sample processing

Desorption method development

To test the desorption for all 12 compounds, a stock solution was created containing the six antineoplastic drugs and the six internal standards at a concentration of 5 µg/mL in the desorption solution (H_2O/CH_3OH 50:50 and 0.1% HCOOH). This solution was spiked onto Whatman filter paper (No. 42 ashless, 70 mm) (Millipore Sigma, Burlington, MA). The sample was sonicated for 35 min in a 20 mL glass scintillation vial in 5 mL of the desorption solution. Then, the solution was transferred to a 4-mL glass vial and centrifuged at 1400 revolutions per minute (RPM) for 30 min, adapting previously published methods (Jeronimo et al. 2015; Colombo et al. 2017). A 1-mL aliquot of the solution was placed in an autosampler vial for LC-SRM-MS/MS analysis.

Wiping method development

Stainless-steel plates (100 cm^2, 14ga, 304 #4 brushed stainless steel) were rinsed with CH_3OH and washed with Alconox detergent, then with Optima™ LC/MS Gradewater (H_2O). Plates were spiked with 50 µL of 5 µg/mL of the six antineoplastic drugs or H_2O to simulate clinical surfaces and assess drug wiping recovery. The solution was allowed to dry for 15 min before wiping with Whatman filter paper. The filter paper was wet with 500 µL of the wiping solution (H_2O/CH_3OH 20:80 and 0.1% HCOOH). The entire plate surface was wiped initially with a downwards motion (vertical), then folding the filter paper to wipe with a side-to-side motion (horizontal). The wipe was placed into a 20-mL glass scintillation vial and spiked with 50 µL of the 5 µg/mL internal standard antineoplastic drug solution. Samples underwent the desorption protocol before LC-SRM-MS/MS analysis.

Clinical wipe method application

All surface wipe sampling was conducted at the University of Minnesota Veterinary Medical Center (UMN VMC) from June 2021 to August 2021 under

the guidance of a board-certified veterinary medical oncologist and with assistance from the Clinical Investigation Center (CIC). Surfaces were selected for sampling after discussion with veterinary staff, identifying locations as frequent contact areas (handles, tables, containers) as well as additional surfaces that may potentially have drug contamination (Supplementary Fig. 1) (Arnold and Kaup 2019). Measurements were taken for surfaces with areas less than 100 cm^2 to calculate the approximate surface area. Samples were collected after canine-patients received cyclophosphamide (Cytoxan®, oral administration) or doxorubicin (Adriamycin®, intravenous administration) treatment. A custom sample wiping collection kit was used for the clinical surface wiping, including the following materials: 100 cm^2 wiping template, Whatman filter paper, glass storage vials, gloves, ruler, and tweezers (Supplementary Fig. 2). The samples were returned to the University of Minnesota Masonic Cancer Center same day and stored at -20°C for analysis at the Analytical Biochemistry Shared Resource facility.

Canine-patient wipe method application

Canine-patient wiping was conducted at the UMN VMC and the patient's home environment using an innovative method to detect and quantify antineoplastic drug contamination. The recruitment period lasted 10 months, from October 2022 to July 2023, in a non-randomized, prospective study. Canine-patients' eligibility criteria included (i) receiving clinician-recommended cyclophosphamide or doxorubicin treatment at the UMN VMC and (ii) providing consent for collecting patient wipe samples at approximately 5 and 24 h post-treatment. The canine-patient was wiped in three areas where the contamination from body fluids (saliva and urine) containing the antineoplastic drugs were more likely to be found: the mouth, on the side of the body/back, and the inner thigh (Supplementary Fig. 3). The same lab member conducted the wipe sample collection of all ten canine-patients in the clinic approximately 5-h post-treatment. Additional surface sampling of kennel areas and field blanks were collected at the 5-h time point (Supplementary Fig. 4). As a potential source of secondary exposure outside of clinics, canine-patients were wiped by their owners at their homes approximately 24-h post-treatment. Pet owners were provided a sample collection take-home kit with written instructions explained in-person by a lab member as well as a video tutorial demonstrating the proper wiping protocol as described above (Supplementary Video 1). These samples were returned the same day at-home canine-patient wiping was completed to the University of Minnesota Masonic Cancer Center and stored at –20 °C until analysis at the Analytical Biochemistry Shared Resource facility.

IACUC information

All canine-patient wipe samples were conducted by the protocol approved by the Institutional Animal Care and Use Committee at the University of Minnesota Twin Cities, Protocol ID: 2303-40917A. Pet owners recruited in this study provided informed consent for the participation and were given a $20 UMN ClinCard after study completion.

Data analysis

The peak area, peak height, and the SN ratio for each antineoplastic drug and internal standard were integrated for the calibration curve, drug desorption recoveries, and the LOD and LOQ using Thermo Xcalibur 4.5 Software (Thermo Scientific, Waltham, MA). To confidently identify surface contamination for a specific drug, the chromatographic data from a sample must show an identifiable peak (with five sticks or greater) for the targeted quantitative and qualitative ions.

Results

Surface wipe and desorption method

The average antineoplastic drug desorption recoveries during the wiping method development are reported in Table 1. Triplicate samples for the stainless-steel plates treated with the antineoplastic drug mixture or H_2O were analyzed to calculate the wiping method recovery, comparing the peak areas for each drug. Cyclophosphamide, etoposide, and paclitaxel had average recoveries close to 80%. Doxorubicin, methotrexate, and 5-fluorouracil had recoveries close to 50%. The relative standard deviation percent (RSD %) for cyclophosphamide, methotrexate,

Table 1. Quantitation and precision of antineoplastic drug desorption recovery from wiping method.

Drugs	Desorption recovery %	Standard deviation	RSD %
Cyclophosphamide	75	0.03	4.6
Doxorubicin	55	0.03	6.2
Methotrexate	51	0.03	4.9
Etoposide	79	0.02	3.1
Paclitaxel	77	0.04	4.9
5-Fluorouracil	49	0.13	26

etoposide, and paclitaxel was below 5%. Doxorubicin and 5-fluorouracil had RSDs of 6.2% and 26%, respectively.

The average antineoplastic drug desorption recoveries from wiping rat fur for the applicability of detecting surface contamination canine-patients are reported in Table 2. Triplicate fresh rat carcasses were spiked with the antineoplastic drug mixture or H_2O, and wipe samples were collected as outlined in the desorption and wiping method development. Cyclophosphamide, doxorubicin, methotrexate, etoposide, and paclitaxel had average recoveries close to 40%. 5-fluorouracil was not able to be detected on the rat fur.

The average analytical LOD and LOQ for each compound were calculated from triplicate (three individually collected samples) standard injections. The analytical LOD ranged from 0.01 to 0.12 ng/mL, and the LOQ ranged from 0.01 to 0.39 ng/mL (Supplementary Table 2). The method detection limits are shown for the total sample and the surface area, ranging from 0.03 to 1.33 ng/sample and 0.3 to 13 pg cm^{-2}, respectively, to account for different types of sample collection, summarized in Table 3.

Clinical surface wiping sampling

The surface wiping and desorption methods described above were used to collect clinical surface wiping samples from the UMN VMC oncology clinic. Triplicate surface wipe samples were collected using a 100 cm^2 template after canine-patients received cyclophosphamide or doxorubicin treatment reported in Table 4. Contamination from cyclophosphamide and doxorubicin was detected on several surfaces, and the two drugs showed different areas of contamination. The average levels of cyclophosphamide ranged from 6.68 to 17.4 pg cm^{-2} and the average levels of doxorubicin ranged from 13.5 to 40.3 pg cm^{-2} on the clinical surfaces where the drugs were positively identified. A detailed layout of the oncology clinic room is shown in Supplementary Fig. 1.

Table 2. Rat wiping recoveries

Drugs	Desorption recovery %	Standard deviation	RSD %
Cyclophosphamide	43	0.11	26
Doxorubicin	40	0.05	13
Methotrexate	37	0.05	14
Etoposide	40	0.12	26
Paclitaxel	42	0.07	15
5-Fluorouracil	ND	-	-

Table 3. Method detection limits, LOQ of the antineoplastic drugs.

Drugs	Quantitative ion m/z	LOQ_{sample} (ng/sample)	$LOQ_{surface}$ (pg cm^{-2})
Cyclophosphamide	140	0.05	0.5
Doxorubicin	361	0.06	0.6
Methotrexate	308	0.03	0.3
Etoposide	229	0.07	0.7
Paclitaxel	286	0.55	5.5
5-Fluorouracil	86	1.33	13

Canine-patients and kennel wiping sampling post-treatment

A total of ten canine-patients were recruited for this study; five received cyclophosphamide (Cytoxan®, oral pill administration), and five received doxorubicin (Adriamycin®, intravenous administration) treatment. Demographic information of the canine-patients, including breed, size, and chemotherapy, was collected and summarized in Table 5. This cohort of canine-patients was classified into three sizes: small, medium, and large, with weights ranging from 2.85 to 34.6 kg. The mean number of treatments was 4.

Cyclophosphamide and doxorubicin were detected in samples from the UMN VMC clinic, in the kennels, or on patient coats. The levels of cyclophosphamide and doxorubicin measured on canine-patients and clinical surfaces are shown in Table 6. Cyclophosphamide was detected at both time points on the coat of 4 out of 5 participants; however, levels were below the LOQ at the 24-h sample. Samples collected from the kennel mat and kennel floor were negative for the presence of the drug in 4 out of 5 canine-patients examined. One canine-patient, Dog 4, showed the presence of cyclophosphamide on both the kennel matt and floor as well as the 5 and 24-h canine-patient coat samples. Doxorubicin was identified on surface wipe samples from two specific canine kenneling areas 5 h post-treatment administration, the kennel floor and kennel mat, with increased amounts seen on the kennel mat compared to the kennel floor (Supplementary Fig. 7). Doxorubicin was not detected on canine-patient wiping samples.

Discussion

Analytical sensitivity and quantitation for the surface wipe sampling and the desorption method

The antineoplastic drug desorption recoveries calculated during the wiping method development were

Table 4. Veterinary oncology clinic surface contamination results, pg cm^{-2}.

Clinical locations (n = 3)	Cyclophosphamide	RSD %	Doxorubicin	RSD %
Door handle	17.4	27	40.3	17
Treatment table	6.68	64	20.5	14
Treatment preparation table	< 0.5	-	13.5	22
Blanket	< 0.5	-	15.4	13
Pharmacy bag	< 0.5	-	19.1	21
Syringe	< 0.5	-	35.8	16
Oral drug preparation table	14.2	44	< 0.6	-
Hazardous waste bin lid	9.97	24	18.0	10

n = 3 for number of sample collections for each clinical location.

Table 5. Canine-patient demographics.

Dogs	Breed	Weight (kg)	Size*	Chemotherapy	Dose (m^2)	Treatment (number)
1	Miniature poodle	9.34	Small	Cyclophosphamide	0.425	3
2	Australian Shepard	25	Medium	Cyclophosphamide	0.833	7
3	Basset hound	31.8	Medium/large	Doxorubicin	1.018	7
4	Norwegian elkhound	22.3	Medium	Cyclophosphamide	0.786	2
5	Golden retriever	34.6	Large	Cyclophosphamide	1.072	2
6	Yorkshire terrier	2.85	Small	Doxorubicin	0.214	2
7	Corgi	11.1	Small/medium	Doxorubicin	0.492	3
8	Mixed breed	31.3	Large	Doxorubicin	1.003	2
9	Pug	12	Small	Doxorubicin	0.547	5
10	Mixed breed	27.5	Medium/large	Doxorubicin	0.920	3

Determined by the veterinary oncology clinic staff. Small: 1 to 10 kg, Medium: 11 to 26 kg, Large: 27 to 45 kg.

similar to what has been reported in previous literature (Jeronimo et al. 2015; Colombo et al. 2017; Kåredal et al. 2022). Five of the six antineoplastic drugs had ≥ 50% desorption recovery, with 5-fluorouracil as the exception at 49%. OSHA evaluation guidelines for surface sampling methods advocate for the average extraction efficiency of >90% but will consider ≥ 50% removal efficiency adequate (OSHA 2001). Additionally, the coefficient of variation (RSD %) for the majority of the drugs was below 5% emphasizing the precision and reproducibility of the wiping method. Doxorubicin and 5-fluorouracil have higher RSD% at lower concentrations, with 6.2% and 26.4%, respectively. The lower recovery and higher variability observed with 5-fluorouracil may be due to the polarity of the compound, a fluorinated pyrimidine, the instability of the solvent leading to an early retention time at 3.7 min, and a higher background signal influence resulting in greater variation for the quantitation. Steps were taken to increase the sensitivity for this compound, switching to negative electrospray ionization (ESI-) mode and including different MS scan events while maintaining a relatively short MS run time and not compromising the sensitivity of the other antineoplastic drugs. Overall, these results provide evidence that this LC-SRM-MS/MS method has recoveries meeting the OSHA guidelines for surface sampling, ensuring reliable and reproducible data, making it suitable for surface contamination monitoring in real-world settings.

Our LC-SRM-MS/MS method has a LOD range from 0.01 to 0.12 ng/mL and a LOQ range of 0.01 to 0.39 ng/mL (Supplementary Table 2). The LOD and LOQ values were similar or lower than what has been reported in previous literature (Tuerk et al. 2011; Nussbaumer et al. 2012; Jeronimo et al. 2015; Colombo et al. 2017; Walton et al. 2020). The LOQ_{sample} ranged from 0.03 to 1.33 ng/sample, and the $LOQ_{surface}$ ranged from 0.3 to 13.3 pg cm^{-2}. The LOQ_{sample} and $LOQ_{surface}$

are lower than those of methods previously reported in the literature (Jeronimo et al. 2015; Hetzel et al. 2016; Colombo et al. 2017; Lema-Atán et al. 2022). As canine cancer chemotherapy is increasing, it is important to have analytical surface wipe sampling methods that take into account a wide variety of drugs that are commonly administered as combination therapies with one another, such as cyclophosphamide and doxorubicin in CHOP regimens, to better understand the levels of antineoplastic drug contamination that may lead to exposure of workers (Gardner et al. 2016). We developed one of the first methods using capillary LC-SRM-MS/MS by using a lower flow rate to increase sensitivity while maintaining relatively high throughput analysis due to sample volumes (Boychenko et al. 2017). These results demonstrate that our method has the sensitivity to identify antineoplastic drugs contamination from surface wipe samples and quantify the levels of specific drugs in pg cm^{-2}.

Clinical surface wiping application

The LC-SRM-MS/MS and wiping methods developed for this study were used to identify antineoplastic drug surface contamination on samples in a veterinary oncology clinic. We detected cyclophosphamide and doxorubicin on clinical surfaces in an oncology treatment room, shown in Table 4. Our method uses a quantitative and qualitative ion to ensure accurate confirmation of the antineoplastic drug, increasing the confidence detection without false positives (Supplementary Figs 5–7). Cyclophosphamide was found on over 50% of the surfaces tested (4/7), including the door handle, treatment table, oral drug preparation table, and hazardous waste bin lid. The levels ranged between 6.68 to 17.4 pg cm^{-2} and were above our $LOQ_{surface}$. Doxorubicin was found on 100% of the surfaces tested (7/7). The levels ranged from 13.5 to 40.3 pg cm^{-2} and were above our $LOQ_{surface}$. The door handle was the surface with the highest levels of cyclophosphamide and doxorubicin contamination. This is one of the most frequent contact areas within the drug administration room by gloved and ungloved staff. This increased contamination for both chemotherapies may be due to multiple chemotherapy administrations during the workday before cleaning or a breakdown in personal protection equipment (PPE) practices between contact from different drug vehicles (containers, bags, syringes, etc.) throughout clinical surfaces. Following the door handle, the oral drug preparation table (cyclophosphamide) and the syringe (doxorubicin), administration-specific locations, had the second highest levels of antineoplastic drugs. Doxorubicin was found at higher concentrations across all clinical surfaces tested. This may be due to its intravenous administration method, which has an increased amount of time the drug is given to canine-patients (ranging from 20 to 35 min), the increased workforce interaction between veterinary personnel with canine patients and contact with contaminated surfaces, or the greater number of surfaces on which the drug comes into contact. Cyclophosphamide was not seen on as many surfaces in the oncology clinic, which may be due to the shorter administration time, oral (pill) administration, as well as the treatment traveling to fewer areas around the clinic, limiting the transmission of drug residues from primary contact with the pill or secondary contact from the technician's gloves or drug storage container. These results show that the drugs are detected on different surfaces consistent with their application protocols (oral vs. intravenous), and the drug pathway before treatment may play a role in the contamination levels, indicating that different chemotherapy administrations may lead to different contamination patterns.

To address the possibility of cross-contamination, our LC-SRM-MS/MS method simultaneously screens for six antineoplastic drugs, allowing for the identification of multiple drugs on each surface for sample. No cross-contamination was observed; cyclophosphamide contamination was only seen on surface wipe samples from dogs treated with cyclophosphamide, while the doxorubicin contamination was only seen on surface wipe samples from dogs treated with doxorubicin (Supplementary Fig. 5). Additionally, cyclophosphamide and doxorubicin have different stabilities in various solutions, which may impact the variation in contamination levels seen in the study (Negreira et al. 2013; Wood et al. 2008; Kennedy et al. 2010; Chan et al. 2016). To address the differences in drug variability, all samples were spiked with the respective internal standards and immediately stored at −20 °C following sample collection until mass spectrometry analysis.

Canine-patient wipe method application

We identified antineoplastic drug contamination on kennel surfaces and canine-patients' coats, indicating the potential for dermal exposure in secondary environments. This contamination may result from the direct chemotherapy administration for the canine-patient with further spread from contact to additional kenneling surfaces, or potential residual contamination from previous canine-patients before surface decontamination has occurred. We detected cyclophosphamide and doxorubicin at the UMN VMC on kennel surfaces and from canine-patients in home environments. The dose of both the oral and intravenous administered drugs was proportional to the dogs' bodyweights seen in Table 5. There was no correlation between the administered dose (m^2) and levels of antineoplastic drug contamination detected on the

Table 6. Levels of cyclophosphamide and doxorubicin detected on clinical surfaces and canine-patients.

Cyclophosphamide canine-patients (n=5)						
Wiping Locations	**Dog 1**	**Dog 2**	**Dog 3**	**Dog 4**	**Dog 5**	**RSD%**
Dog 5 h (ng/sample)	8.64	4.19	2.61	368	< 50	189
Dog 24 h (ng/sample)	< 50	< 50	< 50	20.2	< 50	-
Kennel mat (pg cm^{-2})	< 0.5	< 0.5	< 0.5	1750	< 0.5	-
Kennel floor (pg cm^{-2})	< 0.5	< 0.5	< 0.5	1310	< 0.5	-
Doxorubicin canine-patients (n=5)						
Wiping Locations	**Dog 6**	**Dog 7**	**Dog 8**	**Dog 9**	**Dog 10**	**RSD%**
Dog 5 h (ng/sample)	< 60	< 60	< 60	< 60	< 60	-
Dog 24 h (ng/sample)	< 60	< 60	< 60	< 60	< 60	-
Kennel mat (pg cm^{-2})	< 0.6	1655	< 0.6	18.1	< 0.6	138
Kennel floor (pg cm^{-2})	< 0.6	17.3	< 0.6	3.53	< 0.6	95

clinical surfaces or dogs, possibly due to the limited sample size. The results have important implications for home environments, especially because of the growing trend of home-infusion of chemotherapy where these drugs are administered in the home by family caregivers or homecare professionals (Loriaux, Desmond, and Li 2022; Roug et al. 2023). Cyclophosphamide was detected on the majority of the canine-patients (4/5) during the wipe sampling at the clinic, with levels ranging from 2.61 to 368 ng/sample. While cyclophosphamide was seen at levels above the LOQ_{sample} in four of the five canine-patients at the 5-h time point, three of the four samples collected 24 h later in their home environments were below the method LOQ. This may be due to various factors, including the decrease in drug levels or variation in the wipe sampling done by the owners. Additionally, the canine-patient coat is an uneven surface that was not used in the wiping method development, which limits the amount of drug levels detected. Previous research using different materials (stainless steel, glass, plastic, fabric, wood) and our recovery testing on the rats showed variation and decreased drug recovery (Ashely et al. 2011). In this study, we were unable to evaluate the antineoplastic drug recovery efficiency from the canine-patient coats, instead using rat fur as a surrogate for dog fur/matrix. This lack of recovery data introduces uncertainty, limiting these values to a semi-quantitative analysis, but these results still show the presence of antineoplastic drugs on dogs as a source of this contamination up to and beyond 24 h post-treatment. One sample was quantified at the 24-h time point at 20.2 ng/sample. Wipe samples from this dog showed cyclophosphamide that were 61 times the average of the other dogs wiped in-clinic as well as the levels seen on the kennel mat and kennel floor, 1.75 and 1.31 ng cm^{-2}, respectively.

Doxorubicin was detected on two specific canine kenneling areas after treatment administration: the kennel mat and kennel floor. The presence of the drug was detected at levels above the $LOQ_{surface}$ at the 5-h post-treatment time point with doxorubicin levels of 3.53 to 18.1 pg/cm^2 on the kennel floor and 17.3 to 1,655 pg/cm^2 for the kennel mat. Doxorubicin was not detected on any of the canine-patient wiping samples. In comparison with other environmental assessments of antineoplastic drugs surface contamination, our method was able to detect chemotherapy drugs at levels lower than what has been seen in human oncology clinics in the non-pharmacy staff areas, oncology pharmacy areas, and patient areas (Connor et al. 1999; Graeve et al. 2017; Astrakianakis et al. 2020; Jeronimo et al. 2021). Additionally, these results align and help verify previous work that has identified antineoplastic drug contamination on surfaces in veterinary oncology clinics (Meijster et al. 2006; Couch et al. 2013; Senyk 2021). While antineoplastic drugs have been seen in these settings, studies have shown heavily censored datasets. Current methods and

techniques (HPLC-UV, HPLC-MS/MS, LC-MS) typically target common antineoplastic drugs, including cyclophosphamide or doxorubicin; yet, they may have several limitations, such as limited analytical sensitivity, low throughput, or large sample volumes. For example, Meijster et al. identified antineoplastic drug contamination on 63% of the veterinarians' gloves and surfaces, including the door handle and administration table, ranging from 2.7 to 104 ng and 1 to 13 ng while only screening for one antineoplastic drug. Other studies have focused on screening for multiple drugs, but the varying methods resulted in sample results falling below their detection limits. Couch et al. (2013) reported that 90% of the surface samples were below the LOD (5 ng/sample for cyclophosphamide and 2 ng/sample for ifosfamide) while Fung and Seneviratne sampled surfaces in veterinary hospitals and clinics reporting cyclophosphamide contamination on 30% of the locations, emphasizing the importance of the increased sensitivity of this method in the identification of sources for chronic, low levels of antineoplastic drug exposure, especially in the case of cytotoxic drugs. Cyclophosphamide and doxorubicin have been detected in canine urine at 24 h post-treatment, but little data is available about the potential dermal exposure to these drugs by dog-owners who may come into contact within their homes (Hamscher et al. 2010). This is the first study that identifies levels of antineoplastic drug contamination in veterinary oncology clinics in tandem with canine-patient coat wipe samples outside of the clinical environment.

These results represent the potential dermal exposure of veterinary healthcare workers and pet owners to antineoplastic drugs. Our work had an immediate impact through sharing the results with collaborators at the UMN VMC, prompting discussion about additional sampling, development of new strategies to reduce antineoplastic drug contamination, and provided better information to pet owners. While wipe sampling can be used as a surrogate marker for hazardous drug exposure, the dermal uptake pathway is complex, and many factors may limit accurate field measurements into direct, translatable results. This study used a sensitive MS method to detect cyclophosphamide and doxorubicin on clinical surfaces and canine-patients at pg and ng levels in a veterinary oncology clinics and pet-owners' homes, providing evidence of antineoplastic drug contamination from separate wiping sample collections over a 2-yr period. Currently, there are no standardized, widespread PPE or cleaning protocols in veterinary oncology clinics. Several organizations offer recommendations, including the American and European College of Veterinary Internal Medicine, but the training and safe handling of antineoplastic drugs is clinic dependent with different levels of PPE (gloves, lab coats, and cleaning protocols) varying between locations and staff (ECVIM 2007; Smith et al. 2018). Information about potential hazardous exposures should be more widely communicated to increase workplace safety and awareness among pet owners. Unlike healthcare workers, pet owners typically lack training on handling antineoplastic drugs; instead, oftentimes rely on conversations with staff or receive informational materials without detailed explanations. As secondary exposures may occur through dermal contact with treatment administered at home, bodily fluids, or residue on the companion animal's coat, it is important that owners are informed of their risk and use gloves and other protective measures and limit contact with their pets following treatment. The chronic, low-level exposure provides grounds to implement decontamination methods and stresses the importance of surveillance in workplace and patient settings to improve the safety of anyone handling these drugs.

Conclusion

We developed an LC-SRM-MS/MS method for the identification and quantification of six commonly used antineoplastic drugs from surface wiping samples. Through the validation of this method, we generated LODs and LOQs for the antineoplastic drugs at levels that were comparable to those published previously in the literature as well as a wiping and desorption method that met the surface wipe sampling guidance criteria set by OSHA.

Our method was used to identify chemotherapy surface contamination in a veterinary oncology clinic in combination with evaluating the potential secondary contamination resulting from canine-patients returning to their households as surrogate markers for home environment exposure. Two antineoplastic drugs, doxorubicin and cyclophosphamide, were quantified on clinical surfaces, and cyclophosphamide was detected on canine-patients' coats outside of the clinic. Based on these results, we conclude that this method can be used for the investigation of trace-level surface contamination from antineoplastic drugs and for the exposure identification of veterinary healthcare workers administering a variety of chemotherapies alongside of owners home exposure with canine-patients in treatment.

This work sets the stage for the implementation of surface sampling in all areas with potential chemotherapy contamination. This method is not only suitable for surface contamination monitoring in veterinary oncology clinics but also for secondary

contamination risk assessment in home environments, providing comprehensive exposure risk evaluations for veterinary healthcare workers and pet owners. We developed an approach to evaluate the potential for antineoplastic drug dermal exposure that stresses the importance of monitoring strategies in part due to the increasing veterinary oncology demand, companion animals serving as sources of contamination in homes, and the increasing use of home-infusion for human cancer treatment. Future work can build upon these results to evaluate the efficacy of decontamination protocols, improving the safety of veterinary workers and caregivers administering these drugs.

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Conflict of interest

Authors have no conflict of interest to declare.

Data availability

The authors confirm that all data supporting the study findings are included in the paper and supplementary materials. Raw data are available from the authors (AF) request.

Supplementary material

Supplementary material is available at *Annals of Work Exposures and Health* online.

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