THESIS

OCCUPATIONAL DOSE ASSESSMENT OF ^{64}Cu-ATSM IN A VETERINARY SETTING

Submitted by

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In partial fulfillment of the requirements

For the Degree of Master of Science

Colorado State University

Fort Collins, Colorado

Spring 2014

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ABSTRACT

OCCUPATIONAL DOSE ASSESEMENT OF ^{64}Cu-ATSM IN A VETERINARY SETTING

^{64}Cu-ATSM is an emerging radiopharmaceutical for diagnostic use in Positron Emission Tomography (PET) and has potential utility for radiation therapy but to date there are no studies that assess the occupational doses delivered to workers in either a hospital or veterinary environment. This study consisted of canine patients that were recruited at the Colorado State University James L. Voss Veterinary Teaching Hospital (VTH). The study was aimed at determining the radiation dose to veterinary workers from clinical PET/CT procedures using ^{64}Cu-ATSM. To determine the dose to the workers, each worker was assigned two Electronic Personal Dosimeters (EPDs) to be worn on the chest and waist during the entirety of each procedure. The workers monitored during this study involved included a radiobiologist, a nuclear medicine technician, an anesthesiologist, and a veterinary surgeon. Seven canine patients were imaged over a ten month period with an average mass of 33.7 kg (a range of 20.0 – 55.1 kg) with an average injected activity of 5 MBq kg^{-1}. The dose range for the radiobiologist was 2 -17 µSv, for the nuclear medicine technician 0 -14 µSv, for the anesthesiologist 0 – 12 µSv, and for the surgeon 0 -10 µSv. In a comparison between the results of this study and published literature on occupational exposures from human/veterinary FDG PET/CT procedures, ^{64}Cu-ATSM veterinary PET/CT procedures, on a per patient bias, exposed workers to less radiation.

ACKNOWLEDGEMENTS

Thank you to my advisor and my committee. Especially my original advisor David Zhang, whose early correspondence with me was the inspiration for me to choose this field of study and attend this institution. Thank you to all my professors and guest lecturers that have all helped me reach this point in my academic career. Thank you to my fellow HP students for support through the many classes we shared and for being my support group for my thesis writing. Thank you to Kalielyn Petefish for helping me with the VTH protocols and the EPDs. Thank you to Dayton McMillan for preparing the radiopharmaceutical for each procedure. I wanted to give a special thanks to Jeff, Liz, Chris, Billie, and also the various anesthesiologists and surgeons who participated in this study. Thank you Palo Verde for calibrating the EPDs used in this study. You all made this project progress smoothly with your incredible patience with me. Thank you Nicole for taking me under your wing and helping me make sense of my research.

Like so many others that have come before me, I would not have been capable of attending graduate school without funding. So thank you to the Mountains and Plains Education Research Center and Dr. Johnson. Special thanks to Thomas Johnson who always made sure that I was being funded as well as providing me with many career building opportunities. Thank you NIRS and MAP ERC for funding this project. Thank you Jeanne Brockway and Julie Asmus for taking care of the mountains of paperwork that comes with graduate school. In addition, thank you NIRS and EHRS Department for funding the project.

I want to take this opportunity to thank my parents for blessing me with the opportunities they provided me to reach this point. You have given me unconditional love and support in all my endeavors and without you, none of this would have been possible. I also want to thank the

many friends I have made while here in Colorado for providing me with the many great memories and experiences. Thank you friends back home for providing me with hours of procrastination. I also want to thank the CSU climbing gym for being my escape from homework, exams, and my thesis. John, thanks for being my climbing buddy and keeping me alive as I learned to climb. And thank you to all my other friends and family who humored me on occasion by allowing me to discuss my research with you and pretending to understand and be interested. And finally, I would like to thank God, through which all things are made possible.

DEDICATION

To my best friend and only love, Megan

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INTRODUCTION

Background and Motivation

Positron emission tomography (PET) is one of multiple nuclear medicine imaging techniques. The concept of PET was introduced in the 1950s but the first PET procedure was not documented until 1970 [1-2]. While in its early stages, PET was primarily used only for research purposes, but with the advancement of technology, PET was adopted for use in the medical field. Over the years PET has proved itself useful in many aspects of medicine but especially in the discipline of oncology. PET has distinct advantages over other diagnostic imaging modalities. The main advantage of PET is the ability to provide functional and metabolic information. PET has a distinct edge over imaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI) in the staging, diagnosis, and prognosis of malignant processes due to the ability to provide metabolic information [3-4].

PET is typically combined with CT. The CT provides anatomical information and the PET data is then combined with the CT scans, allowing simultaneous viewing of physiological and anatomical characteristics of the region of interest. The technique of combining PET with CT allows more information to be gathered than either PET or CT could provide separately because the combination of CT data improves the anatomic localization of the metabolic acuity provided by PET. Fusing PET with CT data also helps correct for attenuation based on tissue density values derived from the CT scans. An example of CT and PET/CT is shown below in Figure 1. Figure 1 demonstrates the effectiveness of fusing PET and CT by showing areas of necrosis and rapidly proliferating tissues in the tumor while also showing normal tissues.

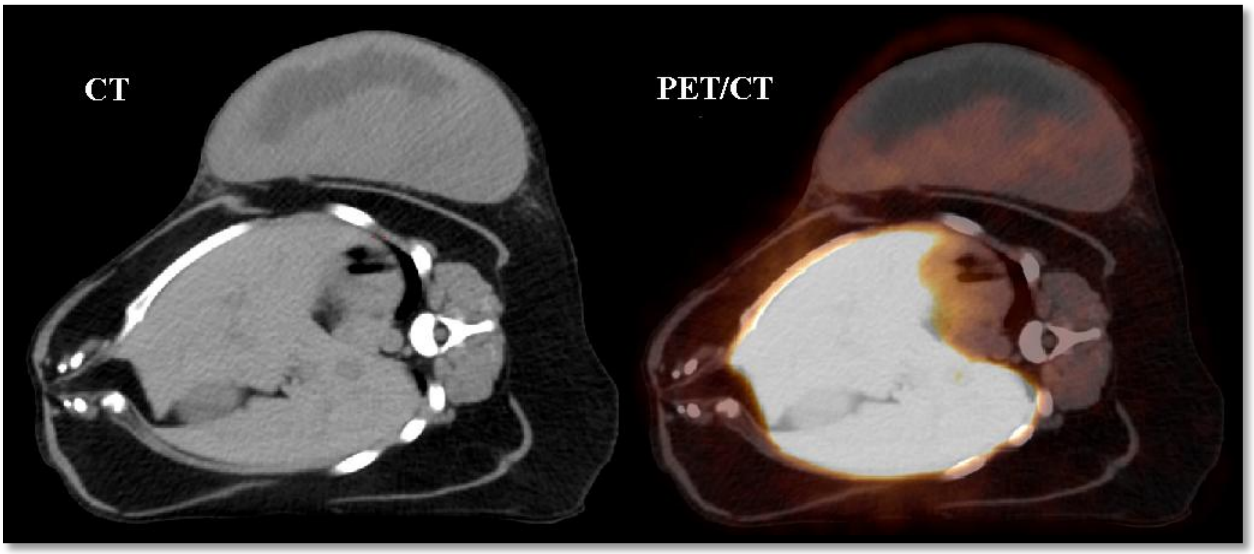

Figure 1: Example of PET/CT – Left: Illustration how CT effectively describes the anatomy of a patient. Right: Example of how fusing metabolic information gathered from PET with CT can increase the clinical significance of the image. The central area of the tumor with decreased metabolic activity derived from PET indicates the necrotic nature of the tumor.

The clinical benefits and widespread use of PET/CT has resulted in a growth in popularity over the past decade. PET/CT became available clinically in 2001 and has since become a standard medical diagnostic procedure. Approximately 1.25 million PET or PET/CT scans were performed in the United States in 2005 according to the Society of Nuclear Medicine and Molecular Imaging. The 2011 IMV Imaging Market Report stated that approximately 1.75 million PET or PET/CT scans were performed annually (0.5 million more than in 2005) and on average 140-160 new PET/CT units are being purchased and installed each year in order to meet the continual rise in demand for PET/CT procedures.

Positron Emission Tomography in Veterinary Medicine

The increasing popularity of PET/CT in human medicine combined with the growing number of new PET studies over the past decade has caused the veterinary community to consider the benefits of PET/CT [5-6]. Veterinary clinics have also begun to be influential in research regarding difficult nuclear medical issues. Examples of recently conducted veterinary

studies include evaluating the utility of PET [7-12], PET/CT [13-15], and PET/MRI [16-17]. Colorado State University (CSU) James L. Voss Veterinary Teaching Hospital was one of the first universities to install a dedicated veterinary PET/CT in 2009. The first PET/CT procedure completed at CSU was of a Boston Terrier on October 27, 2009. Since the installation of the PET/CT in 2009, more than two hundred scans on a variety of animals have been conducted utilizing PET, CT, or combined PET/CT. Dogs, cats, and sheep have been imaged at CSU. As PET/CT continues to be integrated into the medical community for its numerous benefits [1], it can only be assumed that the popularity of the imaging modality will continue to be adopted into the veterinary community as veterinarians become more familiar with the technology and its application [5-6].

Positron Emission Tomography (PET) [7]

PET is a nuclear imaging modality that provides detailed information about how a patient's tissues and organs are functioning physiologically and metabolically. PET is commonly utilized for disease detection, diagnosis, staging, surgical and/or radiation treatment planning, and treatment assessment. In human medicine, PET is primarily used for oncology but PET is also becoming routinely applied in neurologic and cardiac studies [3].

The PET imaging process relies upon radiopharmaceuticals to decay by positron emission. Positron decay only occurs in radionuclides that have an abundance of protons in the nucleus and at least 1.02 MeV of excess energy. When a positron emitter decays, one of the protons in the nucleus is converted into a neutron, positron, and a neutrino; the positron and the neutrino are emitted out of the nucleus with a specific amount of energy. The reason an energy threshold exists for positron emission is because of the conversion of a proton into a neutron,

positron, and neutrino requires energy to create mass. An example of positron decay of copper-64 to nickel-64 is shown below.

$$^{64}_{29}\mathrm{Cu} \rightarrow {}^{64}_{28}\mathrm{Ni} + \beta^{+} + \nu$$

Neutrinos have no net charge and nearly no mass and due to these qualities neutrinos have an exceptionally low probability of interaction with matter and are considered insignificant in radiation protection [37]. The ejected positron will travel a short distance (on the order of a few millimeters) from the original nucleus and will interact with an electron. The positron and electron will annihilate each other during the interaction. The masses of both the positron and the electron are converted into electromagnetic energy and produce two 511 keV gamma rays (photons). The gamma rays are formed simultaneously and are oriented 180 degrees from each other. As mentioned earlier, PET relies upon positron emission to generate a pair of 511 keV photons to image the patient. Figure 2 provides a simple visual example of positron decay and the annihilation photons that are created from the annihilation of the positron with an electron.

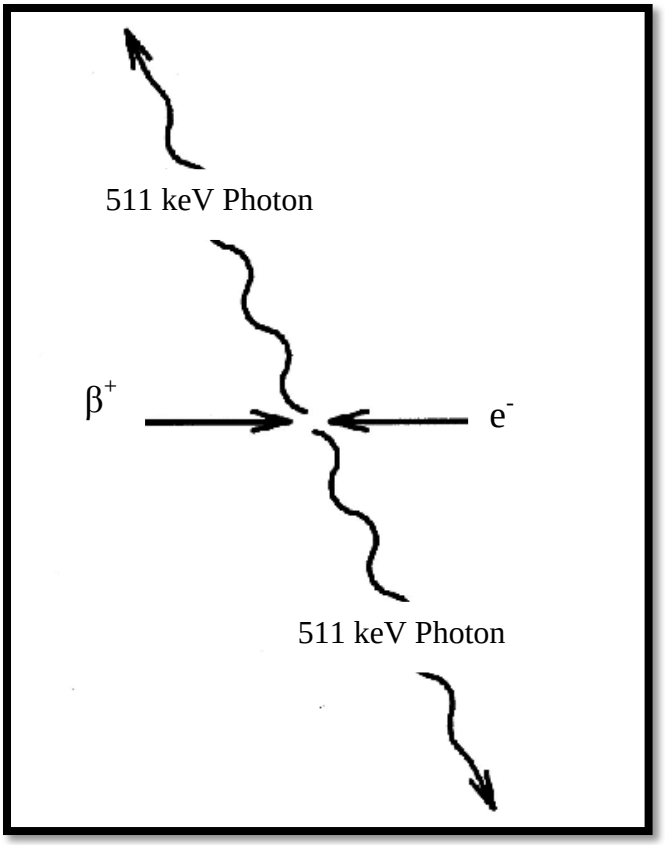

Figure 2: Positron Decay and Annihilation – Simple illustration of a positron and electron annihilating, producing two 511 keV photons approximately 180° in opposite directions.

A limiting factor in PET/CT is the amount of radiation exposure to the patients and to the occupational workers. This study focuses on comparing the doses received by occupational workers during routine procedures from the radiopharmaceutical ^{64}Cu-ATSM with the common radiopharmaceutical Fludeoxyglucose (FDG). There have been multiple studies that assess the occupational dose received by workers in the human medical field utilizing a variety of imaging radiopharmaceuticals [19-30] but the literature on occupational doses to veterinary personnel is extremely limited [2]. Veterinary nuclear medicine offers challenges that are not encountered in human nuclear medicine. For example, it is standard veterinary procedure to place patients under anesthesia to ensure the patient remains stationary for optimal image acquisition. Patients must be closely monitored when under anesthesia. The amount of time anesthesiologists and nuclear technicians spend in close proximity to the patient is increased resulting in increased

occupational exposure. Placing veterinary patients under anesthesia is a key difference between human and veterinary nuclear medicine. Human nuclear medicine patients generally can be told to remain stationary during procedures, eliminating the need for an anesthesiologist. Human patients can also be placed in isolation during the imaging procedure, reducing patient contact with the workers involved. Anesthetized patients require additional workers to be present during the procedure as well as requiring direct contact with the patient. Thus PET/CT procedures that anesthetize patients have the ability to exposure more workers to a higher amount of radiation exposure. Additional differences between veterinary and humane nuclear medicine procedures include, but are not limited to, the quantity of injected radioactivity and patient size variance. The typical radiopharmaceutical doses for humans ranges between 370-740 MBq [31] with up to thirty patients being seen on a single day [32]. In this study, the injected activity ranged from 98.6-218.3 MBq (approximately 5 MBq kg^{-1}), with seven procedures performed over approximately one year or an average of 0.02 patients per day.

Radiation Interactions in Matter

In this study the word "radiation" is defined as energy emission, in the form of either a particle or a wave that will ionize electrons in a material. Radiation can interact with matter by causing excitations (raising an electron to a higher energy level) or by ionizations (creating ion pairs by separating electrons from the nucleus). When radiation interacts with a material by either of these methods, the radiation will lose a portion or all of its associated energy. Energy is lost by the radiation and is deposited in the material. The amount of energy deposited depends on the type of interaction. PET scans are based on the detection of 0.511 MeV annihilation photons, which interact with matter by either the photoelectric effect or by Compton Scattering (primary

mechanism) [33]. Both of these mechanisms are photointeractions because the mechanisms are specific only to electromagnetic radiation (photons).

When radiation is deposited in living tissues, the primary biological effect observed is DNA damage. Photons do not typically damage DNA directly, but photons damage DNA indirectly by interacting with the medium surrounding the DNA (cellular fluids). Interactions with cellular fluids create charged particles which can then lead to free radical formation. Free radicals may cause single stand breaks (SSB) or double stand breaks (DSB) in the DNA. Low level exposures may cause SSB, and larger exposures may result in multiple simultaneous SSB in the same strand of DNA leading to a DSB. SSB can be repaired efficiently while DSB are difficult to repair [34].

Basic Radiologic Principals

Absorbed Dose, *D*, is the average amount of energy absorbed per unit mass of a material. The basic concept of dose assessment is to determine the amount of Absorbed Dose in specific organs or tissues, apply radiation weighing factors (w_R) to take into account the different types of radiation (Equivalent Dose, H_T), then apply tissue weighing factors (w_T) for different organ/tissue sensitivities (Effective Dose, H_E). Radiation protection quantities like Equivalent or Effective Dose are not directly measureable. However, operational quantities can be measured and these quantities can be used to determine equivalent or effective dose. For routine monitoring, operational quantity values are an accurate and precise assessment of effective dose [33].

During routine area monitoring, the operational quantity used to assess effective dose is Ambient Dose Equivalent, $H^*(d)$, where d is depth in millimeters. Since the primary radiation of concern in our study is deeply penetrating 0.511 MeV photons, the dose rate measuring

instruments were calibrated to properly measure the Ambient Dose Equivalent of deeply penetrating radiation, $H^*(10)$. However, many instruments do not measure Ambient Absorbed Dose but instead measure the rate of exposure. Exposure is a measure of the quantity of x-ray or gamma radiation that produces a number of ions in a volume of air. The unit of exposure is the Roentgen (R) and it is defined as 2.58×10^{-4} C kg^{-1} or 1 sC cm^{-3} at STP (T = 273 K, P = 760 mm Hg, and $\rho_{Air} = 1.293 \times 10^{-3}$ g cm^{-3}) [33].

Another operational quantity is Personal Dose Equivalent, $H_P(d)$, where d is depth in millimeters. The difference between Personal Dose Equivalent and Ambient Dose Equivalent is that ambient dose is measured in free air while personal dose is measured incident on the body. The reason for this is that a radiation field is strongly influenced by backscatter and absorption of radiation by the body. Therefore Personal Dose Equivalent is suited for monitoring individuals. Since the radiation of concern from ^{64}Cu is deeply penetrating, worker's dosimeters were calibrated to a depth of ten millimeters, $H_P(10)$.

The SI unit for Absorbed Dose is the Gray (Gy). It is defined as the absorption of 1 J kg^{-1}. The Sievert (Sv) is the unit used to express Equivalent Dose and Effective Dose. A measure of a quantity of radioactivity of a material is the Becquerel (Bq). A Becquerel is defined by the quantity of radioactive material in which one atom is decayed per second or 1 dps. The units of Gy, Sv, and Bq are part of the SI unit system and have not been completely adopted in the US [35]. The US and SI units measure the same quantities but are expressed using differing units. The table below provides a summary of the dosimetric and radiometric units [36].

Table 1: Units of Radioactive Materials and Dose

Measure	Unit	Abbreviation	Conversion(s)
Activity (*A*)	Becquerel	Bq	1 Bq = 2.7×10^{-11} Ci

			1 Bq = 1 dps
	Curie	Ci	1 Ci = 37 GBq
	Gray	Gy	1 Gy = J kg^{-1}
Absorbed Dose (*D*)			1 Gy = 100 rad
	Rad	rad	1 rad = 0.01 Gy
Equivalent Dose (H_T) and	Sievert	Sv	1 Sv = 100 rem
Effective Dose (H_E)	Rem	Rem	1 rem = 0.01 Sv
			1 R = 2.58×10^{-4} C kg^{-1} (air)
Exposure (*X*)	Roentgen	R	1 R = 8.76×10^{-3} Gy (air)
			1 R = 9.5×10^{-3} Gy (soft tissue)

Positron Emission Tomography

PET relies upon the detection of a pair of photons. This is known as coincidence detection, meaning that any single interaction event is ignored unless there is another interaction on the opposite side of the detector. After the detection of a single photon, a period of up to 495 picoseconds may elapse before the detection of the second photon will be considered coincidence and not random [38]. Coincidence detection is a way to discriminate all other radiation processes except for the photons created during the annihilation process. When coincidence photons are detected in the scintillating crystals, the radiation is absorbed in the LYSO crystals. The photons cause the scintillating crystals to produce flashes of light, with the intensity of light being proportional to the amount of radiation absorbed. Each crystal is connected to a Photomultiplier Tube (PMT). A PMT converts the light in the crystals into electrons using a photocathode. These generated electrons are then accelerated across multiple potential differences, creating a cascade of electrons thus amplifying and generating a signal. The figure below shows details of the scintillation process [2].

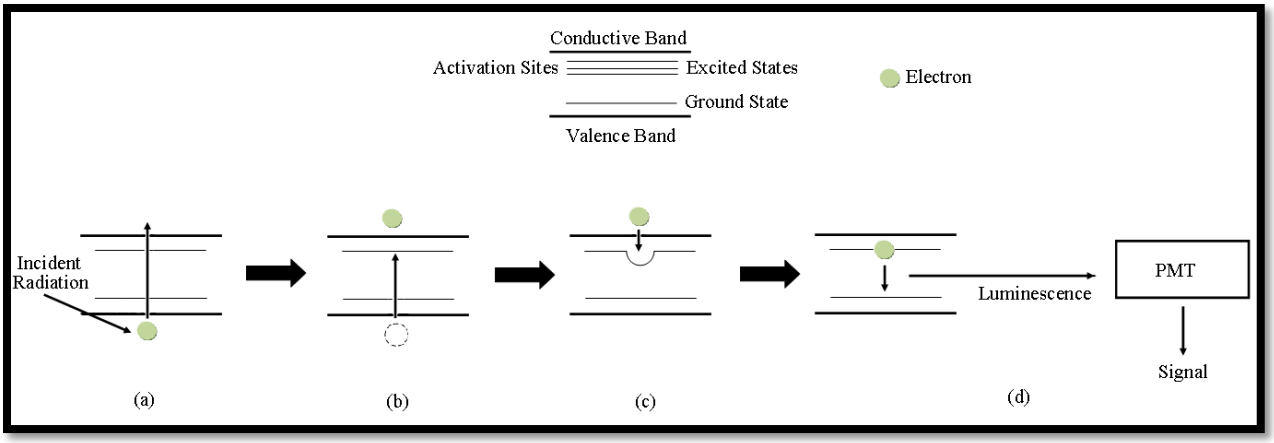

Figure 3: Scintillating Process - Incident radiation interacts with the crystal causing the formation of an electron-hole pair, (a). The hole then migrates to the activation site and ionizes it, (b). The electron is trapped in an ionized activation site, (c). The electron relaxes into the activation ground state by emitting light, which is then converted into an electric signal by the PMT, (d) [45].

The signal generated by the PMT is then passed through a preamplifier, energy level discriminators and on to coincidence circuitry for appropriate processing. The straight line between the two annihilation photons is known as the line of response and the PET scanner utilizes the fact that the origin of annihilation photons occurs on the line of response. Detectors with Truflight technology, also known as time-of flight technology, measure the difference in time (as the photons travel at the speed of light) between the detection of the coincidence photons, and use this information to attain more precision in the location of the annihilation event. There are several ways to reconstruct an image from numerous lines of response, but the end result is that the statistics collected from the analysis of all coincidence events can be used to create a three dimensional map of radioactivity within the patient's body, as shown by the figure below.

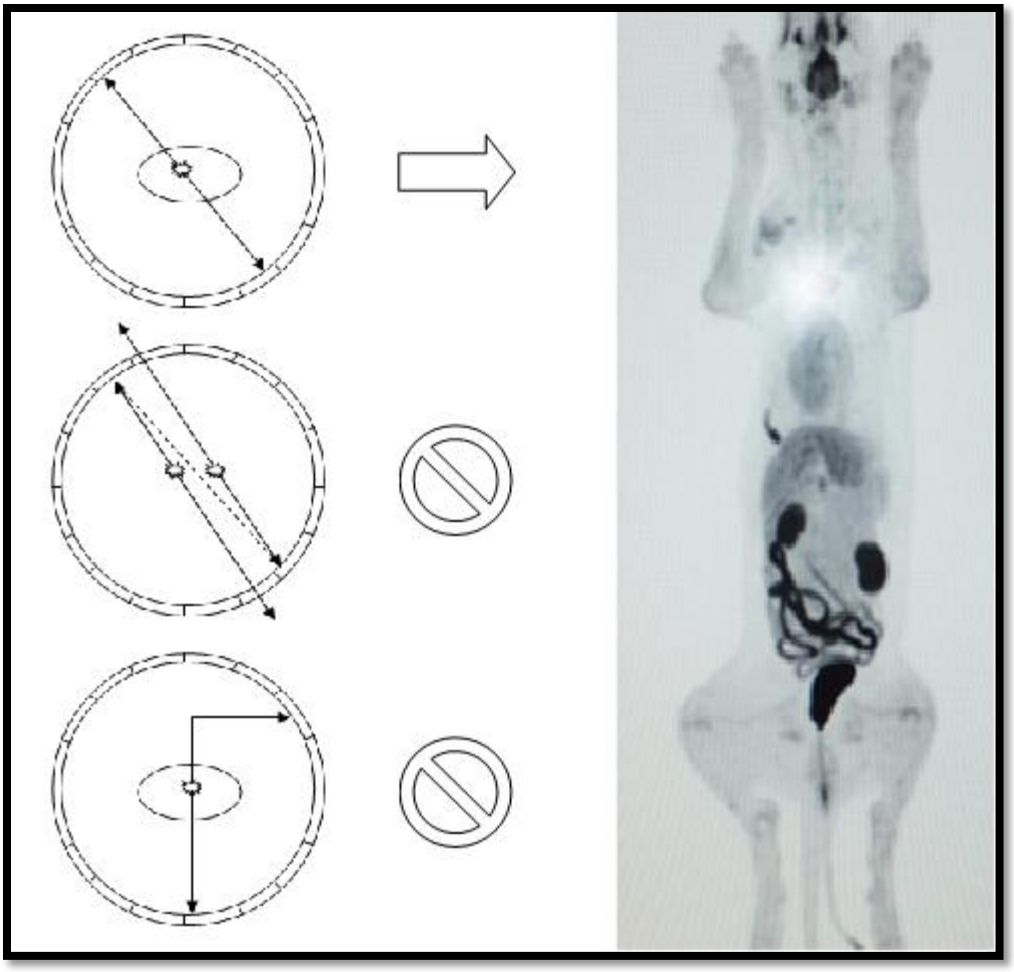

Figure 4: PET Imaging – Individual pairs of annihilation photons ether scatter or generate a signal. The summation of signals from many annihilation pairs pieced together can be used to generate a map of a body.

Radionuclide Details

Radiopharmaceuticals are formed by taking a positron emitting radionuclide and binding it to a biologically relevant compound such as glucose, water, or ammonia. This compound is known as a tracer and the tracer will determine the biological distribution of the radiopharmaceutical. A short half-life is a desirable trait of radionuclides that are used in PET, to study biological processes that have relatively rapid turnover. In general, having a short-lived radiopharmaceutical allows better quality images to be obtained quickly. The predominant radionuclide used in PET is ^{18}F (half-life of 110 minutes) which is commonly labeled with a

glucose compound to become Fludeoxyglucose (FDG). FDG is currently the only PET radiopharmaceutical approved by the FDA for cancer imaging. Because of the acceptance and use of FDG in the medical field, FDG has become the ideal standard to compare potential imaging radiopharmaceuticals against.

The radionuclide used for this study was ^{64}Cu, which has a half-life of 12.7 hours. One of the distinct advantages of ^{64}Cu is that the longer half-life allows the nuclide to be produced off-site and shipped to the clinic but the radionuclide is still short enough to be useful for diagnostic imaging. ^{64}Cu has a complex decay scheme compared to other positron emitters used for imaging, such as ^{18}F. Approximately 97% of the ^{18}F decays are from positron emission while just fewer than 18% of decays from ^{64}Cu are via positron emission as depicted in Figure 3.

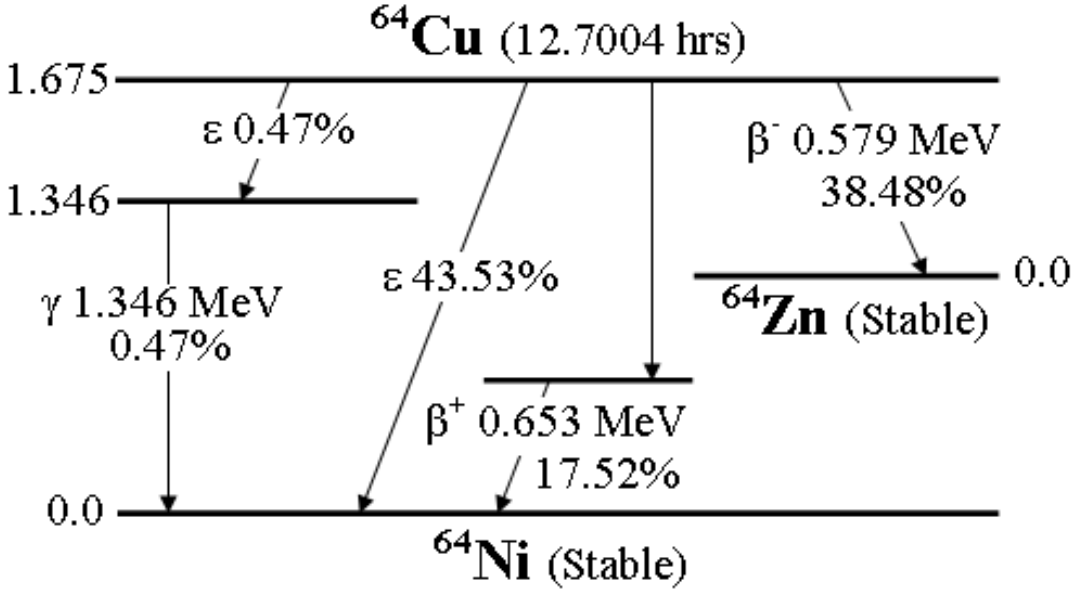

Figure 5: ^{64}Cu Decay Scheme

^{64}Cu-ATSM is a complex of copper(II) paired with the tracer diacetyl-bis (N4-methylthiosemicarbazone), as shown in Figure 4. One of the unique aspects of ^{64}Cu-ATSM is its hypoxia-selectivity. Hypoxia is a key element to consider for tumor diagnosis and radiotherapy planning. Hypoxia occurs when oxygen levels in tumor cells are below normal due to poor

vasculature in the tissue. The lack of oxygen causes the cells to become resistant to specific types of radiation, such as β^- or γ radiation, that are commonly used for therapy [34]. However, despite the exhaustive amount of work describing *in vitro* chemical, biological, and spectroscopic studies as well as *in vivo* research using PET imaging and pO_2-dependence of cellular uptake, the exact mechanism of localization and trapping of ^{64}Cu-ATSM in cells is still uncertain [39].

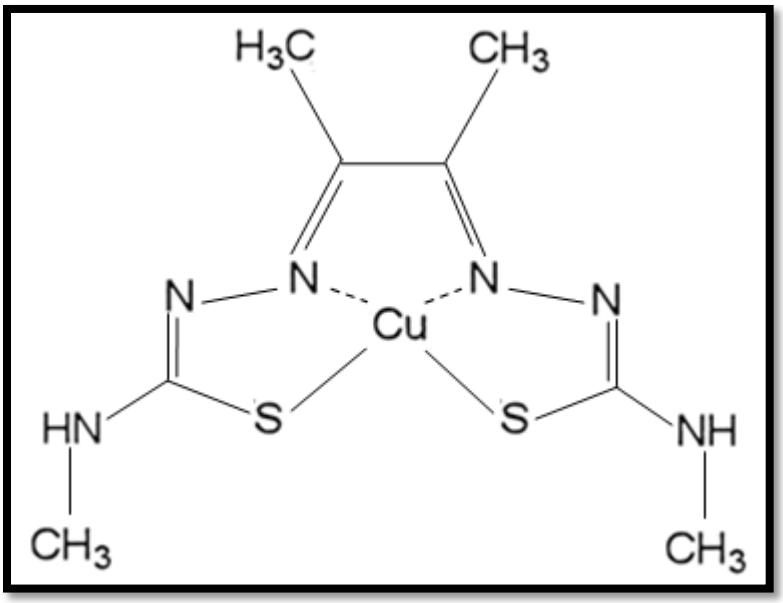

Figure 6: Copper (II) (diacetyl-bis (N4-methylthiosemicarbazone)) Structure

There are two well known theories for describing the trapping mechanism of ^{64}Cu-ATSM in a cell. The first was proposed in 1997 by Fujibayashi *et al* [40]. Evidence supported by experimentation showed that Cu-ATSM accumulated in hypoxic myocardium by means of biological reduction by nicotinamide adenine dinucleotide dependent enzymes. The reduction of Cu-ATSM only occurs in hypoxic cells and the Cu-ATSM becomes irreversibly trapped upon intracellular reduction. The reduction mechanism involves an electron transfer from ubiquinone oxidoreductase using nicotinamide adenine dinucleotide as a two-electron donor. Since the enzymes required for this reduction process are located only in the mitochondria of the cells, it was concluded that the mitochondria is the primary location for trapping of Cu-ATSM [40]. This

method of trapping was furthered by Obata *et al* in 2001. This study showed that in subcellular fractions of Erhlich ascites tumor cells, it was not the enzymes from the mitochondria but those from the microsome/cytosol fraction that mediated the reduction of Cu-ATSM. It was also discovered that the reduction mechanism was heat sensitive and could be enhanced by adding both nicotinamide adenine dinucleotide and reduced nicotinamide adenine dinucleotide phosphate to the cells of interest and that alone neither nicotinamide adenine dinucleotide nor reduced nicotinamide adenine dinucleotide phosphate were capable of reducing Cu-ATSM unaccompanied by the compound [41]. However, these methods have been found to not be fully consistent with observed cellular uptake and washout studies [39].

The second method was proposed by Dearling *et al* in 1998. It was postulated that the Cu-ATSM reduction is reversible and occurs in both normoxic and hypoxic cells. Since the reduction is reversible, the reduction creates an unstable anionic copper(I) complex during uptake. It is then suggested that this copper(I) complex then slowly disassociates in hypoxic cells, leading to the irreversible trapping of the copper(I) ion. If the cell was normoxic, the normal levels of oxygen would oxidize the copper(I) complex to produce neutral copper ions, which would then diffuse back out of the cell [42-44].

Objectives of Study

The purpose of this study was to determine, per patient, the occupational dose delivered to the veterinary personnel working with ^{64}Cu-ATSM imaging agent for PET scans at the Colorado State University's James L. Voss Veterinary Teaching Hospital. The study was conducted by providing veterinary personnel two Electronic Personal Dosimeters (EPDs) to be worn on the chest and waist during each imaging procedure. EPDs measure real-time radiation doses to medical personnel and provide a direct way to calculate the dose received by each

participating member of the study. The VTH workers involved in this study were the following: nuclear medicine technologists, anesthesiologists, and radiobiologists. The dose measured by each of the distributed EPDs was recorded for each of the imaging procedures. Seven canine patients of varying breeds and sizes over a period of approximately one year were imaged. Only the first four patients enrolled into the study were tumor bearing dogs. The remaining three canines enrolled in the study were purpose breed research dogs. Table 2 provides a summary of the patient tumor information.

Table 2: Patient Tumor Information

Patient #	Tumor Classification	Tumor Grade
1	Myxosarcoma	Not Available
2	Soft Tissue Sarcoma	Grade 3
3	Osteosarcoma	Grade 3
4	Soft Tissue Sarcoma	Grade 2

To reiterate, differences exist in human and veterinary PET/CT procedures that leads to an increased potential for veterinary workers to be exposed to higher levels of radiation. The hypothesis of this study is that the doses delivered on a per patient basis to the medical staff of the VTH from PET procedures utilizing ^{64}Cu-ATSM would be comparable to the levels of exposure delivered to human medicine workers from PET procedures using Fluorine-18 (^{18}F) radiopharmaceuticals, specifically FDG. The second part of the hypothesis is that the PET veterinary occupational exposures from ^{64}Cu-ATSM procedures will be equivalent to the occupation exposures seen in veterinary PET using FDG.

MATERIALS

Colorado State University Positron Emission Tomography

The PET/CT scanner at the CSU VTH is a Philips Healthcare Gemini Truflight Big Bore with separate housings for the PET and CT gantries [38] (Figure 5). The scanner consists of a ring (made of 44 individual rings) of scintillation crystals that encircle the patient's body, covering 18 cm of the patient's body at any single moment. There are a total of 28,336 lutetium yttrium oxyorthosilicate (LYSO) scintillating crystals in the detector array [38].

Figure 7: Philips Gemini Truflight Big Bore PET/CT

Prior to a PET scan, an appropriate radiopharmaceutical must be injected intravenously and given time to distribute throughout the body. The radiopharmaceutical is absorbed by cells while being distributed throughout the body. The absorption of the radiopharmaceutical is described as uptake, which varies based upon the metabolic activities of the cells and the biological properties of the radiopharmaceutical. As described earlier, PET is commonly paired with CT; PET/CT provides both detailed anatomical and physiological data as well as providing

precise localization and quantification of radiopharmaceutical uptake. At the VTH, PET is combined with CT to estimate/correct for self-attenuation/absorption and helps improve PET image quality.

Electronic Personal Dosimeters

EPD's were MPG Instruments Mirion Technology model DMC 2000S (San Ramon, CA). The EPD's utilize a single solid state semiconductor detector for detecting gamma radiation. The DMC 2000S is compliant to IEC 1283 and ANSI 4220A standards. The DMC 2000S instantaneously measures, records, and displays the amount of radiation dose from 10 µSv to 10 Sv or radiation dose rates from 0.01 mSv hr^{-1} to 10 Sv hr^{-1}. The DMC 2000S is only sensitive to x-ray or gamma radiation with energies between 50 keV to 6 MeV and the accuracy of the model is within ±10%. The EPDs were calibrated at Palo Verde Power Generating Station July of 2012 and again Oct. of 2013. During the study, the EPDs were operating in autonomous mode, with the doses being manually read and recorded in the units of millirem (mrem). The radiation dose was only recorded once the worker wearing the EPDs completed their assigned duty.

METHODS

Human Use Protocol

The measurement of worker doses was approved by the CSU Institutional Review Board as a minimal risk study. The human use protocol was approved on July 18th, 2012. The human use protocol Notice of Approval is attached as Appendix A.

Animal Use Protocol

The proper care and treatment of the animals used in this study was approved by the CSU Institutional Review Board as a minimal risk study. The animal use protocol Notice of Approval is attached as Appendix B.

Electronic Personal Dosimeters

The study was task oriented to elucidate doses to generic workers performing a task in a position, so as to eliminate variability in the study. At the beginning of each procedure, each worker was given two EPDs, one worn on the chest and the other at the waist. A control EPD was placed in the Animal Cancer Center (ACC) room 148 to monitor background radiation during each of the procedures. The difference in height and weight of each participating worker was not included in the study. Each worker returned their EPDs to ACC 148 to be stored with the control EPD upon completion of their task. Figure 8 demonstrates the positioning of the EPDs during a procedure. The workers wore one of the distributed EPDs in the left front shirt pocket and the other in their pants pockets or in their belt like a pager. Exact EPD placement on the chest or waist was at the discretion of each worker to minimize interference with duties.

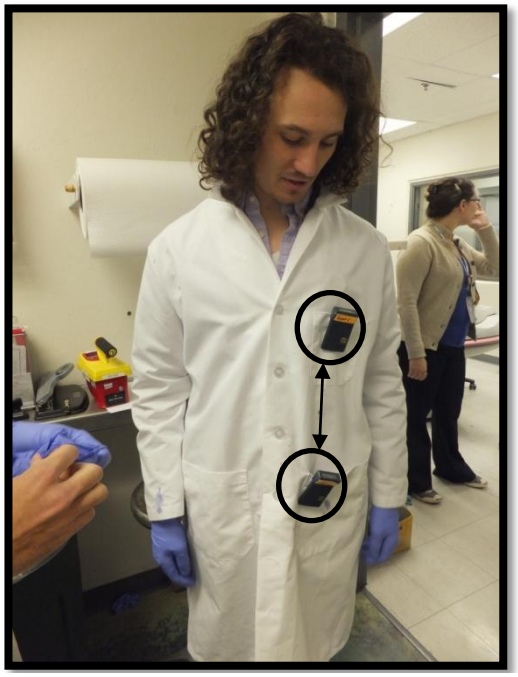

Figure 8: Positioning of EPDS on Workers

Each job position was designated by an abbreviation. Table 3 gives a description of each of the job positions, the corresponding EPDs, along with the duties each worker was expected to perform.

Table 3: Job Descriptions Corresponding to Assigned EPDs

EPD Label	Job Title	Worker Duties
PREP	Radiobiologist	Label ^{64}Cu with ATSM and prepare required amount of activity to be injected
TRANS	Research Associate in Computed Tomography (CT) and Magnetic Resonance Imaging (MRI)	Transport the radiopharmaceutical from the hot lab to the PET/CT suite to be injected
ANEST	Anesthesiologist	Anesthetize the patients, to include catheterization, intubation/extubation, general monitoring and recovery of the patients.
NUC MED	Research Associate in Computed Tomography (CT) and Magnetic Resonance Imaging (MRI)	Primary PET/CT technician. Performs, supervises, oversees safety, provides clinical instruction in CT, PET/CT, and MRI studies
SURGEON	Clinical DVM	Collects samples of tumor tissue for histological assessment

Patient Information Summary

Seven canines were enrolled to be imaged with ^{64}Cu-ATSM during this study. The Clinical Trials team of the Flint Animal Cancer Center was responsible for the recruitment of the four tumor bearing canine patients (patients 1-4). The criterion for selecting patients was that the patient must be in sufficient health to be able to tolerate a long anesthetic process without needing direct medical care. Other criteria included the diagnosis of a soft tissue sarcoma ≥ 4 cm in diameter amenable to biopsy. All the owners of possible patients were informed of the study and offered enrollment. The remaining three dogs enrolled in the study were imaged as part of a study to evaluate the potential use of penicillamine to reduce the uptake of ^{64}Cu-ATSM by the liver.

The seven patients were imaged between the 15th of January 2013 and the 28th of October 2013. Each dog was imaged with ^{64}Cu-ATSM. A summary of the patients is shown below in Table 4.

Table 4: Patient Summary

Patient	Breed	Injected Activity [MBq]	Mass [kg]	Injected Activity / Mass [MBq / kg]
1	Mixed	206.1	42.0	4.9
2	Vizsla	98.6	20.0	6.0
3	Labrador	218.3	36.5	4.9
4	Great Dane	215.5	55.1	3.9
5	Hound	108.1	28.0	6.7
6	Hound	159.1	27.0	5.9
7	Hound	170.0	27.0	6.3
Mean ± SD	-	179.4 ± 42.1	33.7 ± 11.9	5.5 ± 1.0
Range	-	98.6 to 218.3	20.0 to 55.1	4.9 to 6.7

Figure 9 is a picture of the largest patient enrolled in the study, Molly, a Great Dane. Molly was the 4th patient to be enrolled in the study and carried a Grade 2 soft tissue sarcoma.

Figure 9: Largest Patient in Study: 55.1 kg Great Dane

The amount of injected activity was fairly consistent on a per mass basis, approximately 5 MBq kg^{-1}. Figure 10 shows the relationship between injected activity and patient mass.

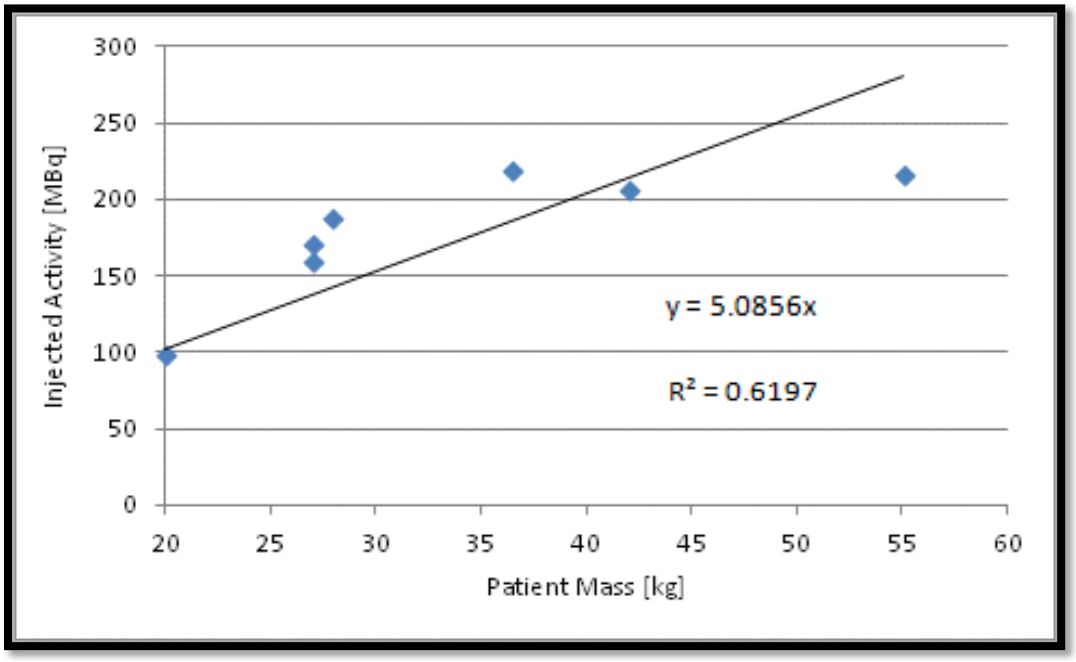

Figure 10: Patient Body mass Plotted against the Injected Activity of 64Cu-ATSM

Animal Imaging Protocol Summary

Approximately fifty mCi (or 1.85 MBq) of ^{64}Cu produced by University of Wisconsin was received at the VTH the morning of each PET scan (the quantity of radioactivity varied based on the weight of the dog being imaged). The ^{64}Cu was delivered in a syringe housed in a lead containment vessel, known as a "Pig" (Figure 11).

Figure 11: Lead Pig Housing – Left: Extracting the 64Cu from the lead pig to determine the activity of the shipment. Right: A picture of the lead pig inside of the shipping container.

After the arrival of the ^{64}Cu at the VTH, the dog was taken to anesthesia in preparation for the procedure. The dog was placed under anesthesia in Room C108. Once the patient was under anesthesia, urinary and intravenous (IV) catheters are put into place. The dog was then transported from the anesthesia suite to the PET/CT suite (Room H106) and then placed upon the table of the PET/CT. The dog was then positioned on the table for the imaging procedure (Figures 12 -13).

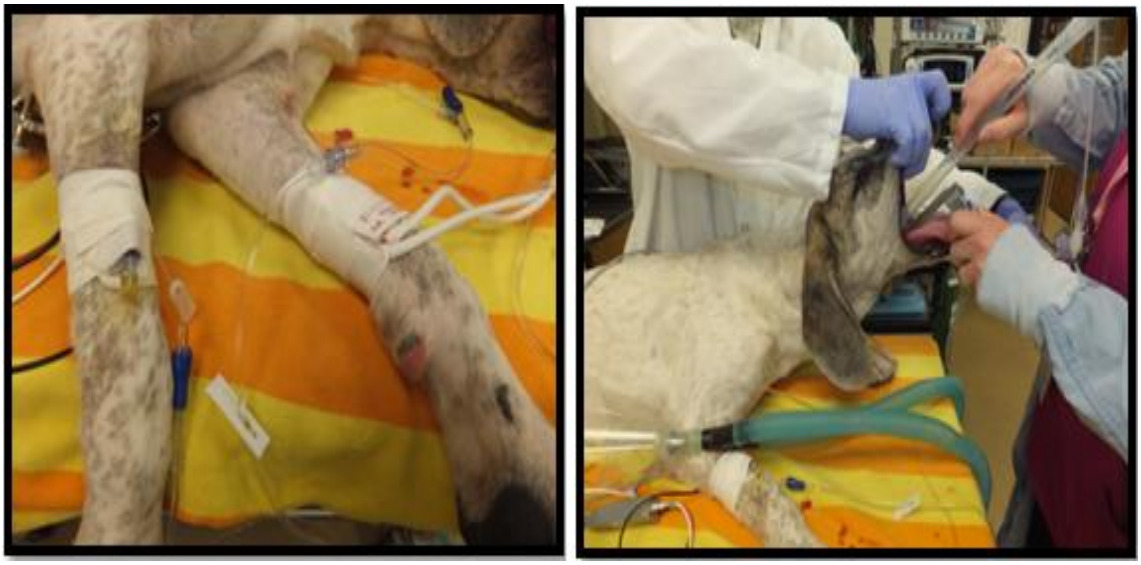

Figure 12: Placement of Urinary and Intravenous Catheters – Left: Intravenous catheters placed for the purpose of the injection of the radiopharmaceutical and anesthesia. Right: Placing tubes to assist the dog with breathing while under anesthesia.

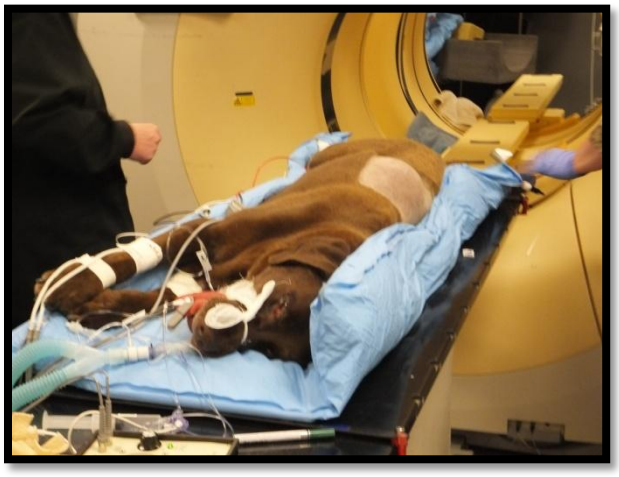

Figure 13: Patient Placement on PET/CT Gurney

Positioning the canine patient may include adjusting ECG leads or covering the patient with blankets in order keep the dog comfortable (Figure 14).

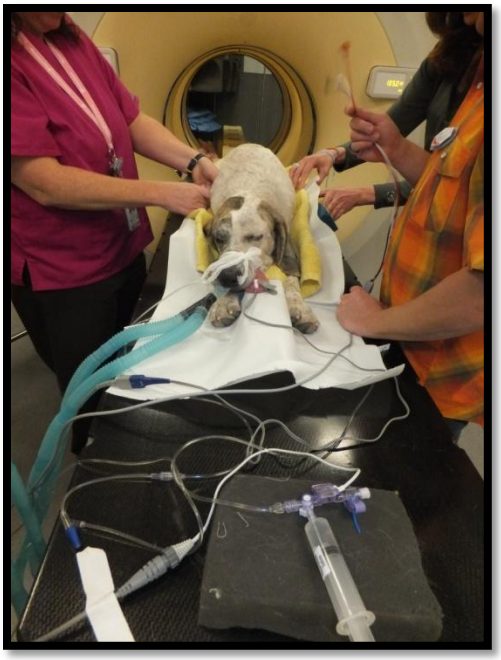

Figure 14: Patient Adjustment Before PET/CT Scans

While the dog was being prepared for the PET/CT procedure, the ^{64}Cu was labeled with diacetyl-bis(N4-methylthiosemicarbazone (ATSM). The labeling was performed in the VTH radiopharmaceutical lab located in room 159a (Figure 15).

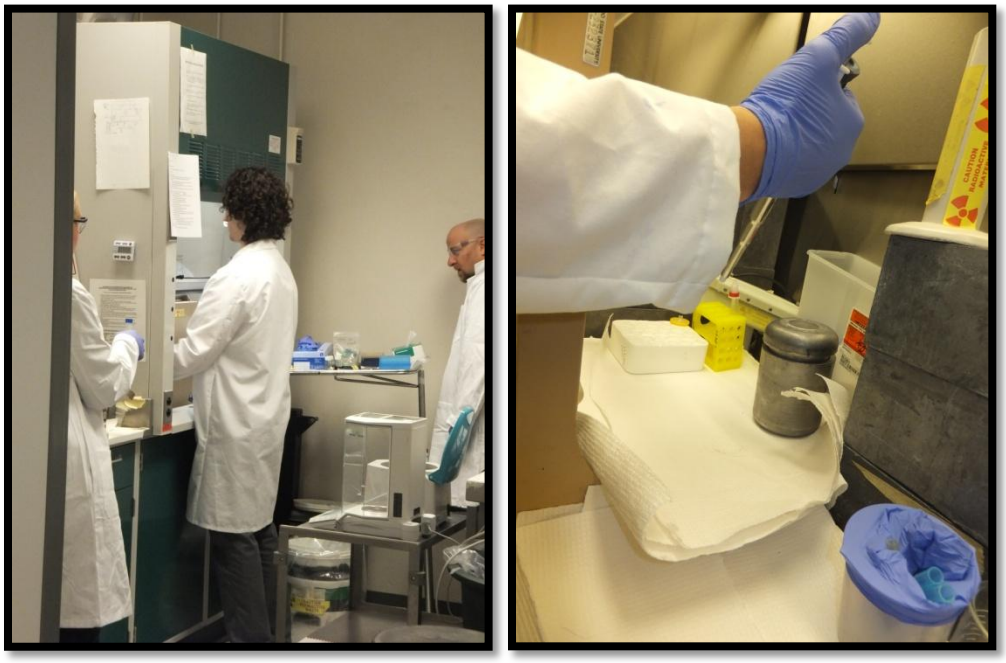

Figure 15: Radionuclide Labeling of 64Cu with ATSM in VTH

Once the radiopharmaceutical was labeled, it was then placed in a lead lined container, transported to the PET/CT suite, and injected into the patient as depicted in the figures below.

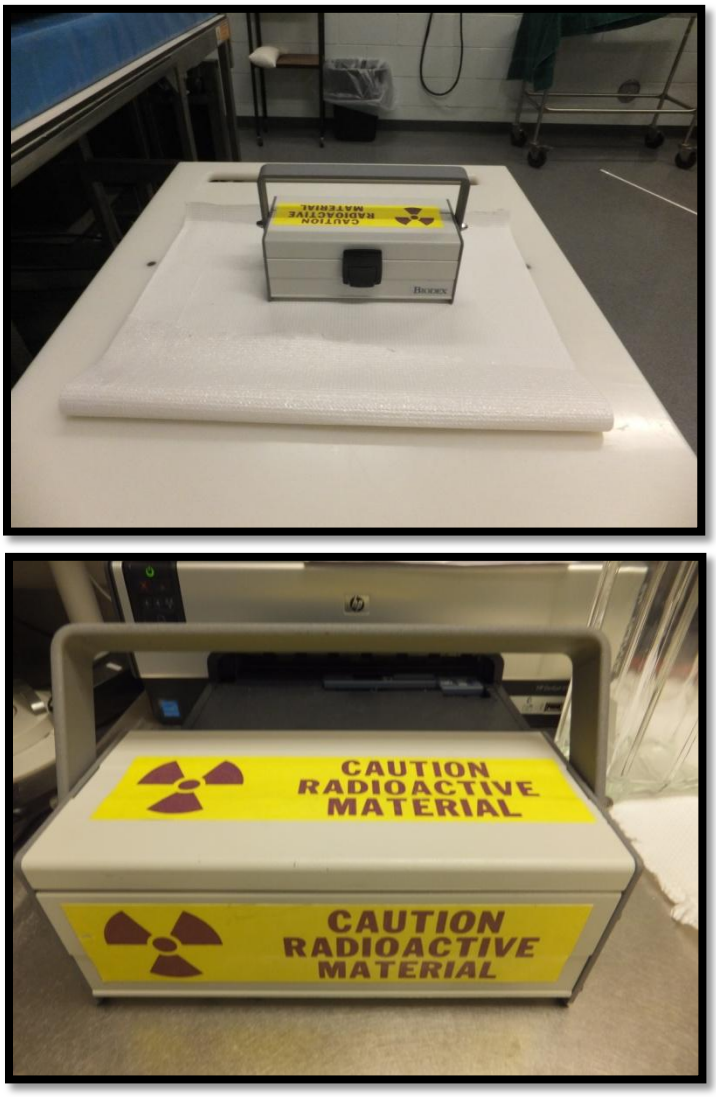

Figure 16: Lead Pig Used to by Technologist to Transport Radiopharmaceuticals

After the injection, the residual dose was transported back to the laboratory used to prepare the radiopharmaceutical to ascertain the net injected activity. Dynamic and/or static PET and CT scans were then performed to collect appropriate diagnostic imaging data.

Once the imaging procedure was complete, all catheters were removed and the canine patient was removed from the PET/CT table and transported to the nuclear medicine ward

located in ACC 162. The dog was then woken up from under anesthesia and allowed to recover (Figure 17).

Figure 17: Canine Patient Recovery

The patient was held in a shielded kennel area until the maximum skin surface reading was ≤ 2 mR/hr (17.5 µGy/hr). The patient was monitored and walked to allow voiding of bladder and bowels. The patient was walked in a designated area that is closed off by a chain link fence. Appendix D shows a sample of a data collection sheet used in the study and Appendix E describes the floor plan of the VTH. In the protocol described above, the potential for radiation exposure to occupational workers exists in the following tasks:

- Dose Package Receipt
- Radiopharmaceutical Preparation
- Dose Transportation
- Injection

- Room Entry During PET/CT Scans to Check Patient
- Moving Patient from Table to Gurney
- Patient Transportation to Nuclear Ward
- Caring for Patient Post-Imaging during Post-Anesthetic Recovery

RESULTS

Data Analysis- EPDs

Data was collected for five different workers during the seven imaging procedures. A detailed description of the workers' positions is in Table 2. All five workers did not participate in each imaging procedure. Also, additional data was collected only for the radiobiologist labeling ^{64}Cu with ATSM because ^{64}Cu-ATSM was also purchased for other research purposes. Table 5 summarizes the readings from the EPDs assigned to the workers. The doses were recorded in millirem (mrem) but are presented here in microSieverts (µSv).

Table 5: Chest and Waist EPD Dose Summary for all Workers (µSv)

Procedure	Anest Waist	Anest Chest	Nuc Med Waist	Nuc Med Chest	Prep Waist	Prep Chest	Surgeon Waist	Surgeon Chest	Trans Waist	Tras Chest
Procedure 1	3	2	11	11	3	3	7	10	0	0
Procedure 2	12	12	2	2	3	2	2	2	0	0
Procedure 3	1	5	0	1	1.1	1.2	3	4	0	0
Additional[1]	-	-	-	-	7	5	-	-	-	-
Procedure 4	3	4	5	8	17	14	0	1	0	0
Procedure 5	2	4	8	14	7	5	-	-	0	0
Procedure 6	1	3	2	3	8	6	-	-	1	0
Procedure 7	2	2	4	7	5	5	-	-	0	0
Mean ± SD	3.4 ± 3.9	4.6 ± 3.5	4.6 ± 3.8	6.6 ± 4.9	7.7 ± 4.6	6.2 ± 4.2	3.0 ± 2.9	4.3 ± 4.0	0.1 ± 0.4	0.0 ± 0.0
Range	1 to 12	2 to 12	0 to 11	1 to 14	3 to 17	2 to 14	0 to 10	1 to 10	0 to 1	0 to 0

A statistical analysis was conducted on several factors that might impact the dose received by the workers during a procedure. The following factors were examined: job duty,

[1] An additional order of ^{64}Cu was prepared for research not related to this study and only the radiobiologist was involved

location of EPD, duration of exposure in minutes, and injected activity in megabecquerels. The mass of patients was not included in the analysis because the injected activity per unit mass was constant throughout the study. It is known that the mass of the patient will alter the attenuation of radiation, but it was beyond the scope of this study to examine the attenuation due to the mass of the patient. Since the EPDs assigned to the transportation of the radiopharmaceutical recorded negligible amounts of exposure, those EPDs were excluded from analysis. Table 6 summarizes the factors for the EPDs worn on the chest. The values listed in Table 6 are identical to the factors for the EPDs worn on the waist, meaning that the only difference in the factors is the location of the EPD.

Table 6: Radiation Dose Affecting Factors for EPDs Located on the Chest

		Anest	**Nuc Med**	**Prep**	**Surgeon**
Procedure	Activity [MBq]	Duration [min]	Duration [min]	Duration [min]	Duration [min]
1	206.1	264	263	79	107
2	98.6	245	245	141	87
3	218.3	280	280	154	77
Additional	-	-	-	70	-
4	215.5	281	281	113	24
5	188.1	400	400	113	-
6	159.1	394	392	122	-
7	170.0	309	308	97	-
Mean ± SD	179.4 ± 42.1	310.4 ± 62.2	309. 9 ± 61.9	111.1 ± 28.7	73.8 ± 35.4
Range	98.6 to 218.3	245 to 400	245 to 400	70 to 154	24 to 107

Only two factors were statistically significant (p-value ≤ 0.05) based on linear regression analysis: duration of exposure ($p = 0.006$) and position of EPD ($p = 0.000$). Since limiting

exposure time has already been established as a core principal of external radiation safety [33], the relationship between dose and the location of EPD was examined further.

The recorded doses of the EPDs worn on the chest were plotted against the doses recorded on the EPDs worn on the waist as shown in Figures 18 to 21.

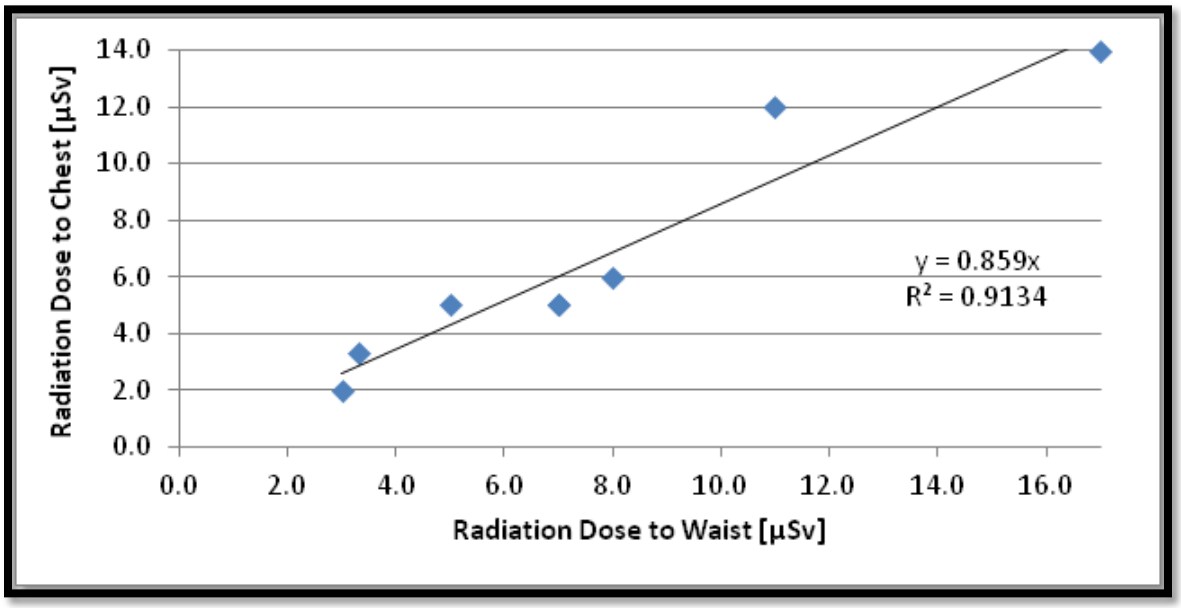

Figure 18: Chest vs. Waist EPD Analysis of Radiobiologist Preparing the Radiopharmaceutical (Prep)

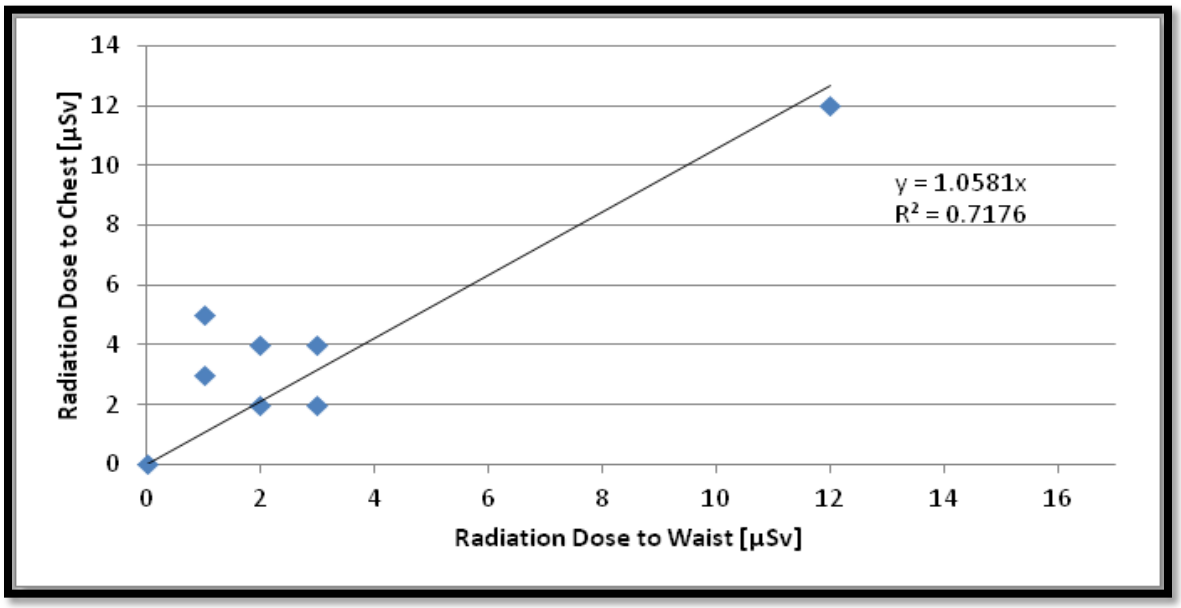

Figure 19: Chest vs. Waist EPD Analysis of Anesthesiologist (Anest)

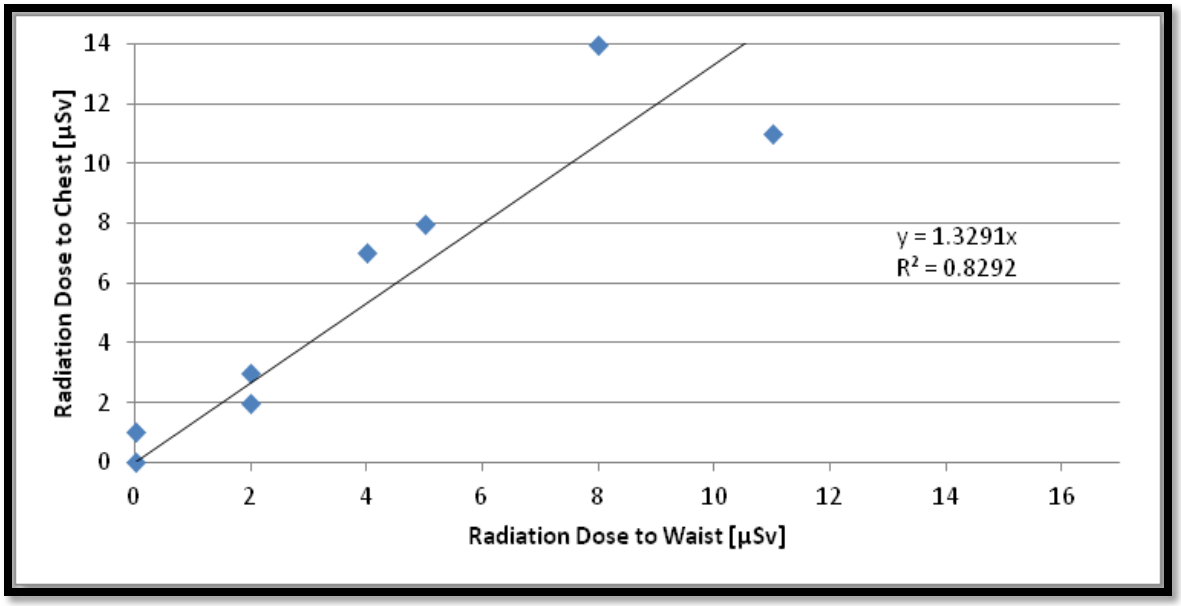

Figure 20: Chest vs. Waist EPD Analysis of Nuclear Medicine Technician (Nuc Med)

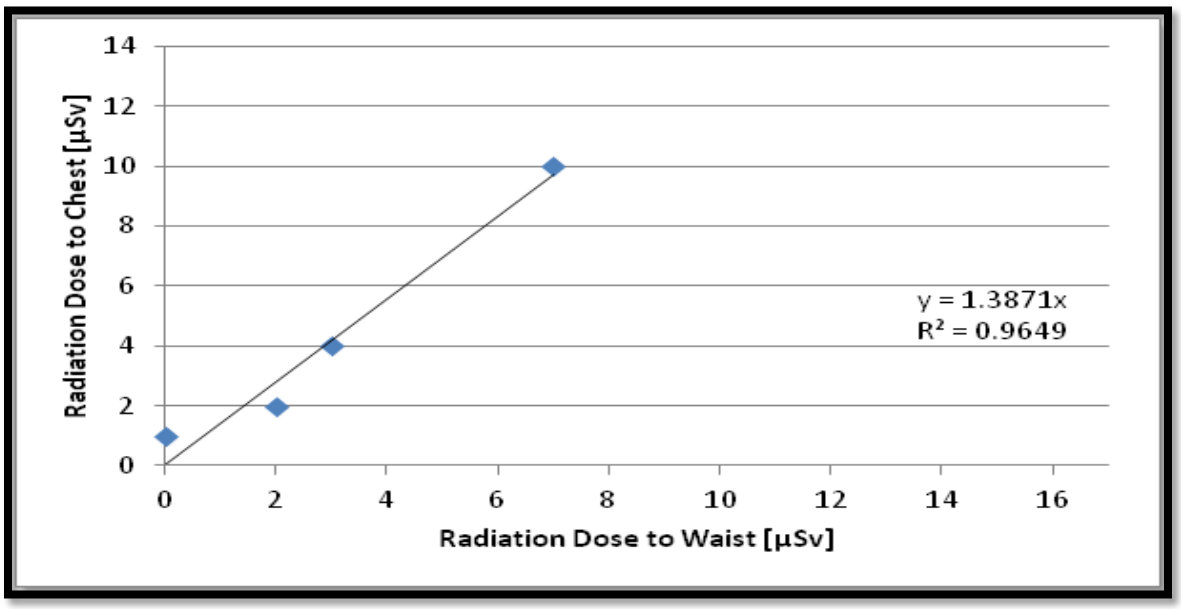

Figure 21: Chest vs. Waist EPD Analysis of Surgeon

Table 7: Summary of EPD Linear Regression Analysis

	Prep	Anest	Nuc Med	Surgeon
R^2 Value	0.9134	0.7176	0.8292	0.9649
P Value	0.0002	0.0019	0.0012	0.0169
Slope	0.859	1.0581	1.3291	1.3871

Table 7 provides a summary of numerical analysis presented in Figures 18 – 21. The anesthesiologist (Anest), the nuclear medicine technician (Nuc Med), and the surgeon plots all have a slope ≥ 1, meaning that the chest EPD recorded a higher dose than the waist EPD. The EPDs assigned to the radiobiologist (Prep), produced the reverse situation, with a slope ≤ 1 and the waist EPDs recording a higher dose. To avoid confusion, the location of the EPD does not change the radiation dose to the worker, only the accuracy of the measurement. The location of the EPD alters the accuracy of the measurement by affecting the geometry of the system. Placing an EPD at different locations on the torso will change the distance between the radioactive source (the patient) and the EPD. Since the quantity of interest is the maximum whole body dose, the EPD should be placed on the part of the torso closest to the radioactive source to achieve an accurate measurement, as Figures 18 - 21 illustrate.

It was assumed the radiation dose was zero upon energizing each EPD used in the study and background radiation was constant during all procedures. By assuming each EPD is absent of any radiation dose upon energizing, the linear regressions in Figures 15 - 18 are forced to pass directly through the origin. This creates a simple linear equation that describes the radiation dose to EPDs worn on the chest as a function of radiation dose of EPDs worn on the waist.

Data Analysis- Comparison to Human Studies

There is a dearth of literature on worker doses from the use of ^{64}Cu-ATSM for PET studies. There have been no reported studies that assess the occupational exposure to medical staff from human ^{64}Cu-ATSM procedures but there have been studies that estimate the absorbed radiation dose to human patients. A concise summary of these studies are shown in Table 8. All doses reported in Table 8 are mGy per MBq.

Table 8: Summary of Absorbed Radiation Doses from ^{64}Cu-ATSM to Human Patients

	Lead Author	
Organ	Laforest [11]	Lewis [48]
Liver	0.390	0.187
Kidneys	0.088	0.064
Spleen	0.047	-
Gallbladder	0.068	-
Adrenals	0.032	-
Heart Wall	0.029	-
Pancreas	0.056	-
Upper Large Intestine	0.022	-
Lungs	0.021	-
Stomach	0.021	-
Small Intestine	-	0.109
Urinary Bladder	-	0.019
Total Body	0.026	0.026

Although some dosimetric studies with ^{64}Cu-ATSM has been published, a comparison between patient and occupational doses is not valid. Patient dose is from internal exposure

directly from the injected radiopharmaceutical and tends to focus more an individual organs while occupational doses are external to the body and focus on whole body exposure. Internal and external dosimetry also rely on drastically different mathematical models to describe the exposure. Since no occupational studies have been conducted with ^{64}Cu-ATSM, a comparison with another PET radiopharmaceutical was made. Fludeoxyglucose (FDG) is the predominant PET imaging agent and is currently the only radiopharmaceutical certified by the FDA. In addition to FDG being the "golden Standard" of PET, multiple studies have been published examining occupational exposure to workers from FDG PET/CT scans in both human and veterinary medicine. The radionuclide used in FDG is ^{18}F and since both ^{18}F and ^{64}Cu are used as PET imaging agents, comparing the two radiopharmaceuticals provides a valid perspective on the occupational exposures from ^{64}Cu-ATSM. The comparison of two different isotopes is reasonable in ascertaining the worker doses, as PET emissions are uniformly 0.511 MeV gamma rays. Table 9 shows a concise summary of the doses to workers in human medicine from various studies. All values reported in Table 9 are study averages.

Table 9: Radiation Dose to Workers from F18-FDG PET in Human Literature

Lead Author	Dose Per Scan [μSv]	Dose per MBq Injected [nSv MBq^{-1}]	Instrumentation
Benatar [20]	-	18	EPD
Biran [47]	7.2	19.5	TLD and EPD
Carson [21]	5.1	13.6	EPD
Chiesa [22]	5.9	11.8	Geiger Muller PD
Dalianis [23]	3.3	8.6	TLD and EPD
Demir [46]	6.3	12.2	TLD and EPD
Guillet [24]	3.2	9.4	TLD and EPD
Leid-Svegborn [25]	4.5	15	TLD

McCormick [27]	14.0	-	TLD
McElroy [19]	10.0	18.6	EPD
Roberts [28]	4.5	15	TLD
Robinson [29]	4.1	11.0	TLD
Seierstad [30]	8.8	25.0	EPD and TLD
Mean ± SD	6.4 ± 3.2	-	-
95% Confidence Interval	4.4 to 8.4	-	-

Making a comparison between the mean radiation doses of the veterinary workers reported in Table 5 and the confidence interval reported in Table 9, three of the eight mean radiation doses are outside of the confidence interval on the low side with the rest of the means falling inside of the interval (Table 10, all values in μSv).

Table 10: Comparison of ^{64}Cu-ATSM Occupational Veterinary Worker Doses Compared to 95% Confidence Interval from FDG Human Occupational Doses

	Anest Waist	**Anest Chest**	**Nuc Med Waist**	**Nuc Med Chest**	**Prep Waist**	**Prep Chest**	**Surgeon Waist**	**Surgeon Chest**
^{64}Cu-ATSM Means	3.4	4.6	4.6	6.6	7.7	6.2	3.0	4.3
95% FDG Confidence Interval (4.4 – 8.8)	Outside 3.4 < 4.4	Inside	Inside	Inside	Inside	Inside	Outside 3.0 < 4.4	Outside 4.3 < 4.4

Note that the studies summarized in Table 9 are all worker doses from human patients and the average injected activity of FDG (not ^{64}Cu-ATSM as in this study) is typically on the order of approximately 370 - 740 MBq, compared to the average injected activity of 179 MBq of ^{64}Cu-ATSM for canine patients. It is surprising that the majority of the mean radiation doses fall inside of a 95% confidence interval because on average the amount of radioactivity involved in

the FDG studies is a factor of two to four times more than the amount of radioactive copper involved in the canine study. The majority of worker mean radiation doses from veterinary use of ^{64}Cu-ATSM are within the 95% confidence interval of human occupational exposures from FDG, one may postulate that on average, veterinary procedures using ^{64}Cu-ATSM deliver a worker radiation dose comparable to that received from workers attending to human FDG procedures.

Data Analysis- Comparison to Veterinary Studies

No studies on ^{64}Cu-ATSM occupational exposure to veterinary workers were located in the literature. Only a single study by Martinez et al was found that discusses veterinary occupational exposures from FDG [2]. Martinez created a mathematical model, for both canine and feline patients, to estimate radiation dose to specified workers. The results of Martinez's study are summarized in Table 11. The values reported in Table 11 are predictions from her model and are reported in µSv from the average amount of injected activity (155.8 MBq) used for the canine patients.

Table 11: Summary of Veterinary Occupational Exposure from Canine FDG Procedures from the Mathematical Model Developed by Martinez [2]

	Tech 1	**Tech 2**	**Tech 3**	**Average Tech**	**Anesthesia**	**Observer**
Chest	14.8	12.2	9.5	12.2	6.9	4.3
Waist	11.2	8.6	6.0	8.6	3.3	0.7

Different workers were monitored in the veterinary FDG occupational exposure study compared to our ^{64}Cu-ATSM study. FDG is produced and shipped ready for injection, eliminating the need for preparing the radiopharmaceutical. In addition, veterinary surgeons were not used in the FDG study. Also the technologist responsibilities were split into three different

tasks (Tech 1, Tech 2, Tech 3) allowing individual monitoring of each worker performing the duty of the nuclear technologist. The average dose of all three nuclear technicians is included in Table 11. The ^{64}Cu-ATSM study did not include an observer and was omitted.

A comparison of the mean veterinary FDG nuclear medicine technologist and anesthesiologist values and the 95% confidence interval for the ^{64}Cu-ATSM nuclear medicine technologist and anesthesiologist are shown here in Table 12. The average doses to the nuclear medicine technologist in the FDG study exceed the 95% confidence interval for both the chest and waist while the anesthesiologist is inside the interval for both positions of the EPD. Since half of the values are outside of the confidence interval on the high side, the results imply that occupational radiation doses from veterinary FDG procedures are higher than veterinary ^{64}Cu-ATSM procedures.

Table 12: Comparison of Veterinary Occupational Exposures of FDG and ^{64}Cu-ATSM for Nuclear Medicine Technologists and Anesthesiologists

	Anesthesia Waist	**Anesthesia Chest**	**Average Tech Waist**	**Average Tech Chest**
FDG Means	3.3	6.9	8.6	12.2
95% ^{64}Cu-ATSM Confidence Interval for Nuclear Medicine Tech Chest (3.0 - 10.2)	-	-	-	Outside 12.2 > 10.2
95% ^{64}Cu-ATSM Confidence Interval for Nuclear Medicine Tech Waist (1.8 – 7.4)	-	-	Outside 8.6 > 7.4	-
95% ^{64}Cu-ATSM Confidence Interval for Anesthesiologist Chest (2.0 – 7.2)	-	Inside 2.0 < 6.9 < 7.2	-	-
95% ^{64}Cu-ATSM Confidence Interval for Anesthesiologist Waist (0.5 – 6.3)	Inside 0.5 < 3.3 < 6.3	-	-	-

DISCUSSION

Variability- Anesthesiologist

Anesthesia technicians rotate through clinical practices, providing anesthesia services for PET/CT patients. Several different anesthesiologists provided services for patients involved in the ^{64}Cu-ATSM study and occasionally the anesthesiologist would change during a procedure so that a single imaging procedure might expose multiple anesthesia technicians (during the analysis, the assumption was made that only a single person was exposed to radiation per imaging procedure). Although each anesthesia technician provides essentially the same care to each patient, each technician has a personal style of care. Another dynamic factor that impacts the anesthesia process is the patient. Each patient responds differently to anesthesia and recovers differently from anesthesia. Differences in response and recovery to anesthesia greatly impact the amount of attention a patient needs. This variability extends to other non-anesthesia related work as others are required to help with patient's positioning, set up, and recovery. The majority of radiation dose to the anesthesiologist is from recovering the patient but dose is also accumulated during room and patient position post injection.

The frequency of room entry is dependent upon the patient and is also a judgment call for the anesthesiologist. Recovery is the main opportunity for additional exposure to the anesthesiologist due to the time spent in close proximately to the patient. Recovery is usually a combined effort of both the anesthesiologist and nuclear medicine technician. It is difficult to predict how a patient will recover from anesthesia; a patient may wake up smoothly and require little assistance or may wake up quickly and require physical restraints and medical intervention. It was not uncommon during the imaging procedures for both the anesthesia and nuclear medicine technologist to have no recorded radiation dose until patient recovery. An

approximation for recovery is forty-five to sixty minutes for the patient to recover to the point where direct human supervision is not required.

Variability- Surgeon

The activities of the veterinary surgeon also displayed a large degree of variance between procedures. Each tumor biopsy was performed by a different veterinary surgeon. Each patient biopsy was in a different location and the tumor types were not consistent throughout the study[2]. The location of the tumor seemed to be the largest factor impacting the duration of time the surgeon spent in close proximity to the patient. For example, the first patient of the study had a tumor filled with a mucus fluid that greatly expanded the size of the tumor. The biopsy process was difficult due to the fluid, and the surgeon remained in close contact with the patient for a longer duration of time than usual due to the complicated geometry of the tumor. The fluids of the tumor were also released during the biopsy adding additional radiation dose to the surgeon. Another example was imaging procedure 3, where the tumor was a large sarcoma on the side of the patient. Collecting the biopsy sample from patient 3 took a fraction of the time compared to patient 1 as there were no complicating factors involved.

Variability- Procedures

Procedures 1 - 4 were conducted with cancer bearing dogs that were volunteered for the study. Procedure 1 went according to the protocol with no abnormalities to report. The nuclear medicine technician was the primary care giver during patient recovery.

Procedure 2 went smoothly until patient recovery. Patient 2 was a Vizsla and this particular breed is known to have difficulty when recovering from anesthesia. The patient awoke and attempted to walk and stand. The Vizsla patient then had to physically be restrained to keep

[2] See Table 1 for tumor information

the patient lying down. The anesthesiologist physically held the patient for a period of time, greatly increasing the amount of radiation dose received.

During procedure 3 there was a problem with the Philips PET/CT machine. After the radiopharmaceutical was injected, software complications prevented the nuclear medicine technician from initializing the CT scans. This problem lasted for approximately ninety minutes. A Philips technician remotely operated the PET/CT machine to diagnose and correct the problem. Since ^{64}Cu-ATSM has an unusually long radiological half-life of 12.7 hours, delaying the imaging process by 1.5 hours only reduced the injected activity to 92% of the original activity, and allowed for quality diagnostic images to be produced. The recovery of patient 3 was ideal. The patient was calm and relaxed during the recovery process from anesthesia.

During procedure 4, the catheter used to inject the radiopharmaceutical was not successfully flushed or cleared from the catheter and a large amount of the injected activity (~ 50%) pooled in the right forearm of the patient just beneath the epidermis. A diagnostic quality scan was achieved that was still clinically useful despite the difficulty. Both the nuclear medicine technician and the anesthesiologist were present during the recovery of patient 4 and as a result, a slightly higher radiation dose was recorded for both workers. It should also be noted that the radiobiologist changed how the radiopharmaceutical was prepared for this procedure. Usually all containers of radiation are kept behind lead shielding during the preparation process but during this procedure, several containers that contained small amounts of radioactivity were left unshielded and to the side of the lead shielding. This slight change decreased the radiopharmaceutical preparation time, and created less contamination in the laboratory but the radiobiologist did receive a higher dose than normal. Thus, the decrease in time did not offset the reduction in shielding.

Procedures 5 - 7 were healthy, purpose breed research hounds and each received an injection of penicillamine (20 mg kg^{-1} intravenously) during the procedure with the injection of the radiopharmaceutical. Penicillamine acts as a copper chelator in the liver. Since patients 5 – 7 were healthy and free of cancer, no surgeon was required. The scans performed on patients 5-7 were longer thus increasing the amount of time for a possible exposure for both the nuclear medicine technologist and anesthesiologist. During procedure 5, the patient had difficulty during recovery. The patient had a low temperature of 91.9°F at the completion of the PET/CT scan. After the patient was transported to the nuclear recovery ward, the anesthesia and nuclear medicine technician chose to warm the patient by rubbing the patient with a towel in an attempt to stimulate the tissues and increase body temperature. Because of the patient's low temperature, recovering the patient from anesthesia took longer than usual (~ two hours). The anesthesiologist was also present during the "warming" process but the anesthesia tech spent much less time in close proximity to the patient.

Procedure 6 was complicated because the ^{64}Cu from University of Wisconsin arrived contaminated. Both the inside and outside of the lead transportation pig used to ship the radionuclide were contaminated with low levels of ^{64}Cu. This delayed the imaging procedure by sixty minutes while decontamination took place. Surprisingly, despite the longer duration spent in the hot lab with the radionuclide, the radiobiologist did not receive a significantly higher dose. Also, the Philips PET/CT experienced another software problem that delayed the imaging process another hour. The injected activity was corrected for decay prior to injection to account for the multiple delays.

For procedure 7, the protocol was altered so that it spanned two days. On the first day of procedure 7, the patient was only sedated and injected with the penicillamine and

radiopharmaceutical. On the second day of the procedure 7, the dog was anesthetized and imaged.

EPD Location Dependency

The location of the EPD has a large impact on the dose reading depending on the worker (see Figures 15-18 and Table 7). Wearing an EPD on the chest or waist does not change the amount of radiation a worker is exposed to, but only the accuracy of the measurement. The nuclear medicine technologist and surgeon EPD located on the chest recorded a radiation dose >30% more than the EPD located on the waist. The EPD located on the waist of the radiobiologist preparing the radiopharmaceutical recorded approximately 20% more radiation dose than the EPD worn on the chest. The location of the EPDs worn by the anesthesiologist did not affect the radiation dose and both EPDs recorded roughly the same dose.

Upon reflection the differences in the doses recorded by each worker can be explained. For the radiobiologist, the majority of the work performed was done in a fume hood with lead shielding and leaded glass. Thus the radioactive materials were generally closer to the waist EPD than the chest EPD during the preparation of the radiopharmaceutical leading to slightly higher readings on the waist EPD. The nuclear medicine technologist typically accumulated exposure when transporting the patient to the nuclear recovery ward and during the recovery of the patient. During both of these tasks, the nuclear medicine technologist was bending over the patient bring their chest close to the patient. This was especially seen during patient recovery when the patient was lying on the floor or being restrained by the nuclear medicine technologist. Thus since the chest EPD was generally the EPD closer to the patient, the chest EPD recorded more exposure. The surgeon spent time to the patient while the patient was still on the PET/CT table. Although the table is waist high the surgeon usually either bent over the patient or crouched to get a better

view when collecting biopsy samples. By bending or crouching, the chest of the surgeon was always brought in close proximity to the patient and as expected the chest EPD always recorded a higher exposure. The anesthesiologist EPDs tended not to discriminate exposure based on location. This can be explained by the fact that the anesthesiologist typically did not spend durations of time in close proximity to the patient compared to the surgeon or nuclear medicine technologist. Thus the patient acted more like a point source instead of a volume source and the distribution of radiation was more equally distributed across the anesthesiologist's body.

Risk Assessment

There are several different standards that radiation exposures can be compared against and assessed. The doses recorded in this study were compared against the following: the quantity of radiation required to observe biological effects, background radiation across the nation and the world, and the radiological limits for the general public and radiation workers. The radiation doses received by the occupational workers in this study (maximum of 17 μSv in a single exposure or 61 μSv maximum cumulative exposure) were small compared to the threshold quantity of radiation needed to cause deterministic effects (roughly 1 – 2 Sv of gamma radiation) [34], but, assuming a linear no-threshold risk model, there is an slight increase in the probability of developing stochastic effects. In the field of radiation safety, the concept that any quantity of radiation will increase the risk of stochastic effects, such as cancer, is known as the Linear No-Threshold Model [33]. Although other models exist, the Linear No-Threshold model is currently supported by the National Academy of Sciences, as well as the regulatory agencies of the USA. To quote the most current National Academy of Sciences Biological Effects of Ionizing Radiation (BEIR) VII report [48],

> "A comprehensive review of available biological and biophysical data supports a "linear-no-threshold" (LNT) risk model—that the risk of cancer proceeds in a linear fashion at

lower doses without a threshold and that the smallest dose has the potential to cause a small increase in risk to humans."

It should be stated that despite widespread use, the Linear No-Threshold the model is not perfect. Evidence supports a linear relationship between effects and dose at high doses but little is known about the consequences of low level exposures of radiation (like those seen in this study).

An example that quantifies the magnitude of the increased probability of stochastic effects due to radiation is shown in Figure 22. Based on an average lifespan of one hundred people, fifty-seven people are expected to be healthy (illustrated by the green circles), forty-two are expected to develop non-radiation induced cancers (depicted by the yellow squares), and an additional incidence of cancer is expected as a consequence of an exposure of 0.1 Sv (1640 times larger than the maximum cumulative dose from this study) above background (shown by the blue triangle) [48].

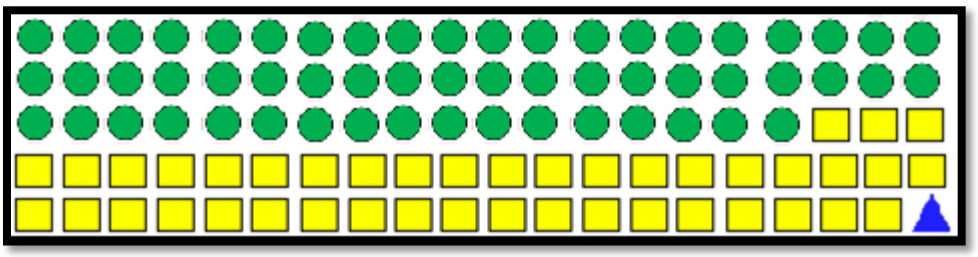

Figure 22: Quantification of Radiation Induced Cancer from 0.1 Sv - Circles represent healthy people, squares represent naturally occurring cancer, and the triangle represents an expected cancer induced by radiation. All 100 persons are assumed to have a dose of 0.1 Sv.

The BEIR VII report also provides a more quantitative example. Assuming a population of 100,000 people (with an age distribution similar to that of the United States) was exposed to 100 mSv (0.1 Sv) of gamma radiation, the corresponding cancer incidence and cancer related deaths are reported in Table 13 [48].

Table 13: BEIR VII Lifetime Attributed Risk Estimates from 0.1 Sv to a Population of 100,000

	All Solid Cancers		Leukemia	
	Males	Females	Males	Females
Excess Cases (including non-fatal cases) from Exposure to 100 mSv	800 (0.8%)	1,300 (1.3%)	100 (0.1%)	70 (0.07%)
Number of Cases in the Absence of Exposure	45,000 (45.5%)	36,900 (36.9%)	830 (0.83%)	590 (0.59%)
Excess Deaths from Exposure to 100 mSv	410 (0.41%)	610 (0.61%)	70 (0.07%)	50 (0.05%)
Number of Deaths in the Absence of Exposure	22,100 (22.1%)	17,500 (17.5%)	710 (0.71%)	530 (0.53%)

The maximum cumulative dose recorded during the study was 61 μSv. According to the International Commission on Radiation Protection, the probability of developing a fatal cancer increases 5% per Sv [49]. Thus the maximum cumulative exposure from the seven procedures completed corresponds to only a 0.0003% increase in the incidence of fatal cancer. Even if every imaging procedure completed in this study had been carried out by a single worker (276.6 μSv of total radiation dose for the seven procedures) and performed the study annually for a total of fifty years (receiving a total radiation dose of 13.83 mSv), the increased chance of developing a fatal cancer is only 0.0692%.

As mentioned, the results of this study can also be compared to average background radiation dose, both national and worldwide. Natural radiation exists all over the globe but the distribution of radioactivity is uneven. The geography and elevation of the location alter the levels of natural radioactivity because naturally occurring radioisotopes exist in the soil and radiation also enters our atmosphere as cosmic radiation. Table 14 summarizes levels of natural background radiation for the United States and the world [50, 51].

Table 14: Average Annual Background Radiation Dose

	National Average	Global Average
Natural Radiation Dose [mSv]	3.1	2.4

The maximum cumulative exposure from this study was 61.4 μSv. The length of the study was approximately one year (ten months) and the maximum cumulative exposure recorded during the study is only 1.12% of the national average annual background radiation dose and 1.44% of the global average annual background radiation dose. A distribution of the average public radiation exposure is shown in Figures 23-24 [50-53].

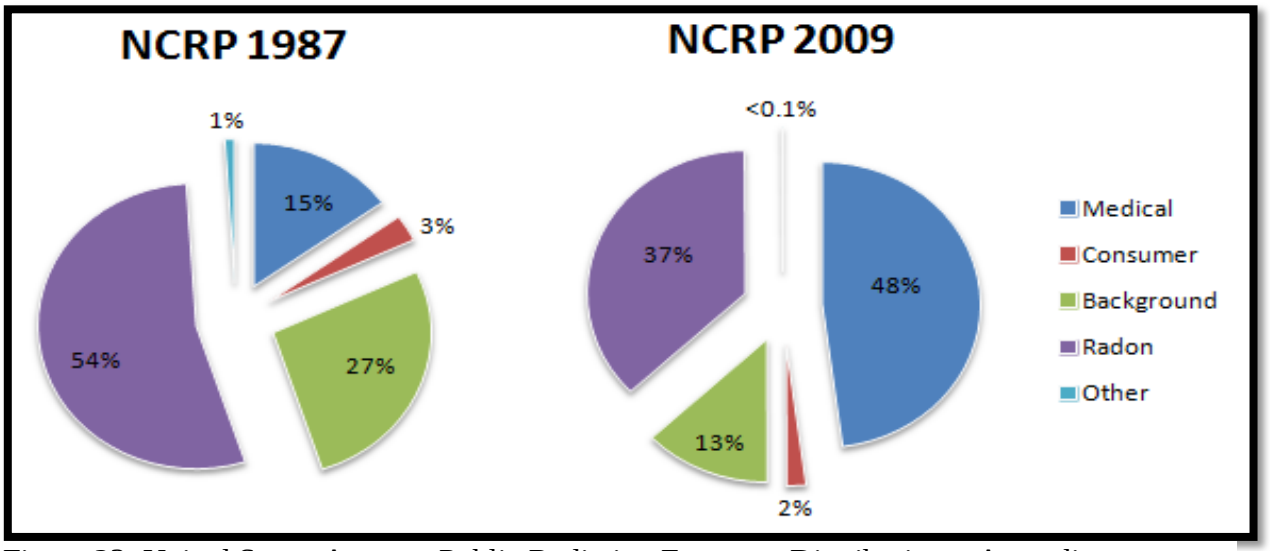

Figure 23: United States Average Public Radiation Exposure Distribution – According to NCRP 1987, the annual exposure to the public nationally was 3.6 mSv and was increased to 6.25 mSv by 2009, mainly due to an increased number of medical procedures performed on Individuals.

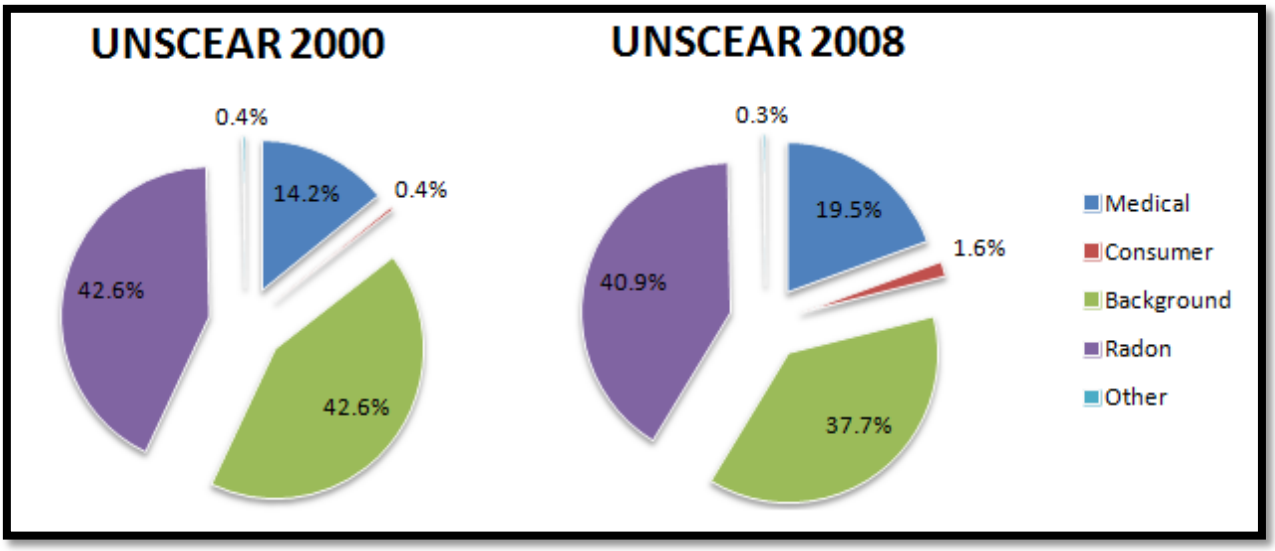

Figure 24: Global Average Public Radiation Exposure Distribution – According to UNSCEAR, the annual exposure to the public globally in 2000 was 2.81 mSv and was increased to 3.0 mSv by 2008.

As Figures 23-24 depict, the global public exposure distribution has remained fairly constant over the last decade with only a minor increase to the medical exposure. However over the last two decades the American public exposure has drastically changed, especially in medical exposure. This is chiefly due to the annually increasing number of CT scans and nuclear medicine procedures performed each year [51].

Lastly, the results of this study can be compared to the annual whole body radiation limits set forth as regulations or recommendations. However several different limits exist. The two general classifications of human exposures are radiation workers and the general public. The national radiation dose limits are set by the United States National Regulatory Commission (US NRC). The International Commission on Radiation Protection (ICRP) has recently published more recent recommendations for radiation dose limits which are more limiting than the US standards. It is important to note that the ICRP limits are only recommendations and that the US NRC regulates all radiation issues in the US. Table 15 summarizes the dose limits from both the US NRC and the ICRP along with the maximum cumulative exposure recorded during the study.

Table 15: Annual Dose Limits for Radiation Workers and General Public

	ICRP 103 [49]	US NRC [54-55]	Maximum Cumulative Dose from Study	Maximum Dose Received from any One Procedure
Occupational [3]	20 mSv	50 mSv	0.0614 mSv	0.017 mSv
Public	1 mSv	1 mSv	-	-

The maximum cumulative dose recorded over the study (approximately one year in length) is only 0.1228% of the US NRC annual occupational dose limit and 0.307% of the more limiting ICRP annual occupational dose limit. Even the annual public limits are a factor of sixteen times greater than the maximum cumulative exposure anticipated for the ^{64}Cu-ATSM canine imaging procedures. The maximum dose received per patient for by any of the workers involved in the study was 17 μSv. Thus, in order to exceed the annual international dose recommendation of 20 mSv, a total of 1,177 ^{64}Cu-ATSM canine imaging procedures would need to occur each year or a total of 2,942 procedures to reach the annual legal dose limit of the US NRC.

When a patient is released from the nuclear recovery ward, the patient is still slightly radioactive. As mentioned previously, the patient is not released until the maximum surface dose rate was ≤ 17.5 μSv hr^{-1}. If an assumption was made that after the patient was released, the patient remained at a constant level of maximum dose rate, it would take a total of 57.15 hrs of direct physical contact in order for a member of the public to exceed the public dose limit of 1 mSv.

Future Work and Direction of Study

Because of the nature of this study, it will be impossible to eliminate the variability between procedures in future studies. Variability will always exist because of the differences

[3] ICRP Report 103 allows up to 50 mSv annually but no more than 100 mSv in a 5 year period

between patients including size, body composition, breed, tumor location, tumor grade, tumor type, anesthesia response, etc…In future studies, what should be focus on is minimizing the changes in the PET/CT procedures to attempt to make each procedure identical. During the seven procedures of this study, the PET/CT procedure was altered on three separate occasions, usually changing the length of the procedure. By keeping the PET/CT procedure set, this would reduce the amount of information that could be gathered from the study but would minimize the variance imaging procedures.

In addition, more data is needed for further analysis and comparison. Because of the clinical nature of this study only seven dogs were enrolled which is a very small sample size. Statistical tests would perform better if there was a larger sample size to draw from and a larger sample size would also increase the statistical strength of the results.

One of the weaknesses of this study was that the main result of the study was the final cumulative exposure recorded by workers. This is an important result to obtain but it is also important to indentify during what duty the workers were exposed to radiation and this information was not recorded. If the study is to be continued or could be repeated, observing when the workers accumulate radiation exposure would be an equally interesting result to observe and analyze.

CONCLUSIONS

Although no data was available to compare the veterinary occupational doses received from ^{64}Cu-ATSM against ^{64}Cu-ATSM occupational doses in human/veterinary medicine, a comparison was made between the occupational veterinary exposures of ^{64}Cu-ATSM and FDG human/veterinary medicine occupational exposures. In the comparison between ^{64}Cu-ATSM veterinary occupational exposures and human medicine worker exposures from FDG, it was found that the occupational doses recorded in this study were slightly lower or equal to the occupational doses seen in human medicine (Table 10). This finding supports the hypothesis that despite the lower levels of radioactivity present in veterinary PET procedures, by anesthetizing patients there is a potential increase for higher radiation exposures to occupational workers. In the comparison between veterinary occupational exposures from FDG and ^{64}Cu-ATSM, it was found that the veterinary occupational exposures from ^{64}Cu-ATSM were equal to or less than the veterinary occupational exposures from FDG (Table 12), depending on the worker. This result was predicted in the hypothesis and can be attributed similarity of the procedures and the emissions of the radionuclides used in the radiopharmaceuticals.

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APPENDIX A

Human Use Protocol

Colorado State University
Knowledge to Go Places

Research Integrity & Compliance Review Office
Office of the Vice President for Research
321 General Services Building - Campus Delivery 2011 Fort Collins, CO
TEL: (970) 491-1553
FAX: (970) 491-2293

NOTICE OF APPROVAL FOR HUMAN RESEARCH

DATE:	May 08, 2013
TO:	Kraft, Susan
	Petefish, Kalie, Martinez, Nicole, Nickoloff, Jac, Johnson, Thomas
FROM:	Barker, Janell, Coordinator, CSU IRB 2
PROTOCOL TITLE:	Phase II: Dose Field Surrounding Veterinary PET/CT Patients and Corresponding Occupational Radiation Dose to Associated Personnel
FUNDING SOURCE:	NONE
PROTOCOL NUMBER:	12-3508H
APPROVAL PERIOD:	Approval Date: May 29, 2013 Expiration Date: May 28, 2014

The CSU Institutional Review Board (IRB) for the protection of human subjects has reviewed the protocol entitled: Phase II: Dose Field Surrounding Veterinary PET/CT Patients and Corresponding Occupational Radiation Dose to Associated Personnel. The project has been approved for the procedures and subjects described in the protocol. This protocol must be reviewed for renewal on a yearly basis for as long as the research remains active. Should the protocol not be renewed before expiration, all activities must cease until the protocol has been re-reviewed.

If approval did not accompany a proposal when it was submitted to a sponsor, it is the PI's responsibility to provide the sponsor with the approval notice.

This approval is issued under Colorado State University's Federal Wide Assurance 00000647 with the Office for Human Research Protections (OHRP). If you have any questions regarding your obligations under CSU's Assurance, please do not hesitate to contact us.

Please direct any questions about the IRB's actions on this project to:

Janell Barker, Senior IRB Coordinator - (970) 491-1655 Janell.Barker@Colostate.edu
Evelyn Swiss, IRB Coordinator - (970) 491-1381 Evelyn.Swiss@Colostate.edu

Barker, Janell

Barker, Janell

Approval is to recruit the remaining 14 participants with the approved recruitment and consent. The above-referenced project was approved by the Institutional Review Board with the condition that the approved consent form is signed by the subjects and each subject is given a copy of the form. NO changes may be made to this document without first obtaining the approval of the IRB.

Approval Period:	May 29, 2013 through May 28, 2014
Review Type:	EXPEDITED
IRB Number:	00000202

APPENDIX B

Animal Use Protocol

Colorado State University

Knowledge to Go Places

Research Integrity & Compliance Review Office
Office of the Vice President for Research
321 General Services Building - Campus Delivery 2011 Fort Collins, CO
TEL: (970) 491-1553
FAX: (970) 491-2293

NOTICE OF APPROVAL FOR ANIMAL RESEARCH
Animal Welfare Assurance Number: A3572-01

DATE:	September 25, 2013	
TO:	Kraft, Susan, 1681 Env & Rad Health Sciences Waldchen, Karen, Nickoloff, Jac	
FROM:	Moseley, Bill, Coordinator, CSU IACUC	
PROTOCOL TITLE:	Use of penicillamine to reduce canine hepatic uptake of 64-Cu-ATSM for applications towards PET/CT Imaging and internal radiotherapy	
FUNDING SOURCE:	Dept. Funding	
PROTOCOL NUMBER:	13-4534A	
APPROVAL PERIOD:	Approval Date: September 24, 2013	Expiration Date: September 23, 2016

Colorado State University's Institutional Animal Care and Use Committee (IACUC) has completed its review of protocol 13-4534A, titled "Use of penicillamine to reduce canine hepatic uptake of 64-Cu-ATSM for applications towards PET/CT Imaging and internal radiotherapy." In accordance with federal and state requirements on the care and use of animals and policies established by Colorado State University, the committee has approved this new protocol. If the committee is placing any special requirements on the approval, they will be included at the bottom of this letter.

This protocol will need to undergo Continuing Review and approval prior to September 23, 2014.

Prior approval to changes in the approved protocol must be obtained before implementation of those changes. If you would like to involve additional personnel or change any aspect of the protocol in the future, please submit an Amendment Request to the Institutional Animal Care and Use Committee for review via eProtocol https://csu.kevusa.net.

Good luck in your research endeavors.

Sincerely,

[redacted]

Moseley, Bill

APPENDIX C

External Radiation Field Protocol

1) PREPARATION:

All measurements will be made using DMC 2000S and DMC 2000XB brand of Electrical Personal Dosimeters or EPD. Each EPD was calibrated by Palo Verde Nuclear Generation Station to ANSI 4220A standards. The batteries of each EPD were changed in Aug of 2012 and each battery should last at least a full year.

Before every treatment, ensure that the previous history on each individual EPD is properly analyzed, stored, and cleared. The EPDs should be placed into pause mode after the last treatment (there are three modes mentioned in for the EPDs and they are the following: pause, sleep, and active). To bring the EPDs out of pause mode, hold the enter button for a few seconds. This will bring the EPDs into active mode so that dose can be collected. It is recommended to turn the EPDs on just before use to minimize any interference.

To ensure that background radiation is not a factor during the treatment, place the EPD labeled *Control* in room ACC 155 in the Southwest corner of the room to monitor any background radiation.

The observer should record all information on the Dose Recording Spreadsheet, a copy of the spread sheet can be found in ACC 155 near the Southwest corner of the room. Any details that may change the dose distribution should also be reported on the spreadsheet as well.

The radionuclide will be delivered to the Nuclear Medicine Lab ACC 159 at approximately 10:00 am. The RCO officer who is picking up the ^{64}Cu from FedEx will communicate with the group to alert them of its pending arrival. The EPD badges *Prep C* (to be worn on chest) and *Prep W* (to be worn on waist) are handed out to the person checking in the nuclide and preparing it for treatment. Record the time that the two EPDs are turned on and after the nuclide has been checked in, collect the EPDs and record the time the EPD's were collected.

The patient should be transported from anesthesia to the PET/CT room. Record the time the patient arrives.

2) DOSE FIELD MEASUREMENTS FROM THE ANIMAL:

Depending on the situation, dose field measurements will be made around the patient during the post-injection time period using EPDs. The EPDs should not be activated until after the injection is made and the CT scan completed. DO NOT put the EPDs through the CT scan because this will add dose to the EPDs and might cause artifacts in the CT images. At this point, activate the following EPDs and place them directly on the patient: *Head C, Right Shoulder C, Right Hip C, Left Hip C, Left Shoulder C, Head W*. Below is a diagram showing approximately where to attach each EPD. During the PET scan, the region being imaged will have to be cleared of the EPDs because the EPDs distort the imaging. So the observer will have to enter the room several times to remove/reattach the EPD's. Record the times that the EPD's are activated, attached, unattached, and collected.

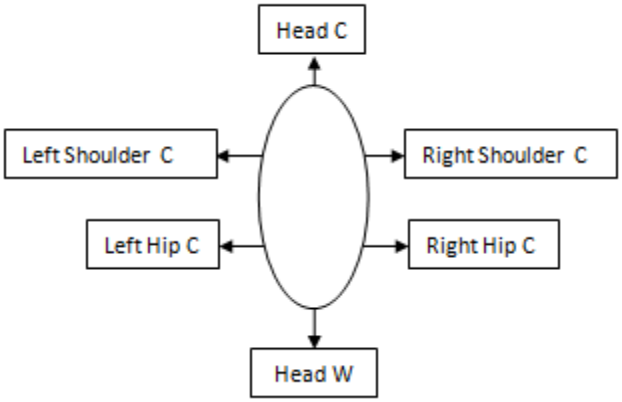


Figure 25: External Field EPD Locations

There is an ion chamber located in the CT/PET control room (H106D). The ion chamber is a Fluke 451 Ion Chamber Survey Meter, Product #: 451P-RYR, Serial #: 0000003459. It was calibrated with a ^{137}Cs source and it is accurate to within 10% up to 101 mR/hr. The last date of calibration was 11/21/12. Once the EPDs have been activated and placed onto the patient, use the ion chamber instrument to get surface and distance dose readings. To activate the ion chamber, just hold the power button then the instrument will display the exposure rate on the main screen. Record the exposure rate and the time of each record as well as the distance from the patient from the place of the ion chamber. The recommended exposure rate locations chosen for the ion chamber are shown on the diagram below. Be sure to measure from the same location each time a measurement is taken and record the distance from the instrument to the patient. Due to the dynamic scans, the data can be collected when the location is not obstructed by the gantry head.

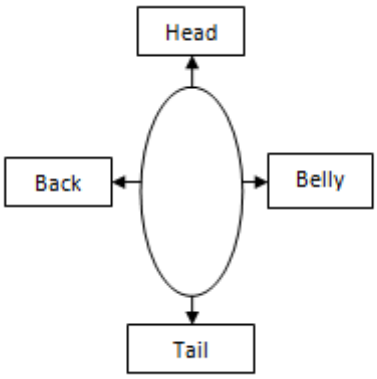


Figure 26: Ion Chamber Measurement Locations for External Field Measurements

3) PERSONNEL DOSES:

Measure the dose to the person transporting the radiopharmaceutical from the hot lab to the PET/CT suite, injecting the nuclide into the patient, and then to that will be coming in contact with the anesthetized patient (anesthesia technologist, the surgeon and nuclear medicine technologists). For each of these tasks, give two EPD's (to be worn at chest and waist height),

record the activation time and activate the EPDs for each individual below. Activate just before the task starts and remove it and record the dose once that task is completed, as follows:

Transport C and *Transport W* – this pair of EPDs should be activated and then recovered to measure the dose experienced by the person transporting the radiopharmaceutical from Nuclear Medicine to the PET/CT room.

Anesth C and *Anesth W* – Activate these EPDs when the animal is being injected, and do not collect after the anesthetist will no longer be exposed, after imaging is completed and the animal is recovered from anesthesia. Whenever the anesthetist enters and leaves the PET/CT room, record the time.

Surgeon C and *Surgeon W* – This pair of EPDs should be worn by the person extracting the tissue sample from the tumor. Activate the badge just before the action takes place the time period that the EPD is in use.

Nuc Med 1 C, Nuc Med 1 W, Nuc Med 2 C, and *Nuc Med 2 W* are given to PET/CT technicians, who may also be exposed if they have to enter the PET/CT treatment room to interact with the equipment or the animal. So two of these badges are reserved for these personnel. Record any time that either of the technicians enters the PET/CT room and collect the EPD's after imaging and anesthetic recovery are completed.

Once imaging is complete, the animal is transported back to the nuclear medicine ward located in room ACC 162 and woken up from the anesthetic. This will require the Anesthesia and nuclear medicine technologists, so those personnel measurements need to be continued until the animal can be left alone. Make sure to record all of the relevant times (time of transport, time when animal is woken up).

4) DATA COLLECTION AND STORAGE:

After completion of the whole process, the observer should ensure that all the EPD badges have been collected from all personnel. Each cumulative dose reading from every EPD should be recorded. Also, the observer should record the cumulative dose readings on the six EPDs that were placed in the PET/CT room on the spreadsheet along with the other readings, occurrences, and all the recorded times.

Now that all the doses are recorded in the EPDs, the data must be saved, the EPDs must be cleared for re-use, and each EPD must be put back into pause mode for the next treatment use. To do this, open up the software Dosimass. One of the tabs at the top of the program's menus is *Administration*. Under this tab is the option to *Log in and Register*. Click on this option. The user name is supervisor and the password is also supervisor.

Once the observer has logged into the software, attach the scanner into the port that was configured to use the scanner. Now click on the menu tab labeled *Dosimeter*. Under this tab is the option of *Entry/Exit*. Click on this option. Now each EPD can be placed in pause mode by scanning the dosimeter by placing the EPD directly in front of the scanner then clicking on the *Exit* button. There is an option in to read another EPD, so after clicking on the Exit button repeat until all EPDs have been read and exited. This step will place the EPDs in the sleep mode.

Once the EPDs have been placed in sleep mode, go back to the top tab that reads *Dosimeter* and click on it. There will be an option labeled *History*. Click on this and place an EPD to be read in front of the scanner then click on the "Play" button located at the bottom of the screen. This will display the history of the EPD. To save the history, click on the floppy disk with a "T" on it. This will save the file in a text format which can then be read into Excel. Repeat

this step until all the EPDs histories have been saved. It is recommend to save each text file with a name to reflect the date of treatment and which EPD. An example is like 1-15-13 Head C.

Enter into each EPD and double check that all recorded dose has been removed to ensure the EPDs have been cleared. The program should show you that there is no dose recorded on the EPD if the process above was done properly. Then click *Exit* to put the EPD back into sleep mode. Then scan the next EPD and repeat the process.

After the EPDs have been cleared, place them into pause mode. This can be done by selecting *Dosimeter -> Single Configuration* and reading in an EPD. Then select the box that reads *Enable Pause Mode* and click *Write Dosimeter*. Repeat this process for each EPD and this concludes the external dosimetry process.

APPENDIX D

SAMPLE OCCUPATIONAL DOSE DATA SHEET

EPD Identity	Time Activated	Time Collected	Dose [mrem]	Comments
Prep C				
Prep W				
Transport C				
Transport W				
Anest C				
Anest W				
Nuc Med 1 C				
Nuc Med 1 W				
Nuc Med 2 C				
Nuc Med 2 C				
Control				

Calibrated Dose [mCi] _____

Residual Dose [mCi] _____

Injected Dose [mCi] _____

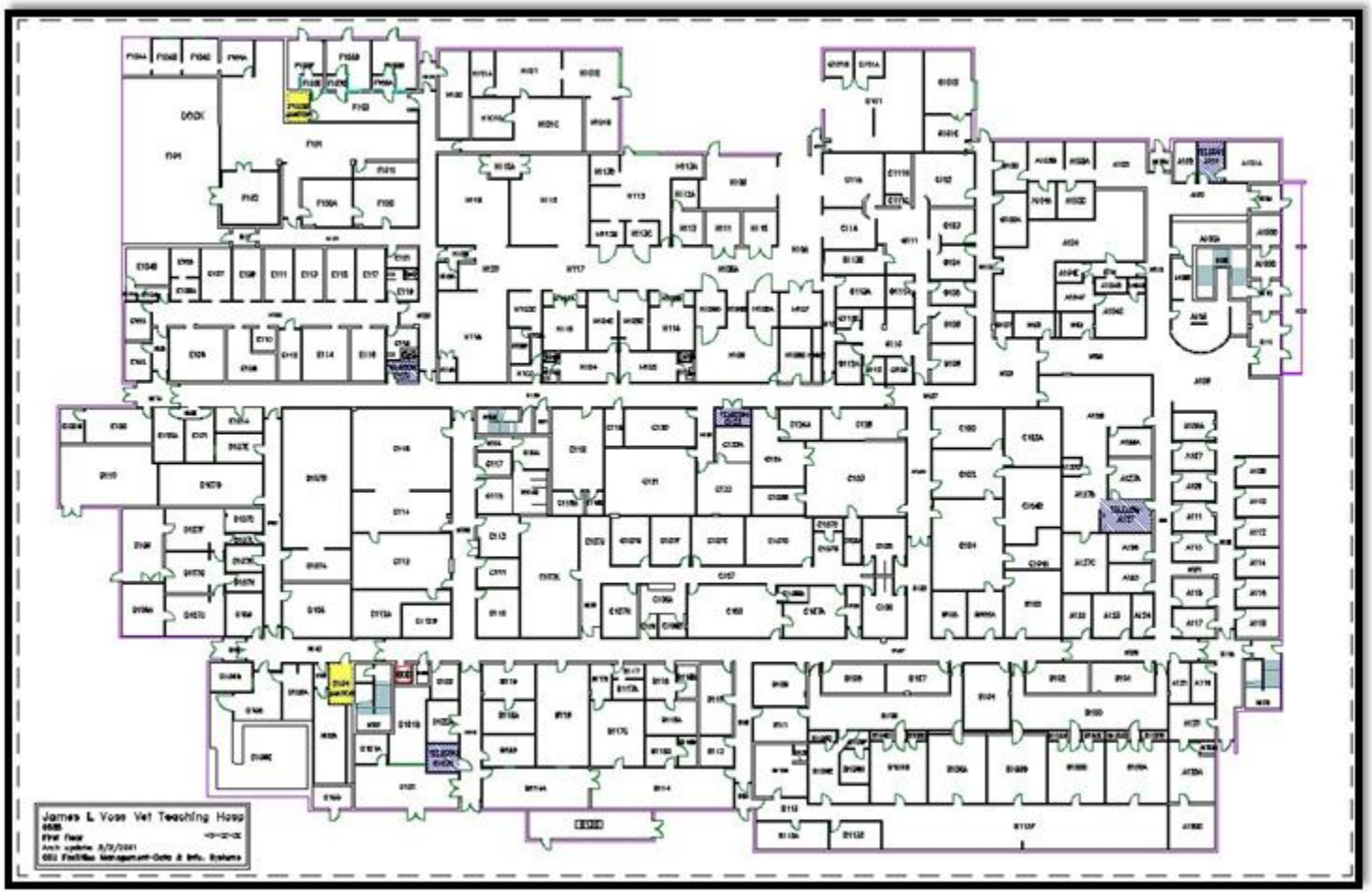
Injection Time _____

Breed _____

Weight [kg] _____

APPENDIX E

VTH FLOOR LAYOUT


James L. Voss Vet Teaching Hosp

ACRONYMS AND ABBREVIATIONS

ACC	Animal Cancer Center
Bq	Becquerel
BEIR	Biological Effects of Ionizing Radiation
CT	Computation Tomography
CSU	Colorado State University
EPD	Electronic Personal Dosimeter
FDG	Fludeoxyglucose
ICRP	International Commission on Radiation Protection
Kg	Kilogram
LNT	Linear No-Threshold
Lutetium Yttrium Oxyorthosilicate	LYSO
MRI	Magnetic Resonance Imaging
PET	Positron Emission Tomography
PET/CT	Combined PET and CT imaging
PMT	Photomultiplier Tube
Rad	Radiation Absorbed Dose
Rem	Roentgen Equivalent Man
ROI	Region of Interest
Sv	Sievert
US NRC	United States Nuclear Regulatory Commission
VTH	James L. Voss Veterinary Teaching Hospital
VOI	Volume of Interest

^{64}Cu-ATSM ^{64}Cu-diacetyl-bis(N^{4}-methylsemicarbazone)