In-Depth Survey Report

Engineering Control Evaluation at Veterinary Hospital C

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Division of Applied Research and Technology
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EPHB Report No. DART 18-74
Animal Specialty & Emergency Center

Revised June 2021

Site Surveyed: Veterinary Hospital C

NAICS Code: 541940 Animal hospitals

Survey Dates: July 2017

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Abstract

NIOSH researchers conducted a field survey at Veterinary Hospital C in July 2017. The purpose of the site visit was to identify and evaluate hazardous drug engineering controls as well as to sample for potential surface contamination at the hospital. NIOSH researchers also observed and interacted with the hospital's veterinarians and staff to obtain information about the hazardous drug work practices, daily activities, and oncology treatment processes.

A TSI® VelociCalc™ Plus Model 9565-P thermal anemometer was used to measure air velocities at the face of the biological safety cabinet (BSC), while a Wizard Stick handheld smoke generator was used to visualize air movement inside and around the periphery of the hood. Both the qualitative and quantitative tests showed that the BSC was operating appropriately. The BSC's average face velocity measured (0.51 m/s [131 fpm]) which was above the minimum recommended face velocity of 0.51 m/s (100 fpm) for a Class II Type A2 BSC. A TSI Accubalance® Plus Air Capture Hood Model 8373 was used to measure the supply (0.42 m^3/s or 884 cfm) and exhaust (0.09 m^3/s or 201 cfm) ventilation in the oncology department. The air changes per hour (ACH) of the oncology department was calculated to be 7, which is less than the required ACH (minimum 12 ACH) for an unclassified containment segregated compounding area.

The presence of potential surface contamination was evaluated with wipe samples. These were collected in areas where the staff handled chemotherapy drugs within the oncology department. Wipe samples were also collected in less obvious places (i.e., telephone, door handles, floor of nearby restroom) to determine if current workplace safety practices at the hospital were adequate to prevent inadvertent contamination of these surfaces. Sampling and analytical procedures varied by the hazardous drug for which they would be evaluated (i.e., the analyte). In some cases, a single sample could be evaluated for more than one analyte simultaneously. Carboplatin, cyclophosphamide, lomustine, vincristine, mitoxantrone, and doxorubicin were the only hazardous drugs actually in use during the NIOSH visit. Sample analyses results revealed that 16 of 18 wipe samples submitted were non-detectable (ND) for toceranib, lomustine, and chlorambucil. Fifteen of 15 wipe samples, including a mop strand, submitted for N-methyldiethanolamine (MDEA) were positive (6.4 to 145 ng). Five of 5 wipe samples submitted for toceranib, chlorambucil, and lomustine were positive for only toceranib (0.042 to 0.14 ng). MDEA was monitored as a potential stable marker for the highly unstable antineoplastic drug mustargen as explained in the text.

Four out of 9 samples submitted for carboplatin were positive (5.3 to 230,000 ng/sample). Twelve out of 36 samples submitted were positive for vincristine (10,000 ng/sample), methotrexate[1] (5.3 to 480 ng/sample), cyclophosphamide (5.8 to 1,400 ng/sample), and doxorubicin (19,000 ng/sample) while

[1] Two field blanks were positive for methotrexate, 11 and 160 ng/sample. Therefore, the positive methotrexate samples originated from its prior therapeutic use within the oncology department or from an error at the analytical laboratory.

simultaneously being ND for epirubicin. The ND determination means that contamination was either not present, or was present at levels below the detectable limit of the analytical method. In some cases, NIOSH researchers collected wipe samples on certain surfaces that were highly anticipated to contain drug contamination (e.g. suspected drug droplet at end of a CSTD connection). This strategy was done to verify the analytical methods' ability to detect drug contamination under the sampling, handling, shipping variables specific to this evaluation. These "known" contaminated samples were for carboplatin (230,000 ng/sample), vincristine (10,000 ng/sample), and doxorubicin (19,000 ng/sample).

Although many of the wipe sample analytical results were ND, there is no safe level of exposure when handling hazardous drugs. The presence of the carboplatin, cyclophosphamide, toceranib, and MDEA contamination is a reminder that the patients themselves can be a source of exposure, even when the drugs are not being directly handled. The cyclophosphamide and methotrexate[2] presence (on surfaces) serves as two reminders: (1) that hazardous drug contamination can sometimes linger despite cleaning efforts and (2) the detected contamination on desk and cabinet surfaces one might ordinarily think of as "safe," emphasizes the importance of proper work practices regarding the use of gloves and shoe covers, hand washing, and food/drink prohibitions within the hazardous drug handling environments. The detected contamination on the outside of the chemo transport bag serves as a reminder of the meticulous work practices required to avoid cross-contamination of surfaces expected to be "clean" as well as a reminder to treat all surfaces as potentially contaminated within the oncology treatment areas. Therefore, it is important to continue to use engineering controls (e.g., biological safety cabinets), supplementary controls (e.g., closed system drug-transfer devices), protective work practices (e.g., surface cleaning after every oncology patient, regardless of whether I.V. chemotherapy was administered), and personal protective equipment (e.g., gloves and gowns rated for chemotherapy protection, respirators, shoe covers, eye protection) to reduce unintentional exposures to the staff or pet owners. Additionally, the detection of drug contamination on the floor mop is a reminder that cleaning tools and supplies used in these areas should be dedicated for that purposes alone, and should not be used for cleaning of adjacent areas not expected to be exposed to hazardous drugs.

[2] Two field blanks were positive for methotrexate, 11 and 160 ng/sample. Therefore, the positive methotrexate samples originated from its prior therapeutic use within the oncology department or from an error at the analytical laboratory.

Introduction

Background for Control Technology Studies

The National Institute for Occupational Safety and Health (NIOSH) is the primary Federal agency engaged in occupational safety and health research. Located in the Department of Health and Human Services, it was established by the Occupational Safety and Health Act of 1970. This legislation mandated NIOSH to conduct a number of research and education programs separate from the standard setting and enforcement functions carried out by the Occupational Safety and Health Administration (OSHA) in the Department of Labor. An important area of NIOSH research deals with methods for controlling occupational exposure to potential chemical and physical hazards. The Engineering and Physical Hazards Branch (EPHB) of the Division of Field Studies and Engineering has been given the lead within NIOSH to study the engineering aspects of health hazard prevention and control.

Since 1976, EPHB has conducted a number of assessments of health hazard control technology on the basis of industry, common industrial process, or specific control techniques. Examples of these completed studies include the foundry industry; various chemical manufacturing or processing operations; spray painting; and the recirculation of exhaust air. The objective of each of these studies has been to document and evaluate effective control techniques for potential health hazards in the industry or process of interest, and to create a more general awareness of the need for or availability of an effective system of hazard control measures.

These studies involve a number of steps or phases. Initially, a series of walk-through surveys is conducted to select plants or processes with effective and potentially transferable control concept techniques. Next, in-depth surveys are conducted to determine both the control parameters and the effectiveness of these controls. The reports from these in-depth surveys are then used as a basis for preparing technical reports and journal articles on effective hazard control measures. Ultimately, the information from these research activities builds the data base of publicly available information on hazard control techniques for use by health professionals who are responsible for preventing occupational illness and injury.

Background for this Study

The 2004 *NIOSH Alert: Preventing Occupational Exposure to Antineoplastic and Other Hazardous Drugs in Health Care Settings* introduced a standard of universal precautions for handling hazardous drugs safely [NIOSH 2004]. The health effects due to occupational exposure to these drugs are extensive and can include chromosomal and other types of genetic damage, reproductive damage [NIOSH 2004], and exposure can cause adverse pregnancy outcomes [Albin 2010]. The NIOSH Alert states that its guidance applies to any worker who handles hazardous

drugs, including veterinary medicine and animal care (VM/AC) workers [NIOSH 2004]. Cancer is a leading cause of death among cats and dogs and attributes to 50 percent of pet deaths each year [Crump 2013]. In addition, chemotherapy is widely used to treat animals with cancer and other ailments as owners wish to prolong the lives of their beloved pets [Fielding and Lacroix 2009]. As chemotherapy drug (most are identified as hazardous drugs) use increases and lower-cost generic drugs become available, many veterinarians are administering chemotherapy drugs on their own or through a veterinary oncologist [MacDonald 2009].

In the U.S., there are an estimated 500,000 VM/AC workers, not including young adults who work part-time or during school breaks [Mobo et. al 2010]. This project specifically benefits special population/priority population groups as 95% of veterinary technicians are women of reproductive age with a mean age of 38 [Technicians 2008]. Veterinary medicine is similar to human healthcare in that the professional objective is to provide medical, surgical, and preventive healthcare to a patient. Both veterinary medicine and human healthcare personnel are vulnerable to needlestick injuries, radiation exposure, and hazardous drugs [Hall et. al 2013]. However, VM/AC workers are more likely to have accidents and occupational diseases, as they are susceptible to animal bites, zoonoses, animal-related respiratory hazards, physical injury, and veterinary-related reproductive hazards [Epp and Waldner 2012; Hall et. al 2013]. Although both professions handle hazardous drugs, there are differences in how veterinary clinics obtain, prepare, and administer the drugs, house the dosed patient, and handle a dosed patient's excreta or vomitus [Seibert 2013]. A recent study showed that VM/AC workers were exposed to hazardous drug concentrations 15 times higher than human healthcare personnel, partly due to how chemotherapy is administered in animals versus humans [Klahn 2014]. Cost, time, inconvenience, and discomfort are just some of the reported barriers for VM/AC workers not using safety measures in their practices [Klahn 2014].

Also unlike human health care, veterinary medicine's job duties are not compartmentalized. It is common for administrative personnel to conduct day-to-day animal-care activities, especially in small clinics [Seibert 2013]. Administrative personnel may restrain animals for hazardous drug administration, clean cages, feed the animals, and assist the veterinarian. When they occur, tasks involving unsafe work practices not only affect the primary task worker, they put other VM/AC workers, such as veterinary assistants, kennel attendants, or animal care workers, at risk for occupational exposure to chemotherapy drugs. This work-task diversity emphasizes the need for a thorough evaluation (and cross-training) of safety practices in the handling of hazardous drugs (and the patients the drugs are administered to) in veterinary medicine. VM/AC workers need to be educated in: 1) the risk of the drugs they are handling; 2) how to handle the drugs safely through proper use of engineering controls and personal protective equipment (PPE); and 3) how to avoid exposure to hazardous drugs and their metabolites through carefully delineated safe work procedures.

Conversations with veterinary stakeholders revealed that the warnings and guidance in the NIOSH Alert are not effectively reaching VM/AC workers. Animal oncology clinics are staffed with general practitioners and clinic staff without awareness of chemotherapy safety [Klahn 2014]. In one reported case study, a veterinarian admitted pouring hazardous drugs down the sink at his clinic. He then developed thyroid cancer at the age of 35, reportedly as a result of handling hazardous drugs. It was further estimated that over 4,000 veterinary practices administer chemotherapy without any safety measures [Smith 2010]. While the NIOSH Alert has had a significant impact upon hazard awareness and exposure prevention within human healthcare, there are significant differences (real and perceived) between the practices of human and veterinary medicine. These differences have reportedly been a roadblock in the NIOSH Alert's positive impact upon veterinary medicine. Controlling exposures to occupational hazards is the fundamental method of protecting workers. Traditionally, a hierarchy of controls establishes preferences in determining how to implement feasible and effective controls. The most preferred control, the elimination or substitution away from the use of hazardous drugs, is not realistic for this industry. The use of PPE is considered to be the least effective exposure control on a consistent basis [Mobo et. al 2010]. Therefore, engineering controls and work practice guidelines are the first lines of defense for VM/AC worker protection against hazardous drug exposure.

Hospital Description

The veterinary hospital, which is the subject of the report, is referred to as Veterinary Hospital "C" in order to preserve its anonymity. The Veterinary Hospital C provides primary, specialty, and emergency care to small animal patients. The oncology department has four staff members, which include veterinarians and technicians. The oncology department staff typically administers chemotherapy to patients five days a week. The oncology department shares a large room with the radiation oncology. The room consists of a large desk area, kennels for large dogs (Figure 1), a kennel area for cats and small dogs (Figure 2), and two examination tables. Chemotherapy drugs are prepared in a biological safety cabinet (BSC), a Class II Type A2 Model BBF-3SSRX (Germfree Laboratories Incorporated, Ormond Beach, FL, last certification on June 22, 2017) (Figure 3).

Chemotherapy Preparation and Administration

Closed System Drug-Transfer Devices (CSTDs)

Veterinary Hospital C uses the PhaSeal closed system drug-transfer device (CSTD) system (Becton, Dickinson and Company, Franklin Lakes, NJ) to prepare and administer liquid I.V. forms of chemotherapy (Figure 4). By definition, a CSTD mechanically prohibits the transfer of environmental contaminants into the system and the escape of hazardous drug or vapor concentrations outside the system [NIOSH 2004]. CSTDs limit the potential for aerosolizing drug contamination and can reduce worker exposure to sharps, thus reducing the likelihood of occupational

exposure to hazardous drugs [NIOSH 2004]. Each CSTD system traditionally consists of a syringe adapter (i.e., CSTD syringe connector) plus three component adapters: vial adapter, intravenous (I.V.) port adapter or Y-site adapter, and a bag adapter or infusion adapter. Each of these adapters mates with the syringe adapter.

Oral Chemotherapy

For oral chemotherapy, the patient is given the pill in either in a flavored pill pocket or a pill gun (or piller) (Figure 5). After the technician verifies the patient swallowed the pills, the patient is placed in a holding kennel until discharged to go home.

Chemotherapy Injection

For chemotherapy injection, the patient is given the liquid drug by subcutaneous or intramuscular route using a CSTD.

I.V. Chemotherapy

Sometimes a patient needs to receive chemotherapy through I.V. dosing via catheter (Figure 6). Although technique varies among technicians administering the dose, the overall process is similar. First, the area is prepped by shaving the injection site and cleaning the area with alcohol. After the injection area is prepped, the indwelling intravenous catheter and the T-port are inserted. The catheter and T-port are wrapped with bandage to keep the catheter in place. The CSTD Y-site adapter is connected to the catheter and the catheter is flushed with saline. The cap is removed from the I.V. line and the syringe adapter is attached to the end of the I.V. line. The syringe adapter is then connected to the Y-site adapter, which is attached to the catheter. The chemotherapy is given until the I.V. bag is empty. Once the bag is empty, saline is pushed into the I.V. bag through the bag adapter. This process is used to ensure all the drug is cleared from the I.V. line. Next, an additional amount of saline is pushed into the catheter to flush the line. The T-port line is closed and the catheter is removed from the patient's vein. The patient is bandaged and placed in a holding kennel until discharged to go home.

Occupational Exposure Limits and Health Effects

As a guide to the evaluation of the hazards posed by workplace exposures, NIOSH investigators use mandatory and recommended occupational exposure limits (OELs) when evaluating chemical, physical, and biological agents in the workplace. In the U.S., OELs have been established by Federal agencies, professional organizations, state and local governments, and other entities. The U.S. Department of Labor OSHA (PELs) [CFR 2003] are occupational exposure limits that are legally enforceable in covered workplaces under the Occupational Safety and Health Act. NIOSH *recommended exposure limits* (RELs) are based on a critical review of the scientific and technical information available on the prevalence of health effects, the existence of safety and health risks, and the adequacy of methods to identify and control hazards [NIOSH 1992]. Other OELs that are commonly used and cited in the U.S. include the *threshold limit values* (TLVs®) recommended by ACGIH®, a professional organization [ACGIH 2010]. ACGIH TLVs are considered voluntary

guidelines for use by industrial hygienists and others trained in this discipline "to assist in the control of health hazards." *Workplace environmental exposure levels* (WEELs) are recommended OELs developed by the American Industrial Hygiene Association (AIHA), another professional organization. WEELs have been established for some chemicals "when no other legal or authoritative limits exist" [AIHA 2007].

OSHA requires an employer to furnish employees a place of employment that is free from recognized hazards that are causing or are likely to cause death or serious physical harm [Occupational Safety and Health Act of 1970, Public Law 91–596, sec. 5(a)(1)]. Thus, employers are required to comply with OSHA PELs. Some hazardous agents do not have PELs, however, and for others, the PELs do not reflect the most current health-based information. Thus, NIOSH investigators encourage employers to consider the other OELs in making risk assessment and risk management decisions to best protect the health of their employees. NIOSH investigators also encourage the use of the traditional hierarchy of controls approach to eliminating or minimizing identified workplace hazards. This includes, in preferential order, the use of: (1) substitution or elimination of the hazardous agent, (2) engineering controls (e.g., local exhaust ventilation, process enclosure, dilution ventilation), (3) administrative controls (e.g., limiting time of exposure, employee training, work practice changes, medical surveillance), and (4) PPE (e.g., respiratory protection, gloves, eye protection, hearing protection).

Occupational Exposure Limits and Hazardous Drugs

Currently there are no PELs, RELS, or TLVs® for hazardous drugs [NIOSH 2004]. However, a PEL, REL, and TLV® have been established for inorganic arsenic compounds, such as arsenic trioxide, an antineoplastic drug [NIOSH 2004]. A WEEL has been established for some antibiotics. Some pharmaceutical manufacturers develop risk-based OELs and that information may be listed on the product's safety data sheets (SDSs) [NIOSH 2004].

Methodology

BSC and Oncology Department Performance Evaluations

Equipment: BSC Face Velocity Measurements

A TSI® VelociCalc™ Plus Model 9565-P thermal anemometer (TSI Incorporated, St. Paul, MN) was used to measure air velocities at the face of the BSC located in the oncology department (Figure 7).

Procedure

To determine the Compounding Hood's average face velocity, the open face of the hood was divided into an equal-area grid of twelve squares measuring

approximately 0.09 square meters (m^2) (1 square foot [ft^2]) each. A 5-second average velocity measurement was taken at the center of each square, while holding the anemometer perpendicular to the inward airflow direction. The average face velocity across the entire hood face was then determined by calculating the average of the equal-area square velocity measurements.

Equipment: Hood Qualitative Smoke Test

A Wizard Stick (Zero Toys, Inc., Concord, MA) handheld "smoke" generator was used to visualize air movement inside and around the periphery of the chemical fume hood in the research laboratory (Figure 8). The wizard stick produces a stream of safe, condensed vapor droplets and contains no actual solid 'smoke' particles, however the vapor droplets float in the air, appearing similar to smoke, and their flow path is indicative of the flowpath of the air in which they are suspended.

Procedure

The "smoke" was released around the periphery of the fume hood's open face and in the interior of the hood to qualitatively evaluate the capture efficiency and evaluate potential areas of concern. If the smoke was captured quickly and directly by the hood at the point where compounding operations are performed, it indicated acceptable control design and performance. If the smoke was slow to be captured or took a circuitous route to the hood exhaust intake, this indicated a potential problem. In addition, the adverse effect of cross drafts upon hood capture was evaluated by releasing smoke near the periphery of the hood face. Lack of direct capture or evidence of reverse-flow turbulence would be indicative of poor hood performance.

Equipment: Measurement of Supply and Exhaust Airflow Rates in the Oncology Department

A TSI Accubalance® Plus Air Capture Hood Model 8373 (TSI Incorporated, St. Paul, MN) was used to measure airflow for the supply and return ventilation in the oncology department (Figure 9).

Procedure

The instrument was setup according to the manual using the appropriate flow hood 0.6 m x 0.6 m (2 ft x 2 ft) or 0.6 m x 1.2 m (2 ft x 4 ft) to match the corresponding sized supply and exhaust louvers. The instrument was turned on and the hood was placed over the supply or exhaust vent. The measured airflow was displayed in cubic feet per minute (cfm) on the instrument's screen during measurement. Air measurements were taken using the instrument's backpressure compensation to ensure accurate readings.

Wipe Sampling Methods

Surface wipe samples were collected throughout Veterinary Hospital C using different sampling methods. Samples were collected in areas where drugs were handled by the workers, such as the oncology, laundry room, and common area used by all departments, and in places similar to those where traces of drugs have been found in human studies, such as door handles and telephones [Connor et. al 2010; Hon et. al 2013]. Wipe samples were also taken in less obvious places to determine if the hospital's current workplace safety practices were successful in preventing secondary contamination. NIOSH researchers were careful not to collect two samples from the same surface area. It should be noted that each of these wipe sampling methods are internal methods created specifically for this research study. There is limited data on recovery studies from various surfaces.

Wipe Sampling Method 1: Bureau Veritas North America Analytical Methods

The Bureau Veritas North America wipe sample collection method uses Texwipe™ Alpha™ Polyester Series Swabs (TX715, ITW Texwipe, Kernersville, NC) and a 50:50 methanol and water (both high-performance liquid chromatography grade) solvent to collect surface wipe samples. Although the subsequent analytical methods may vary by analyte, this wipe sample collection method is applicable for analysis of carboplatin, vincristine, methotrexate, cyclophosphamide, epirubicin, doxorubicin, and vinblastine (sulfate). Carboplatin is analyzed using Bureau Veritas North America's internal method, BV-2017-30843 (Bureau Veritas North America, Novi, MI), which uses high performance liquid chromatography/mass spectrometry (HPLC/MS) to find platinum. Vinblastine (sulfate) is analyzed using Bureau Veritas North America's internal method NAT 2006-14763, which uses HPLC. Vincristine, methotrexate, cyclophosphamide, epirubicin, and doxorubicin are analyzed using Bureau Veritas North America's internal method BV-2016-29599, which also uses HPLC/MS. Table I shows the analytical limit of detection (LOD), limit of quantification (LOQ), and analytical range for each of the analytes.

Prior to the visit to Veterinary Hospital C, several 16 mL amber vials with screw caps were filled with 1 mL of 50:50 methanol and water. During the site visits, once a sampling location was identified, a surface wipe sample was collected using the Texwipe™ Alpha™ Polyester Series Swabs and solvent. First, the cap of the amber vial was removed and one of the swabs was inserted. After the swab was wetted with the solvent, the swab was pressed against the sample location and moved back and forth, progressing over an approximate 10 centimeter (cm) x 10 cm surface. The swab was then turned over and the same back and forth movement was repeated in a perpendicular direction to that first taken over the same 10 cm x 10 cm surface area. The excess solvent in the vial was poured onto an absorbent pad in a sealable plastic bag for later disposal. The swab (head first) was placed partially into the vial opening and lateral pressure was applied to the swab stick to snap the head off and into the vial without touching. The cap and a label were placed on the vial. This surface wipe sampling collection method was repeated throughout the hospital. The samples were placed on ice packs until they were

delivered to the NIOSH contract laboratory and stored frozen until analysis. Results are reported in nanogram of drug per sample (ng/sample). Vinblastine results are reported in microgram of drug per sample (µg/sample).

Wipe Sampling Method 2: NIOSH Internal Analytical Method

NIOSH developed a solvent system for surface wipe sampling and analysis of lomustine (or CCNU), toceranib, N-methyldiethanolamine (MDEA), and chlorambucil sampled using two different wipe sampling media: Texwipe™ Alpha™ Polyester Series Swabs and Whatman™ filter papers (number 1442-055, 55-mm ashless circles, GE Healthcare, Chicago, IL). MDEA was analyzed as a likely indicator for mustargen after the rapid degradation expected for the compound in typical open environments (see Discussion). Table II lists the LOD, LOQ, and calibration plot concentration range for each of the analytes. Sampling media used to collect this set of analytes was moistened with a solvent blend of 83% acetonitrile/17% dimethylsulfoxide/0.20% hydrochloric acid, selected through extensive experiments conducted during method development for the survey. It provided stability in solution and adequate recoveries from in-house spiked quality control samples for all four of the antineoplastic drugs in this set via control of pH, solubility and other factors. The same solvent was used to prepare calibration standards and quality control samples to ensure compatibility with field samples during analysis.

After a swab was wetted with the solvent, the wipe sample procedure was the same as that described in Wipe Sampling Method 1. Upon collection, the swab was placed (head first) over the opening of a 125 mL translucent polypropylene jar (Nalgene™ Wide-Mouth Straight-Sided Polypropylene copolymer [2118-0004], Thermo Scientific™, Rochester, NY). Lateral pressure was applied to the swab stick to snap the head off and into the jar without touching. A second swab was wetted and the surface wipe sample collection was repeated for the same area using the same technique. The two wetted swabs made up one sample.

If filter paper was used for wipe sampling, then a petri dish, separated into its top and bottom halves, was used for preparing the sample. First one Whatman™ filter paper was placed into each half of the petri dish. A pipettor and disposable pipet tip were used to measure 250 microliters (µL) of the solvent onto each filter paper. An area of approximately 10 cm x 10 cm was wiped with one wetted filter paper and placed into a 125 mL polypropylene jar. The same 10 cm x 10 cm area was then re-sampled, in a wiping progression perpendicular to the first filter using the second wetted filter paper. The second wetted filter paper was placed into the same jar. The two wetted filter papers made up one sample.

Upon sample collection, the jar was capped and a sample label affixed. Samples were placed on ice packs and transported to a NIOSH laboratory freezer for storage at approximately -10ºC until analysis. Samples were returned to room temperature and were processed by extraction via orbital shaker using a total of 10 mL of the aforementioned solvent blend. The supernatant was filtered and 2 mL was

transferred to autosampler vials and fortified with internal standard (see Discussion) for analysis via HPLC/MS. Results are reported as mass of drug (ng).

Results

BSC and Oncology Department Performance Evaluations

BSC Face Velocity Measurements

Hood velocity measurements were collected on a Class II Type A2 BSC, located in the Oncology Department. The average face velocity of the hood (n=12 measurements) was 0.67 meters per second (m/s) (131 feet per minute [fpm]) as measured by the anemometer. The maximum face velocity was 0.86 m/s (169 fpm) with a minimum face velocity of 0.51 m/s (100 fpm).

Hood Qualitative Smoke Test

The Wizard Stick smoke generator was used to qualitatively test the capture efficiency of the lab hood. Smoke was released inside the hood at the center compounding position, inside the hood along the perimeter of the open hood face, outside of the hood along the perimeter of the open hood face, and outside of the hood directly in front of the hood face opening. In each case, the smoke was captured quickly, pulled further into the hood, and removed via the exhaust system. This showed the fume hood had acceptable performance.

Measurement of Supply and Exhaust Airflow Rates in the Oncology Department

The TSI Accubalance® Plus Air Capture Hood was used to measure mechanically generated supply and exhaust airflows in the oncology department. The total measured supply air was 0.42 cubic meter per second (m^3/s, or 884 cfm). The total mechanical exhaust airflow was 0.09 m^3/s (201 cfm). The measured supply airflow and the room volume (207 m^3 [7296 ft^3]) were used to calculate the ventilation rate in air changes per hour (ACH) for the room (Equation 1). The ACH was calculated to be 7.

Equation 1:

$$ACH = \frac{Airflow\ (^{m^3}/_{s}) \times 3600\ sec}{Room\ Volume\ (m^3)}$$

$$ACH = \frac{Airflow\ (^{ft^3}/_{min}) \times 60\ min}{Room\ Volume\ (ft^3)}$$

Wipe Sampling

Surface wipe samples were collected throughout Veterinary Hospital C's oncology department (which housed the BSC), laundry room, and common area used by all departments. Tables III through VIII report the analytical chemistry results from these samples. Sample analyses results revealed that 16 of 18 wipe samples submitted were non-detectable (ND) for toceranib, lomustine, and chlorambucil. Fifteen of 15 wipe samples, including a mop strand, submitted for MDEA were positive (6.4 to 145 ng). Five of 5 wipe samples submitted for toceranib, chlorambucil, and lomustine were positive for only toceranib (0.042 to 0.14 ng). Seven of the MDEA and three of the toceranib positive samples were between the LOD and LOQ. The ND determination means that contamination was either not present, or was present at levels below the LOD of the analytical method. Three out of 9 samples submitted for carboplatin were positive (5.3 to 10 ng/sample); however, the results were between the LOD and LOQ. Twelve out of 36 samples submitted for simultaneous methotrexate[3] (5.3 to 480 ng/sample) and cyclophosphamide (5.8 to 180 ng/sample) analyses were positive (5.3 to 480 ng/sample) while simultaneously ND for vincristine, doxorubicin, and epirubicin. Two of the cyclophosphamide and one of the methotrexate samples were between the LOD and LOQ. Three out of the 36 samples were intentionally collected from surfaces highly anticipated to be contaminated with hazardous drugs. These three "known" samples were positive for carboplatin (230,000 ng/sample), vincristine (10,000 ng/sample), and doxorubicin (19,000 ng/sample).

General Observations

NIOSH researchers observed and interacted with Veterinary Hospital C's veterinarians and staff to obtain information about the day-to-day activities along with oncology treatment processes. General observations are listed below:

[3] Two field blanks were positive for methotrexate, 11 and 160 ng/sample. Therefore, the positive methotrexate samples originated from its prior therapeutic use within the oncology department or from an error at the analytical laboratory.

- Cabinets and refrigerator used to store antineoplastics were properly labeled (Figures 10 and 11).
- Chemotherapy laundry and waste bins were properly labeled (Figures 12 and 13).
- Disposable gowns were used throughout the day and reported to be disposed of at the end of the work day.
- The disposable pad in the BSC is only changed once a month or if there is a known spill.
- BSC and its contents are reportedly cleaned once a month.
- BSC's air flow monitor was unplugged (Figure 14).
- Scissors were not wiped down or cleaned after each use.
- Areas where chemotherapy is administered were not cleaned after each patient.
- During chemotherapy administration, other personnel entered the room despite signs on the door.
- During one chemotherapy administration, a pair of gloves was placed on the biological waste container before being donned.
- The infusion pole was continually used as a placed to store disposable gowns until the next patient (Figure 2). During one of the administrations, the same pole was used to hold the saline bag.
- Gloves were not used during some procedures, such as inserting a catheter.
- Cleaning staff was observed pushing down the chemotherapy waste bag to get the air out before removing it from the bin. Only gloves were worn during this activity.

Discussion

The engineering assessment showed that the BSC was operating effectively. The hood's average face velocity (0.67 m/s [131 fpm]) was above the minimum recommended face velocity of 0.51 m/s (100 fpm) for a Type A2 BSC [CDC 2009; USP 2019]. However, the room did not meet the required minimum ventilation rate (12 ACH) for an unclassified containment segregated compounding area [USP 2019].

The NIOSH researchers' strategy was to collect surface wipe samples after each chemotherapy treatment as well as randomly throughout the hospital. Carboplatin, cyclophosphamide, lomustine, vincristine, mitoxantrone, and doxorubicin were the only drugs used during the NIOSH visit. Sampling for some drugs, such as toceranib, was conducted even though the drug was not used during the visit. Surface wipe samples were analyzed by either the NIOSH lab or a contract lab, Bureau Veritas North America. The analytical results from all of the Bureau Veritas North America's field samples were positive for carboplatin, cyclophosphamide, vincristine, and methotrexate with a range from 5.3 to 1,400 ng/sample. Six of these positive wipe samples were between the LOD and LOQ. The three carboplatin positives were from a blood spot on the examination table, the disposable gowns (the cuffs, belts, and sleeves), and the large kennel. Carboplatin was given to a patient the day of sampling. The four cyclophosphamide positives were from sampling a kennel where a patient on vincristine was housed; saliva spots on the floor after a patient was given cyclophosphamide; the outside of the cyclophosphamide chemo transport bag; outside surface of BSC; and the disposable pad in the BSC.

Field blanks were also collected during the surface wipe sampling. Field blanks are used to evaluate the amount of contamination that may have occurred during sample preparation, packaging, shipping, and/or storage before laboratory analysis [NIOSH 2016]. Field blanks are prepared in the same manner as a typical wipe sample except the media does not touch any surface. Field blank results are expected to result in NDs, however, sometimes field blanks yield positive results. For NIOSH visit, 2 of 7 field blanks were positive for methotrexate, one of which was higher than all but one collected wipe sample for methotrexate. One field blank was 11 ng/sample, which is between the LOD and LOQ. The second field blank was 160 ng/sample. The exact cause of the two contaminated field blanks is difficult to determine. While meticulous procedures are in place to minimize such occurrences, contamination does sometimes occur and in this case, the contamination could have occurred anytime within the sample preparation to the sample analysis processes. Therefore, NIOSH researchers were not able to determine whether the positive methotrexate samples on the back wall, water bowl in the large kennel, pair of scissors that are used to cut bandages, outside surface of BSC, and disposable pad in the BSC originated from its prior therapeutic use within the oncology department or from an error at the analytical laboratory.

NIOSH researchers collected wipe samples on certain surfaces that were highly anticipated to be contaminated with hazardous drugs. This strategy was done to verify the analytical methods' ability to detect a drug contamination under the sampling, handling, shipping variables specific to this evaluation. The known contaminated samples are highlighted in yellow in the tables. For example, a vincristine wipe sample was very high with a result of 10,000 ng/sample. This was anticipated because the sample was collected inside the vincristine chemo transport bag. A doxorubicin sample was 19,000 ng/sample. This sample was collected from

the syringe. Carboplatin had a high sample result of 230,000 ng/sample. The sample was also collected from the syringe. In the end, the analyses results from all of the samples anticipated to be known contaminated samples indicated positive drug contamination results.

In-house NIOSH HPLC/MS analyses employed controlled fragmentation (MS/MS) of the parent ion of each analyte. Two fragment ions were monitored for each, with the more intense ion used for quantification and the other for confirmation. Positive response for an analyte was indicated by quantification ion response above the calculated LOD (q.v.) and by the presence of both expected fragment ions. Additionally, the ratio of intensities of the two fragment ion responses observed for field samples was compared to the average ratio observed for pure analyte (i.e., the calibration standards) as an additional metric for assessing positive analyte response in samples. If both ions were present but their ratio differed significantly from the expected value, it suggested that the quantitative value determined for the analyte might be affected by an unresolved interference and could thus be suspect. These results are designated appropriately in Table IV, VI, and VIII (q.v.).

No isotopically labeled standards for the analytes of interest were available for the HPLC/MS analysis. To monitor instrument stability during quantification, samples were fortified with 5 ng/mL of hexamethylphosphamide, a compound which responds strongly in LC-MS under the conditions of analysis, as an internal standard. However, this compound did not coelute with any of the analytes. Therefore its response could not be used directly to correct for analyte signal drift, but did provide some indication of instrument stability over the course of analysis. Additionally, low-level calibration standards were periodically interspersed with field samples and responses were compared to expected levels. Quality controls were prepared in triplicate by spiking three levels of analytes onto applicable wiping media, which were processed and run with field samples to demonstrate extraction procedure efficacy and instrument performance. Note: since no appropriate “blank” media was available for the mop strand sample in the form of unused and unexposed material, quality controls could not be generated for this media and analyte extraction efficiency could not be documented. Finally, several field samples were rerun to determine whether reanalysis produced analyte values similar to initial values; in these cases both separate results are listed in Table IV, VI, and VIII.

Instability has been anecdotally observed for lomustine and chlorambucil in the course of NIOSH analytical method development, and documented for doxorubicin and other drugs elsewhere [NIOSH 2012]. Degradation of unstable compounds is expected to be especially rapid in open workplace environments absent controlled parameters. Mustargen is also very reactive in uncontrolled environments and rapidly decays to several products, of which the ethanolamine MDEA is the most important in environments with typical humidity levels. Since it was unlikely that intact mustargen would be detected at a workplace site if sampling and/or analysis took place long after a spill event, the decision was made to quantify MDEA, which

was readily detectable via HPLC/MS, as a potential marker for the original compound. However, positive sample results for MDEA may not be indicative of actual mustargen contamination, since ethanolamine compounds (of which MDEA is one) are often used in modern manufacturing techniques and cleaning media. For purposes of this investigation, MDEA presence in workplace samples should only serve as a potential warning and cannot be conclusively linked to a particular source. After quantification of the antineoplastic drugs was completed via the NIOSH method, several of the field samples were subsequently screened for other ethanolamine compounds, which were generally found to be present. However, no meaningful quantitative correlations existed between these compounds and MDEA, suggesting that when MDEA was present it could not be automatically regarded as a contaminant or intentional component of whatever sources had contributed the other ethanolamines. It is therefore not possible to guarantee or to dismiss that detection of MDEA in a field sample, as occurred in the present survey, signals the presence of a prior mustargen contamination event.

Although mustargen was not used during the time of the survey, 15 of 15 of the field samples plus the mop strand sample analyzed for MDEA were positive. MDEA was found around the bathroom toilet in the common area outside of the oncology department, in the exhaust vent located above the examination table where chemotherapy administration occurs, on the laundry room floor, and on other surfaces around the Oncology Department. The BSC exhaust downstream from the high efficiency particulate air (HEPA) filter was also positive for MDEA. Studies have shown the vaporization potential of certain antineoplastic drugs, including mustargen [Connor et. al 2000; Kiffmeyer et. al 2002].

It is common to have a wipe sample analyses for hazardous drug contamination result in a ND finding, even in the presence of a hazardous drug manipulations [NIOSH 2012]. Some of the hazardous drugs, such as doxorubicin, are not stable and can decay rapidly as noted above [NIOSH 2012]. These drugs are less likely to be detected from surface wipe samples. The hospital also used CSTDs to prepare and administer chemotherapy, which studies have shown can reduce surface contamination [Sessink and Bos 1999; Nygren et al. 2002; NIOSH 2004; Harrison et al. 2006; Nyman et al. 2007; Yoshida et al. 2009; Sessink et al. 2010; Vyas 2013]. Another possible reason most of the samples did not detect drug contamination is that the level of hazardous drugs on surfaces may vary over time. This variation is influenced by drug amounts handled, patient load, and work practices [NIOSH 2012].

One limitation of the study is there are currently only a handful of analytical methods covering a small fraction of the 218 hazardous drugs on the *NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings* [NIOSH 2016]. The hospital uses several hazardous drugs for which the NIOSH researchers were not able to sample due to the absence of an analytical method. An additional limitation is the time between sample collection and analysis. Although surface wipe samples are shipped on ice within 24-hours of their collection, it may be much

longer before the analytical laboratories can analyze the samples. This delay in sample analysis could decrease the chances of detecting a positive wipe sample due to the analyte instability as discussed above.

Conclusions and Recommendations

The presence of carboplatin and cyclophosphamide contamination is a reminder that the patients themselves can be a source of exposure, even when the drugs are not handled directly. The presence of cyclophosphamide (on surfaces) and methotrexate[4] serves as two reminders: (1) that hazardous drug contamination can sometimes linger despite cleaning efforts and (2) the detected contamination on desk and cabinet surfaces one might ordinarily think of as "safe," emphasizes the importance of proper work practices regarding the use of gloves and shoe covers, hand washing, and food/drink prohibitions within the hazardous drug handling environments. The detected contamination on the outside of the chemo transport bag serves as a reminder of the meticulous work practices required to avoid cross-contamination of surfaces expected to be "clean" as well as a reminder to treat all surfaces as potentially contaminated within the oncology treatment areas. Therefore, it is important to continue to use engineering controls (e.g., biological safety cabinets), supplementary controls (e.g., CSTDs), protective work practices (e.g., surface cleaning after every oncology patient, regardless of whether I.V. chemotherapy was administered), and PPE (e.g., gloves and gowns rated for chemotherapy protection, respirators, shoe cover, eye protection) to reduce unintentional exposures to the staff or pet owners. Additionally, the detection of drug contamination on the floor mop is a reminder that cleaning tools and supplies used in these areas should be dedicated for that purposes alone, and should not be used for cleaning of adjacent areas not expected to be exposed to hazardous drugs.

NIOSH researchers observed proper work practices that Hospital C had in place during the visit. The hospital is encouraged to:

- Continue to get the BSC recertified on a yearly basis and after it has been repaired or relocated [CDC 2009].
- Continue to use the BSC to prepare chemotherapy treatments for patients [NIOSH 2004; USP 2019].
- Continue to clean the BSC each time a hazardous drug is used inside the cabinet even if there is no noticeable spill or leak. United States Pharmacopeia (USP) <797>, Pharmaceutical Compounding: Sterile

[4] Two field blanks were positive for methotrexate, 11 and 160 ng/sample. Therefore, the positive methotrexate samples originated from its prior therapeutic use within the oncology department or from an error at the analytical laboratory.

Preparations, has a section on cleaning and disinfecting compounding areas [USP 2019].

- Continue to use disposable absorbent underpads on surfaces where the drug will be compounded and/or administered [NIOSH 2010].

- Continue to use PPE for handling hazardous drugs [NIOSH 2004; NIOSH 2010; USP 2019].

- Continue to dispose PPE after each use or whenever it becomes contaminated [NIOSH 2004].

- Continue to use gloves during all tasks involving a chemotherapy patient [USP 2019]. Staff should wear American Society for Testing and Materials (ASTM)-tested chemotherapy gloves [USP 2019]. Change gloves every 30 minutes unless otherwise recommended by the glove manufacturer or if contaminated, torn, or punctured [USP 2019].

- Continue to use CSTDs while compounding and administering hazardous drugs [NIOSH 2004; USP 2019]. Although, CSTDs may reduce worker exposure to hazardous drugs, they may not entirely eliminate exposure [Sessink and Bos 1999; Nygren et al. 2002; NIOSH 2004; Harrison et al. 2006; Nyman et al. 2007; Yoshida et al. 2009; Sessink et al. 2010; Vyas 2013]. The NIOSH Alert identifies CSTDs as supplemental controls that should only be used in combination with primary engineering controls (biological safety cabinets and containment isolators) to further protect against worker exposures to hazardous drugs [NIOSH 2004]. Therefore, it is important to continue to use the BSC and proper PPE to protect the staff, even when CSTDs are used.

- Continue to use the *Chemotherapy Treatment in Process* sign (Figure 15). This deters other staff from entering the room unprotected when hazardous drugs are in use [USP 2019].

- Continue washing hands after compounding, administering, or handling hazardous drugs [NIOSH 2010].

- Continue using the hospital oncology department's standard operating procedures for administering of drugs, spills, post administration cleaning, and patient management.

- Continue to identify patients that received chemotherapy treatment (Figure 16).

- Continue to wash clothing and blankets that could be contaminated with drug separately from items with no anticipated drug contamination [USP 2019].

Below are a few recommendations for consideration within the hospital's work practices as well as towards the facility design that could reduce unintentional exposures to hazardous drugs:

- Ensure that all employees expected to wear respiratory protection are trained and fit-tested on the specific respirator in use. The respirator must be used as part of a comprehensive respiratory protection program and the user must be enrolled into a Respiratory Protection Program in accordance with the requirements of OSHA 1910.134 [OSHA 2011].

  Respirators should be used in a proper respirator program under the supervision of a properly trained respirator program administrator. Respirators used without such a program, with all its essential elements, cannot be relied upon to protect workers.

  Each worker required to wear a respirator must be medically evaluated and cleared by a physician to wear the specific respirator before performing assigned tasks. For respirators to be effective and protect workers from harmful exposures, they must be selected, inspected, and maintained properly. Respirators should be inspected by the worker prior to each use for any defects. Reuseable respiratory protective equipment should also be cleaned, disinfected, and re-inspected after each use. Respiratory protective devices should never be worn when a satisfactory face seal cannot be obtained. Many conditions may prevent a good seal between the worker's face and the respirator. Some of these conditions include facial hair, glasses, or an unusually structured face. All workers required to wear a respirator must be properly trained on the selection, use, limitations, and maintenance of the respirator. They also must be fit–tested to assure a proper seal between the workers face and the specific make/model of respirator assigned for their use, prior to performing work tasks in a contaminated area.

  All workers should receive annual fit–testing with a quantitative testing device. When not in use, respirators must be stored in a clean environment located away from any source of contamination.

- Do not reuse disposable gowns. Use gowns once and throw them away in chemotherapy waste [USP 2019].

- Clean area after each chemotherapy administration [USP 2019].

- Do not allow drinks (caps and no caps) to be in areas where chemotherapy is prepared or administered.

- Ensure that all hazardous drugs, including refrigerated hazardous drugs, are stored in a negative pressure room with at least 12 air changes per hour [USP 2019].

- Clean scissors and other tools after each use with chemotherapy patients [NIOSH 2010; USP 2019].

- Ensure dedicated cleaning supplies (mops, rags, buckets, etc.) used within the oncology department are not used in other areas of the hospital [NIOSH 2004].

- Cleaning staff should be trained in appropriate procedures when in and around the oncology department. Cleaning staff should also wear appropriate PPE, such as ASTM-tested chemotherapy gloves, disposable chemotherapy gowns, and respirator (if applicable) [NIOSH 2004; USP 2019].

Acknowledgements

NIOSH researchers would like to thank the staff at Veterinary Hospital C. The staff allowed the researchers to observe their work practices, complete an engineering assessment, collect wipe samples, and ask questions. Without the staff's willingness to participate in the research, the project's goals are not possible. The NIOSH researchers would also like to thank Jack Pretty, Ph.D., of NIOSH/HELD/CBMB and the Bureau Veritas North America contract laboratory for their analysis of the field samples.

References

ACGIH [2010]. 2010 TLVs® and BEIs®: threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH: American Conference of Governmental Industrial Hygienists.

AIHA [2007]. 2007 Emergency Response Planning Guidelines (ERPG) & Workplace Environmental Exposure Levels (WEEL) Handbook. Fairfax, VA: American Industrial Hygiene Association.

Albin K [2010]. Administrating chemotherapy: is it safe for pregnant or breast-feeding veterinary technicians? Vet Tech October 2010.

CDC [2009]. Biosafety in microbiological and biomedical laboratories. 5th ed. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, HHS Publication No. (CDC) 21-1112.

CFR [2003]. 29 CFR 1910.1000. Code of Federal Regulations. Washington, DC: U.S. Government Printing Office, Office of the Federal Register.

Connor TH, Shults M and Fraser MP [2000]. Determination of the vaporization of solutions of mutagenic antineoplastic agents at 23 and 37° C using a desiccator technique. Mutat Res 470:85-92.

Connor TH, DeBord G, Pretty JR, Oliver MS, Roth TS, Lees PSJ, Krieg EF, Rogers B, Escalante CP, Toennis CA, Clark JC, Johnson BC, McDiarmid MA [2010]. Evaluation of antineoplastic drug exposure of health care workers at three university-based US cancer centers. Am College of Occup Environ Med 52(10):1019-1027.

Crump KT [2013]. Veterinary oncology. [http://www.vspn.org/Library/Misc/VSPN_M02045.htm]. Date accessed: February 2018.

Epp T, Waldner C [2012]. Occupational health hazards in veterinary medicine: physical, psychological, and chemical hazards. Can Vet J 53: 151-157.

Fielding SL, Lacroix C [2009]. Chemotherapy safety in small animal practice. The NAVTA J Fall 2009:44-49.

Hall AL, Davies HW, Demers PA, Nicol AM, Peters CE [2013]. Occupational exposures to antineoplastic drugs and ionizing radiation in Canadian veterinary settings: findings from a national surveillance project. Can J Public Health 104(7):e460-e465.

Harrison BR, Peters BG, Bing MR [2006]. Comparison of surface contamination with cyclophosphamide and fluorouracil using a closed-system drug transfer device versus standard preparation techniques. Am J Health-Syst Pharm 63: 1736-1744.

Hon C, Teschke K, Chu W, Demers P, Venners S [2013]. Antineoplastic drug contamination of surfaces throughout the hospital medication system in Canadian hospitals. J Occup Environ Hygiene 10: 374–383.

Kiffmeyer TK, Kube C, Opiolka S, Schmidt KG, Schoppe G, Sessink PJM [2002]. apour pressures, evaporation behaviour and airborne concentrations of hazardous drugs: implications for occupational safety. Pharaceutical J 268:331-337.

Klahn S [2014]. Chemotherapy safety in clinical veterinary oncology. Vet Clin Small Anim 44: 941–963.

MacDonald V [2009]. Chemotherapy: managing side effects and safe handling. Can Vet J 50:665-668.

Mobo BHP, Rabinowitz PM, Conti LA, Taiwo OA [2010]. Occupational health of animal workers. In: Rabinowitz PM, Conti LA, eds. Human-animal medicine: clinical approaches to zoonoses, toxicants and other shared health risks. Maryland Heights: Saunders Elsevier, pp. 343-371.

NIOSH [1992]. Recommendations for occupational safety and health: compendium of policy documents and statements. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 92-100.

NIOSH [2004]. NIOSH alert: preventing occupational exposures to antineoplastic and other hazardous drugs in health care settings. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2004-165.

NIOSH [2010]. NIOSH workplace solutions: safe handling of hazardous drugs for veterinary healthcare workers. By Connor TH and Cordes B. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2010-150.

NIOSH [2012]. Hazard evaluation and technical assistance report: Chemotherapy drug evaluation at a veterinary teaching hospital, Michigan. rev. April 2013. By Couch J, Gibbins J, Connor T. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, NIOSH HETA Report No. 2010-0068-3156.

NIOSH [2016]. SOP 201: submitting samples to the laboratory. By Chemical Exposure and Monitoring Branch Laboratory Services. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) (June 21, 2016).

Nygren O, Gustavsson B, Ström L, Eriksson R, Jarneborn L, Friberg A [2002]. Exposure to anti-cancer drugs during preparation and administration. Investigations of an open and a closed system. J Environ Monit 4: 739–742.

Nyman HA, Jorgenson JA, Slawson MH [2007]. Workplace contamination with antineoplastic agents in a new cancer hospital using a closed-system drug transfer device. Hos Pharm 2(3): 219-225.

OSHA [2011]. 29 CFR 1910.134 Personal protective equipment. Washington, DC: U.S. Department of Labor, Occupational Safety and Health Administration, https://www.osha.gov.

Seibert P [2013]. Telephone conversation on December 18, 2013, between P. Seibert, Safety Vet, and D. Hirst, Division of Applied Research and Technology, National Institute for Occupational Safety and Health, Centers for Disease Control, U.S. Department of Health and Human Services.

Sessink PJM, Bos RP [1999]. Evaluation of methods for monitoring occupational exposure to cytostatic drugs. Drug Safety 20(4): 347-359.

Sessink PJM, Connor TH, Jorgenson JA, Tyler TG [2010]. 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 0: 1-10.

Smith C [2010]. Chemo drugs a concern for veterinary workers, too. [http://www.mlive.com/living/kalamazoo/index.ssf/2010/07/chemo_drugs_a_concern_for_vete.html] Date accessed: February 2018.

Technicians Respond! National Demographic Survey Summary [2008]. TNJ Spring 2008:17-20.

USP [2019]. <797> Pharmaceutical compounding—sterile preparations. Rockville, MD: U.S. Pharmacopeia.

USP [2019]. <800> Hazardous drugs—handling in healthcare settings. Rockville, MD: U.S. Pharmacopeia.

Vyas N, Yiannakis D, Turner A, Sewell GJ [2013]. Occupational exposure to anti-cancer drugs: A review of effects of new technology. J Oncol Pharm Pract 20(4): 278-287.

Yoshida J, Genshin T, Mochizuki C, Masu Y, Koda S, Kumagai S [2009]. Use of a closed system device to reduce occupational contamination and exposure to antineoplastic drugs in the hospital work environment. Ann Occup Hyg 53(2): 153-160.

Appendixes

Table I. LOD[5]/LOQ[6] and analytical ranges of analyte for Bureau Veritas North America's Internal Methods

Analyte	LOD (ng)[7]	LOQ (ng)	Analytical Range (ng)
Carboplatin	5	17	5 to 200
Cyclophosphamide	5	17	5 to 200
Doxorubicin	5	17	5 to 200
Epirubicin	5	17	5 to 200
Methotrexate	5	17	5 to 200
Vincristine	5	17	5 to 200

Table II. LOD/LOQ and analytical ranges of analyte for NIOSH Method

Analyte	LOD (ng)	LOQ (ng)	Analytical Range (ng)
Methyldiethanolamine (MDEA: marker for mustargen)	3.7	12	10 to 2500
Toceranib	0.012	0.039	10 to 400
Lomustine	4.1	14	100 to 7500
Chlorambucil	0.21	0.69	10 to 2500

[5] LOD = limit of detection
[6] LOQ = limit of quantification
[7] ng = nanogram of drug

Table III. Bureau Veritas North America Results: Chemotherapy Drugs in Surface Wipe Samples, Day 1

Location and Sample Identification	Sample Description	Wipe Sampling Method	Results (ng/sample)[8]
Oncology Department	Examination table before patient dose of oral cyclophosphamide	BV-2016-29599 (vincristine, methotrexate, cyclophosphamide, epirubicin, doxorubicin)	ND[9]
Oncology Department	Outside of cyclophosphamide chemo transport bag (inside BSC)	BV-2016-29599	ND
Oncology Department	Keyboard and telephone	BV-2016-29599	ND
Area used by all departments	Kennel floor (vincristine patient housed 9 days before sampling) (Figure 17)	BV-2016-29599	49 (cyclophosphamide)
Area used by all departments	Kennel's back wall and bowl (vincristine patient housed 9 days before sampling) (Figure 17)	BV-2016-29599	53[10] (methotrexate)
Oncology Department	Saliva spots on floor from patient given oral cyclophosphamide (Figure 18)	BV-2016-29599	180 (cyclophosphamide)
Oncology Department	Outside of oral cyclophosphamide chemo transport bag (after dosing) (Figure 19)	BV-2016-29599	1,400 (cyclophosphamide)
Oncology Department	Chemo drug cabinet handle and fridge handle	BV-2016-29599	ND
Oncology Department	Floor in front of BSC	BV-2016-29599	ND
Oncology Department	Scissors (Figure 20)	BV-2016-29599	94 (methotrexate)
Oncology Department	Outside of vincristine chemo transport bag	BV-2016-29599	ND
Oncology Department	BSC exhaust and air flow monitor	BV-2016-29599	ND
Oncology Department	BSC thimble connection gap	BV-2016-29599	ND

[8] ng/sample = nanogram of drug per sample

[9] ND = results are not detected at the LOD

[10] Two field blanks were positive for methotrexate, 11 and 160 ng/sample. Therefore, the positive methotrexate samples originated from its prior therapeutic use within the oncology department or from an error at the analytical laboratory.

Table IV. NIOSH Lab Results: Chemotherapy Drugs in Surface Wipe Samples, Day 1

Location and Sample Identification	Sample Description	Wipe Sampling Method	Results (ng)[11]
Oncology Department	Chemotherapy drug refrigerator (Figure 11)	NIOSH Method (filter paper)	39 and (40)[12,13] (MDEA)[14]; ND for toceranib, chlorambucil, and lomustine
Oncology Department	Floor in front of BSC (Figure 21)	NIOSH Method (filter paper)	18 (MDEA); 0.042 (toceranib); ND[15] for chlorambucil and lomustine
Oncology Department	Inside of chemotherapy drug refrigerator (Figure 22)	NIOSH Method (swab)	13 (MDEA); ND for toceranib, chlorambucil, and lomustine
Oncology Department	BSC exhaust (Figure 23)	NIOSH Method (swab)	120 (MDEA); (0.14) toceranib; ND for chlorambucil and lomustine

[11] ng = mass of drug
[12] () = values for which fragment ion ratios suggest possible quantitative inaccuracy in parentheses
[13] Presence of two numerical values for a sample indicates that the sample was selected for rerun and the second value was obtained for the second analysis
[14] MDEA = N-methyldiethanolamine
[15] ND = results are not detected at the LOD

Table V. Bureau Veritas North America Results: Chemotherapy Drugs in Surface Wipe Samples, Day 2

Location and Sample Identification	Sample Description	Wipe Sampling Method	Results (ng/sample)[16]
Oncology Department	Sterile water vial inside BSC	BV-2016-29599 (vincristine, methotrexate, cyclophosphamide, epirubicin, doxorubicin)	ND[17]
Oncology Department	External front of BSC	BV-2016-29599	ND
Oncology Department	Keyboard by radiation oncology area	BV-2016-29599	ND
Oncology Department	Door handle inside Oncology Department room	BV-2016-29599	ND
Oncology Department	Lids of containers on countertop by examination table	BV-2016-29599	ND
Oncology Department	Small kennel (patient given vincristine)	BV-2016-29599	ND
Oncology Department	Outside of carboplatin chemo transport bag	BV-2017-30843 (Carboplatin)	ND
Oncology Department	Inside of carboplatin chemo transport bag	BV-2017-30843	ND
Oncology Department	Blood spot on exam table's disposable pad (Figure 24)	BV-2017-30843	(5.3)[18]
Oncology Department	Disposable gowns (cuffs, belts, and sleeves) (Figure 25)	BV-2017-30843	(11)
Oncology Department	Large kennel (Figure 26)	BV-2017-30843	(10)
Oncology Department	Floor by exam table	BV-2017-30843	ND
Oncology Department	Carboplatin syringe (Figure 27)	BV-2017-30843	230,000

[16] ng/sample = nanogram of drug per sample
[17] ND = result is not detected at the LOD
[18] () = result is between LOD and LOQ
Yellow shading represents known sample with drug contamination

Table VI. NIOSH Lab Results: Chemotherapy Drugs in Surface Wipe Samples, Day 2

Location and Sample Identification	Sample Description	Wipe Sampling Method	Results (ng)[19]
Oncology Department	PhaSeal vial adapter assembly fixture in BSC (Figure 3)	NIOSH Method (filter paper)	13 (MDEA)[20]; ND for toceranib, chlorambucil, and lomustine
Oncology Department	Chemotherapy waste bin by BSC (Figure 13)	NIOSH Method (filter paper)	6.4 (MDEA); ND for toceranib, chlorambucil, and lomustine
Oncology Department	Small kennel handles (Figure 2)	NIOSH Method (filter paper)	*11*[21] (MDEA); ND for toceranib, chlorambucil, and lomustine
Oncology Department	White chemo laundry hamper (Figure 12)	NIOSH Method (filter paper)	(27)[22] (MDEA); ND for toceranib, chlorambucil, and lomustine
Oncology Department	Keyboard area countertop by radiation oncology area (Figure 28)	NIOSH Method (filter paper)	8.5 (MDEA); ND for toceranib, chlorambucil, and lomustine
Oncology Department	Floor by examination table where chemotherapy is administered (Figure 29)	NIOSH Method (swab)	(40) (MDEA); (0.046) toceranib; ND for chlorambucil and lomustine

[19] ng = mass of drug
[20] MDEA = N-methyldiethanolamine
[21] *Italics* = result is between LOD and LOQ
[22] ( ) = values for which fragment ion ratios suggest possible quantitative inaccuracy

Table VII. Bureau Veritas North America Results: Chemotherapy Drugs in Surface Wipe Samples, Day 3

Location and Sample Identification	Sample Description	Wipe Sampling Method	Results (ng/sample)[23]
Hallway to Oncology Department	Bathroom floor around toilet (no figure)	BV-2016-29599 (vincristine, methotrexate, cyclophosphamide, epirubicin, doxorubicin)	65[24] (methotrexate)
Oncology Department	Exhaust vent	BV-2016-29599	ND[25]
Oncology Department	Floor area where yellow chemo bag was placed	BV-2016-29599	ND
Laundry Room	Handle of washing machine	BV-2016-29599	ND
Oncology Department	Pager	BV-2016-29599	ND
Oncology Department	Stethoscope	BV-2016-29599	ND
Oncology Department	Outside of vincristine chemo transport bag	BV-2016-29599	ND
Oncology Department	Inside of vincristine chemo transport bag (Figure 30)	BV-2016-29599	10,000 (vincristine)
Oncology Department	Doxorubicin syringe (Figure 31)	BV-2016-29599	19,000 (doxorubicin)
Shipping and Receiving	Floor by door	BV-2016-29599	ND
Shipping and Receiving	Computer keyboard and mouse	BV-2016-29599	ND
Oncology Department	Random spots on outside of BSC front surface (Figure 32)	BV-2016-29599	(8)[26] (cyclophosphamide)
Oncology Department	Outside of doxorubicin chemo transport bag (Figure 31)	BV-2016-29599	(5.3) (methotrexate)
Oncology Department	Bathroom floor by toilet (no figure)	BV-2016-29599	480 (methotrexate)
Oncology Department	Bathroom door handle	BV-2016-29599	ND
Oncology Department	Bathroom mop	BV-2016-29599	ND
Oncology Department	Disposable absorbent pad in BSC (Figure 3)	BV-2016-29599	(5.8) (cyclophosphamide)
Oncology Department	Pen and PhaSeal vial machine in BSC	BV-2017-30843 (Carboplatin)	ND
Oncology Department	Outside of carboplatin chemo transport bag	BV-2017-30843	ND

[23] ng/sample = nanogram of drug per sample
[24] Two field blanks were positive for methotrexate, 11 and 160 ng/sample. Therefore, the positive methotrexate samples originated from its prior therapeutic use within the oncology department or from an error at the analytical laboratory.
[25] ND = result is not detected at the LOD
[26] () = result is between LOD and LOQ
Yellow shading represents known sample with drug contamination

Table VIII. NIOSH Lab Results: Chemotherapy Drugs in Surface Wipe Samples, Day 3

Location and Sample Identification	Sample Description	Wipe Sampling Method	Results (ng)[27]
Oncology Department	Bathroom floor around toilet (no figure)	NIOSH Method (filter paper)	(17)[28] (MDEA); ND for toceranib, chlorambucil, and lomustine
Oncology Department	Exhaust above area where chemotherapy is administered (Figure 33)	NIOSH Method (filter paper)	(79) and (88) (MDEA); 0.11 (toceranib); ND for chlorambucil and lomustine
Laundry Room	Laundry room floor where yellow chemo bag was placed the day before sampling (Figure 34)	NIOSH Method (filter paper)	(34) and 37 (MDEA); ND for toceranib, chlorambucil, and lomustine
Oncology Department	Strands of mop stored in bathroom (no figure)	NIOSH Method	(145) (MDEA); ND for toceranib, chlorambucil, and lomustine

[27] ng = mass of drug

[28] () = values for which fragment ion ratios suggest possible quantitative inaccuracy

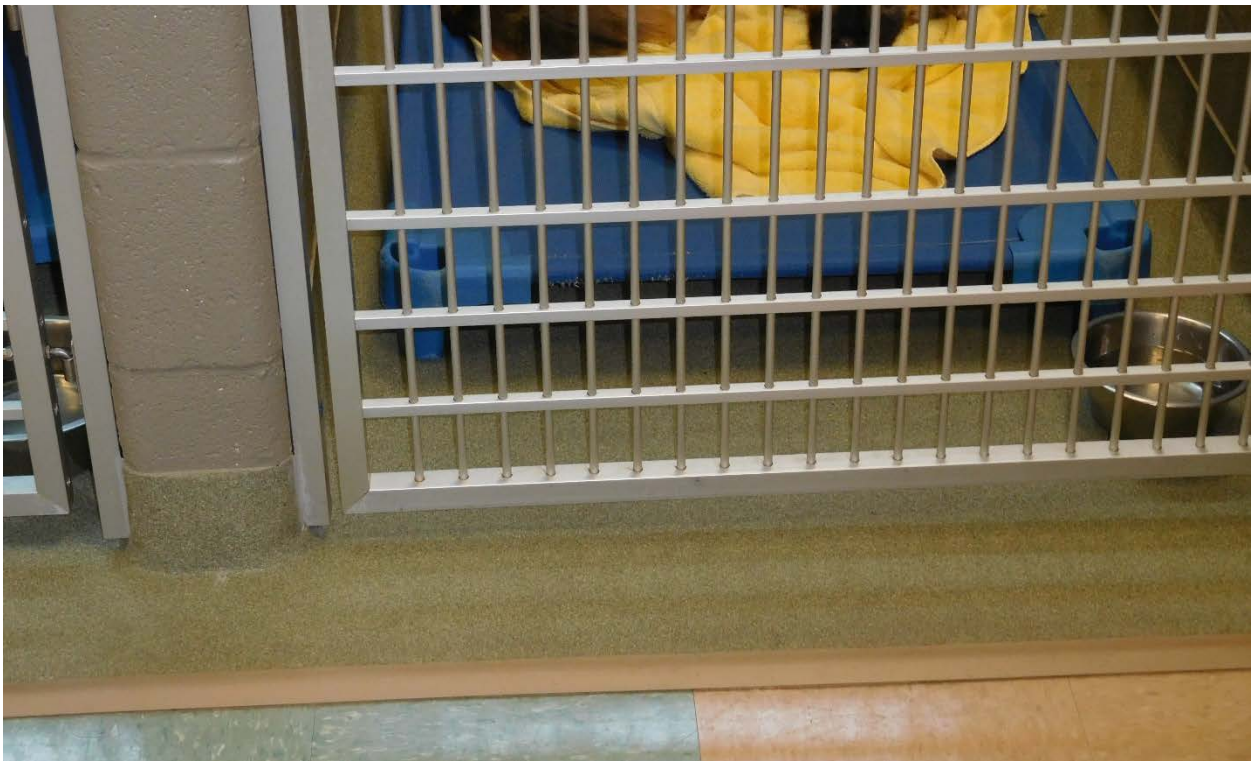

Figure 1. Large kennel area (Photo credit: NIOSH)

Figure 2. Small kennel area. Also shown: infusion pole with disposable chemo gowns. (Photo credit: NIOSH)

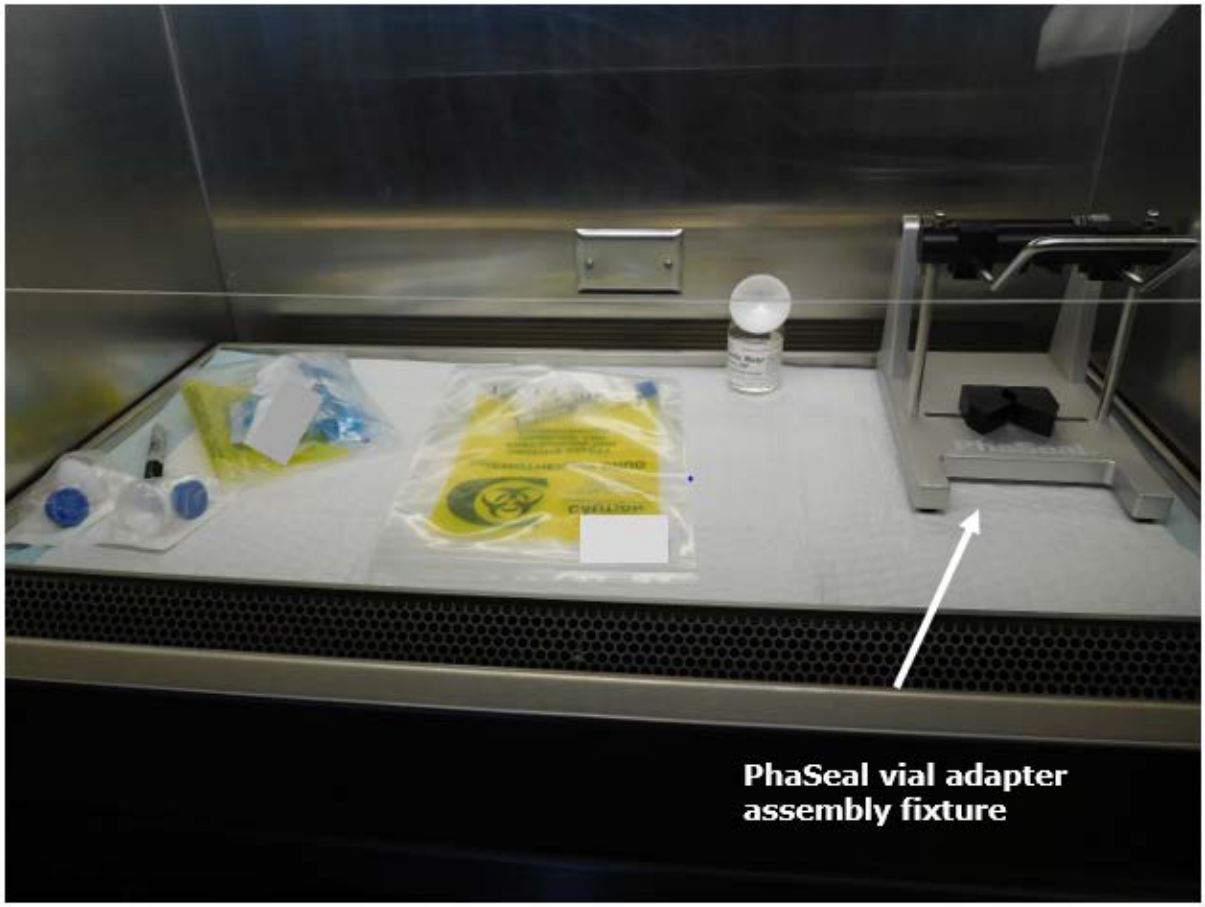

Figure 3. Class II Type A2 Model BBF-3SSRX. Also shown: PhaSeal vial adapter and disposable absorbent pad. (Photo credit: NIOSH)

Figure 4. PhaSeal CSTD system with syringe adapter and vial adapter shown (Photo credit: NIOSH)

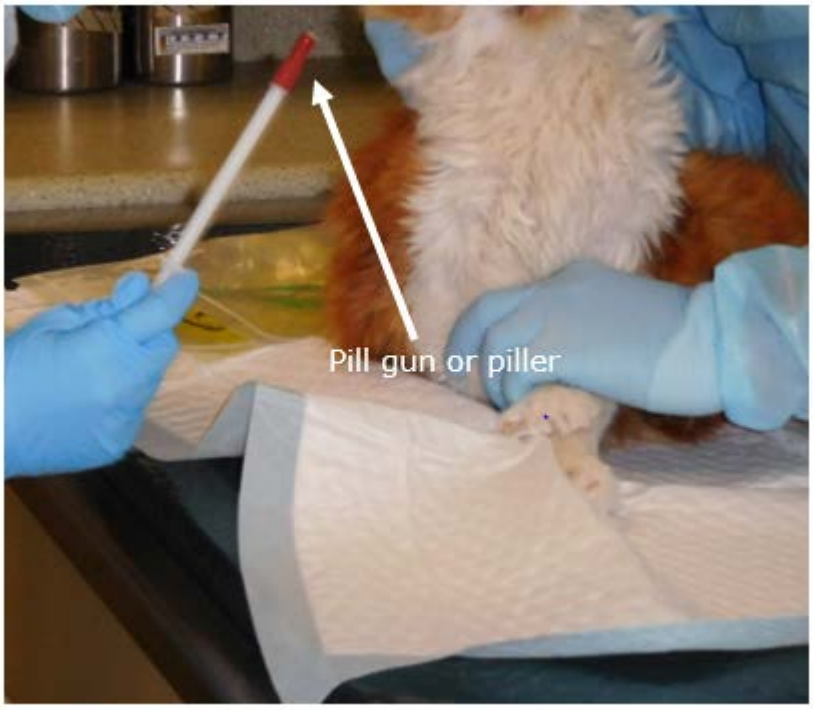

Figure 5. Patient given chemotherapy pill via a pill gun or piller (Photo credit: NIOSH)

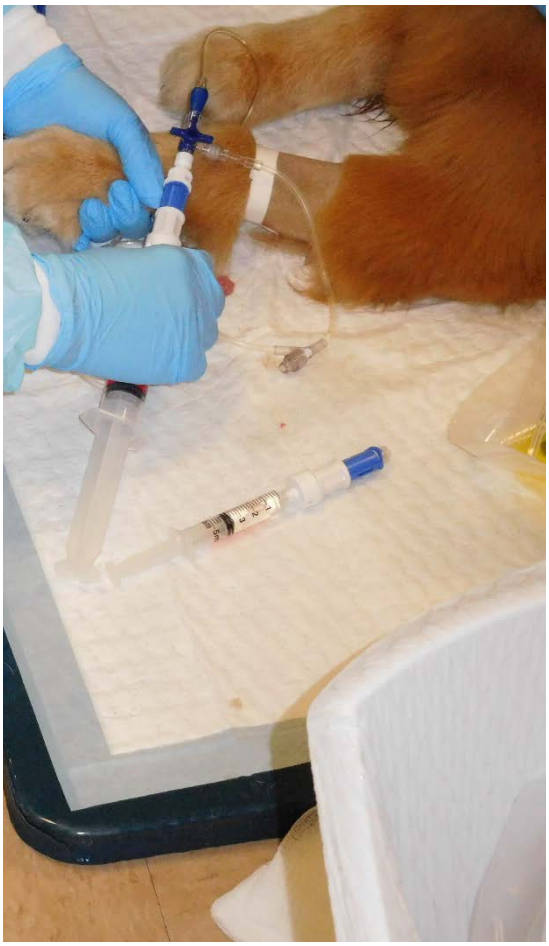

Figure 6. Chemotherapy given via catheter (Photo credit: NIOSH)

Figure 7. TSI® VelociCalc™ Plus Model 9565-P thermal anemometer (Photo Credit: NIOSH)

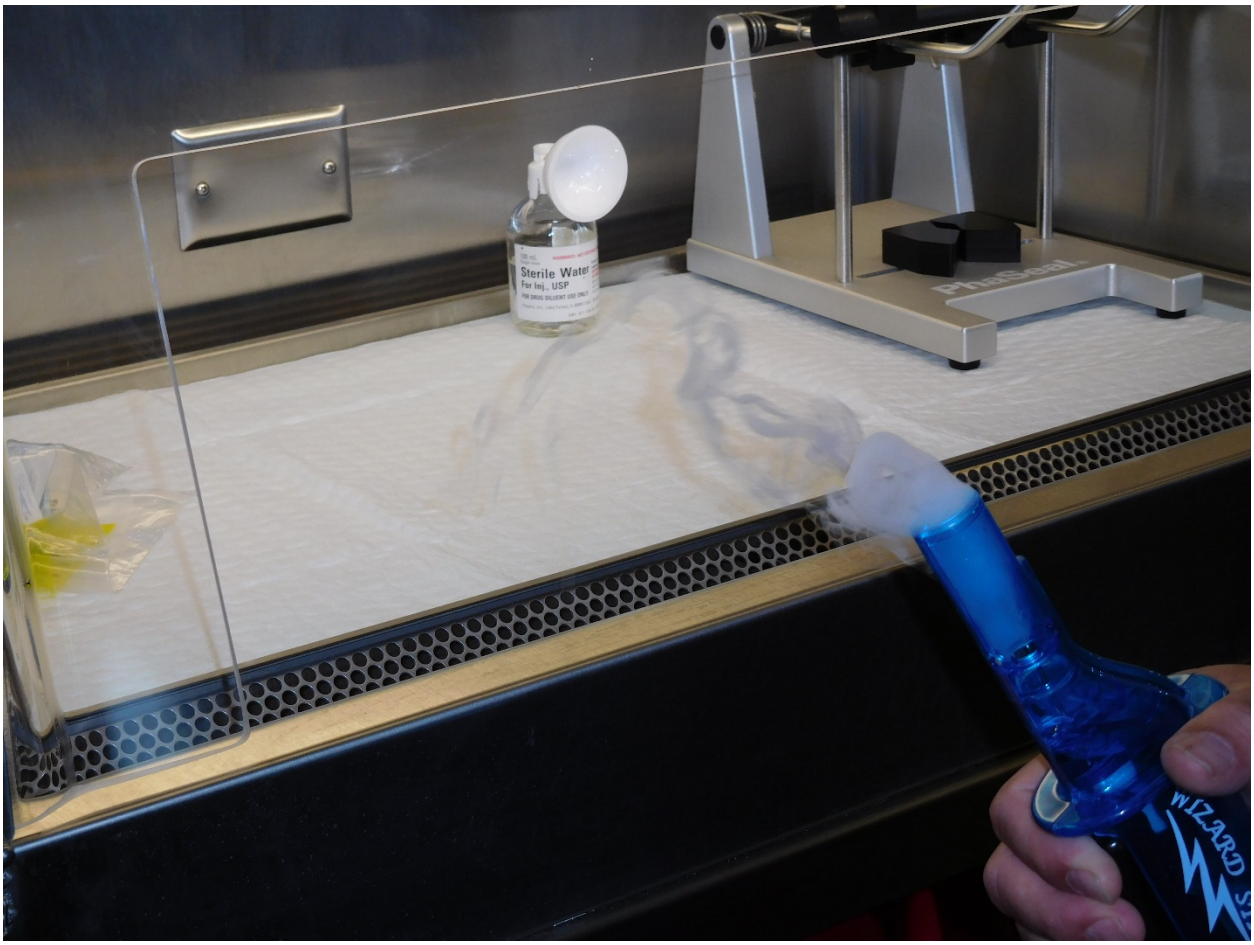

Figure 8. Qualitative smoke test with Wizard Stick Smoke Generator (Photo Credit: NIOSH)

Figure 9. TSI Accubalance® Plus Air Capture Hood (Photo Credit: NIOSH)

Figure 10. Cabinets used to store antineoplastics (Photo Credit: NIOSH)

Figure 11. Chemotherapy drug refrigerator (Photo Credit: NIOSH)

Figure 12. Chemotherapy laundry hamper (Photo Credit: NIOSH)

Figure 13. Chemotherapy waste bin (Photo Credit: NIOSH)

Figure 14. BSC's air flow monitor (Photo Credit: NIOSH)

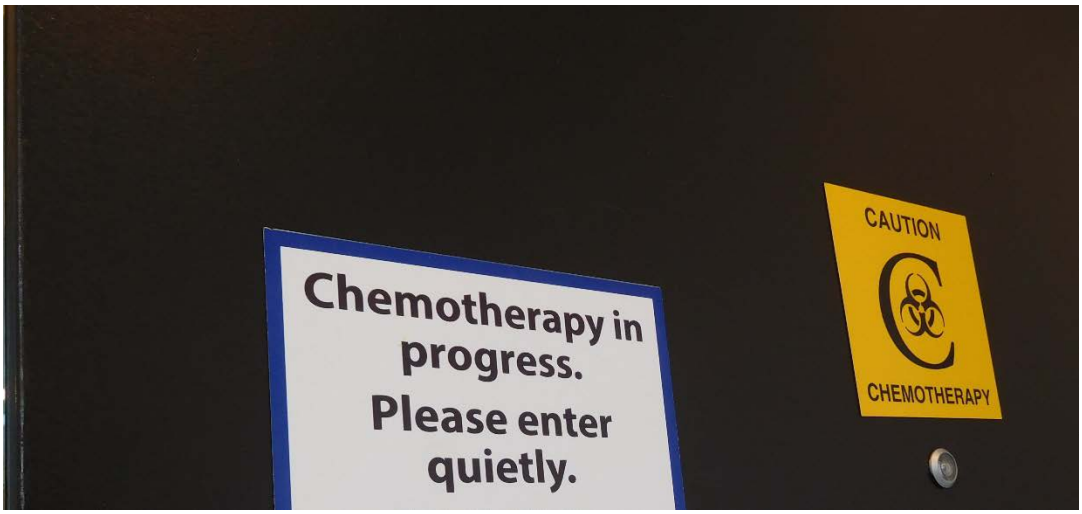

Figure 15. Chemotherapy Treatment in Process sign (Photo Credit: NIOSH)

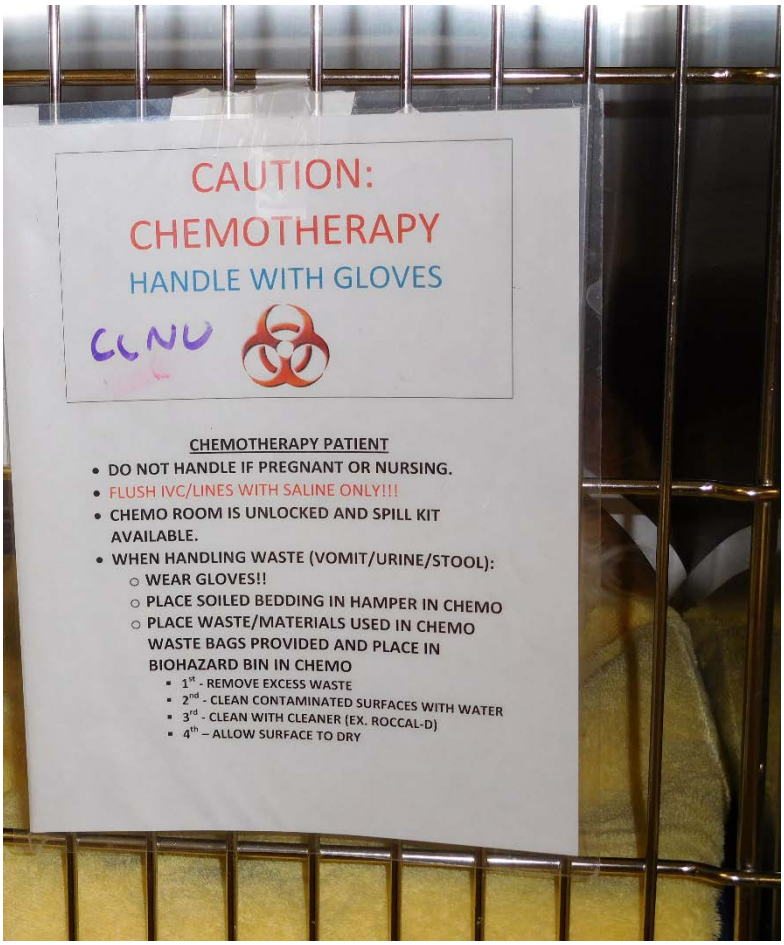

Figure 16. Chemotherapy patient is identified by sign and blanket color (Photo Credit: NIOSH)

Figure 17. Kennel where a vincristine patient was housed (Photo Credit: NIOSH)

Figure 18. Patient given oral cyclophosphamide (Photo credit: NIOSH)

Figure 19. Chemo transport bag with oral cyclophosphamide (Photo Credit: NIOSH)

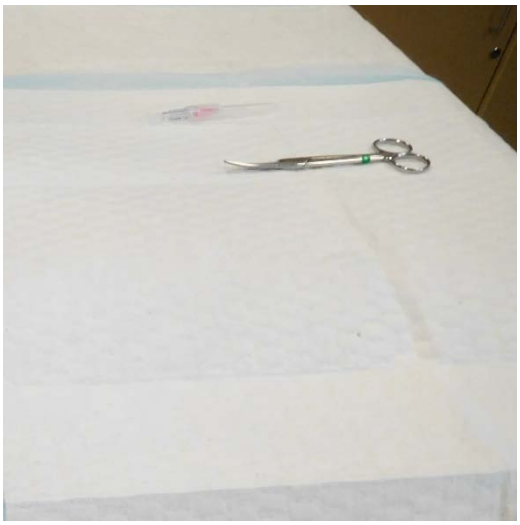

Figure 20. Scissors (Photo Credit: NIOSH)

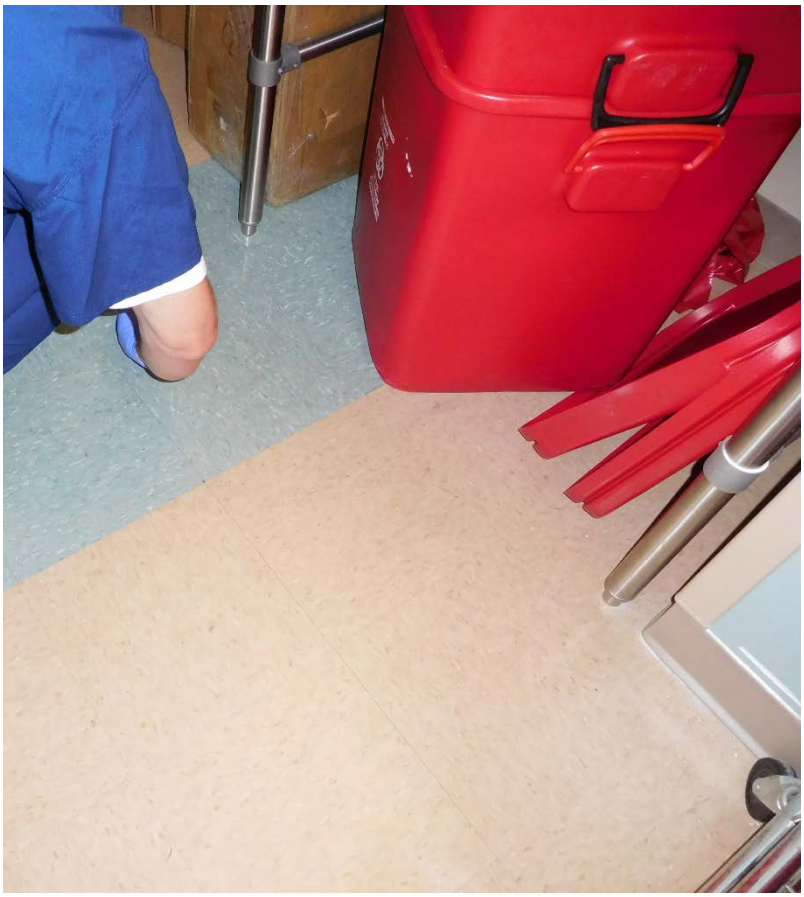

Figure 21. Floor in front of BSC (Photo Credit: NIOSH)

Figure 22. Inside of chemotherapy drug refrigerator (Photo Credit: NIOSH)

Figure 23. BSC exhaust (Photo Credit: NIOSH)

Figure 24. Blood spot on examination table's disposable pad (Photo Credit: NIOSH)

Figure 25. Wipe sample collection from disposable gown (Photo Credit: NIOSH)

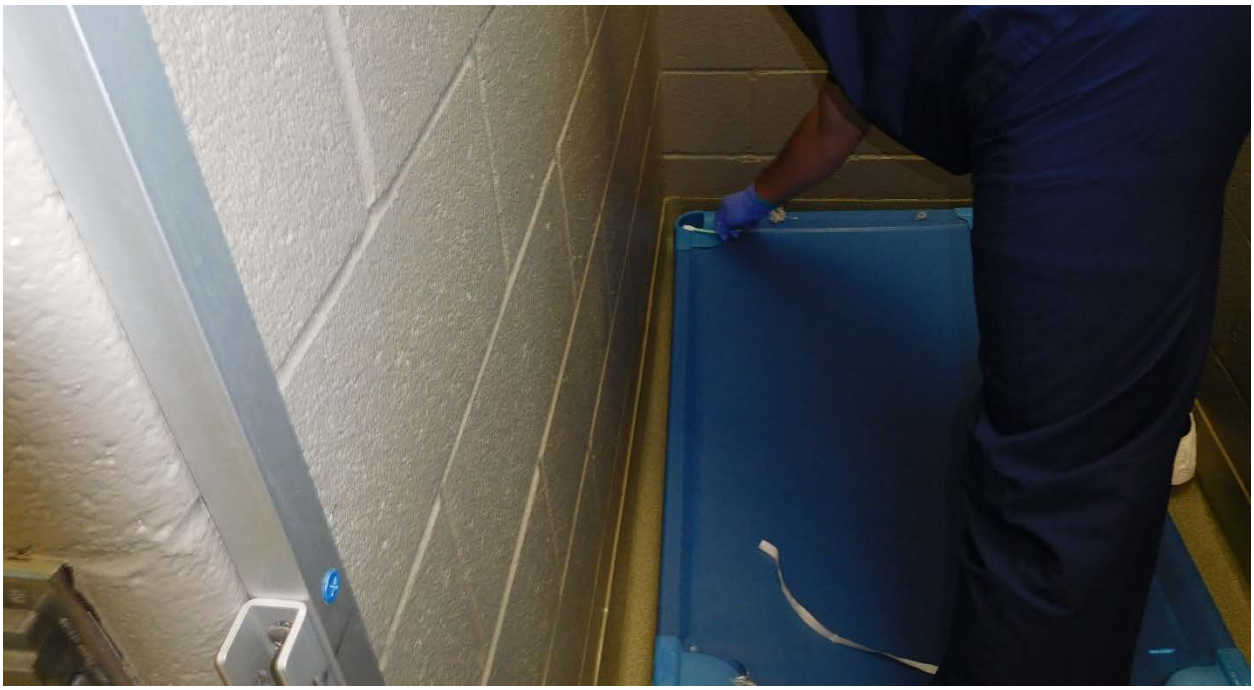

Figure 26. Large kennel (Photo Credit: NIOSH)

Figure 27. Intentional “Hot” wipe sample collected from carboplatin syringe with CSTD adapter. Also shown: PhaSeal vial adapter and adsorbent pad. (Photo Credit: NIOSH)

Figure 28. Keyboard area countertop by radiation oncology area (Photo Credit: NIOSH)

Figure 29. Floor by examination table where chemotherapy is administered (Photo Credit: NIOSH)

Figure 30. Intentional “hot” wipe sample collected from within a vincristine transport bag (Photo Credit: NIOSH)

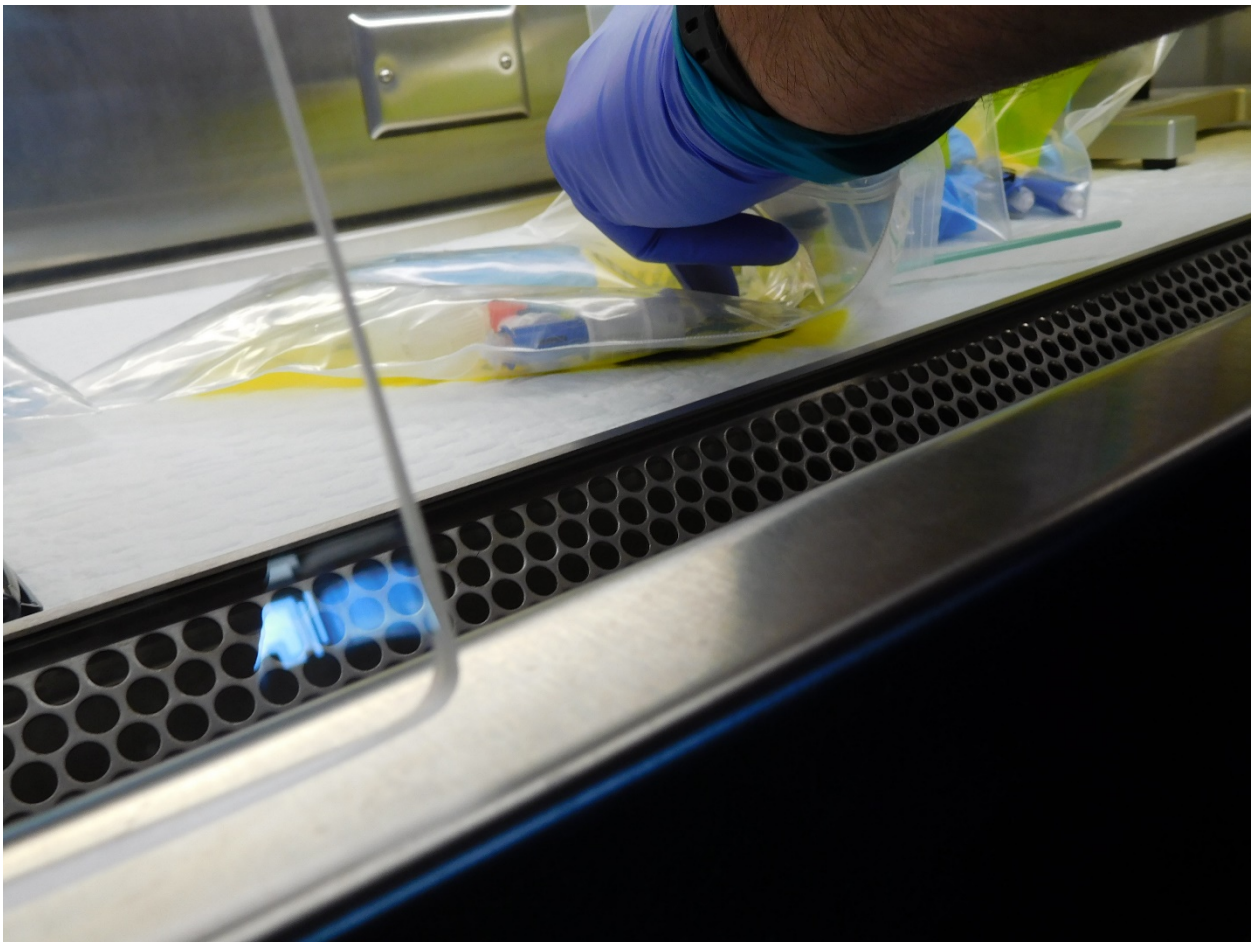

Figure 31. Sample collection from outside of chemo transport bag containing doxorubicin syringe with CSTD adapter. An intentional “Hot” wipe sample was also collected from the doxorubicin syringe. (Photo Credit: NIOSH)

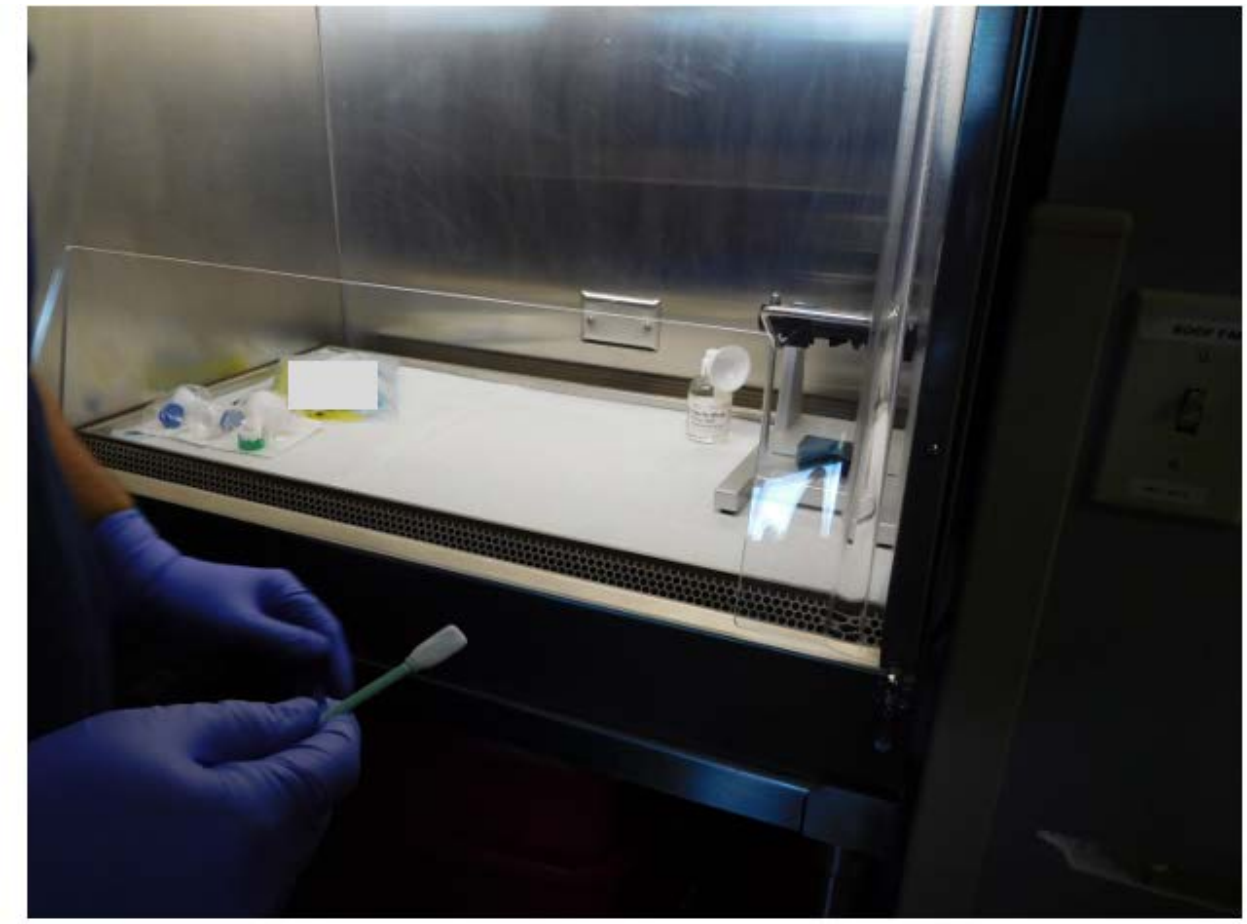

Figure 32. Wipe sample collection from random spots on BSC front surface (Photo Credit: NIOSH)

Figure 33. Exhaust above area where chemotherapy is administered (Photo Credit: NIOSH)

Figure 34. Laundry room floor where yellow chemo bag was placed the day before sampling (Photo Credit: NIOSH)

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