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THE INTERNAL DOSIMETRY OF RUBIDIUM-82 BASED ON DYNAMIC PET/CT IMAGING IN HUMANS

by

Chad R. Hunter, B.Sc.

A Thesis Submitted to
the Faculty of Graduate and Postdoctoral Affairs
in Partial Fulfilment of
the Requirements for the Degree of
Master of Science

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Abstract

Rubidium-82 (Rb-82) is a useful blood flow tracer, and has become important in recent years due to the shutdown of the Chalk River reactor. Published effective dose estimates for Rb-82 vary widely, and as yet no comprehensive study in man has been conducted with PET/CT, and no effective dose estimates for Rb-82 during pharmacological stress testing has been published. 30 subjects were recruited for rest, and 25 subjects were recruited for stress. The subjects consisted of both cardiac patients and normal subjects. For rest, a total of 283 organs were measured across 60 scans. For stress, a total of 171 organs were measured across 25 scans. Effective dose estimates were calculated using the ICRP 60, 80, and 103 tissue weighting factors. Relative differences between this study and the published in-vivo estimates showed agreement for the lungs. Relative differences between this study and the blood flow models showed differences > 5 times in the thyroid contribution to the effective dose demonstrating a limitation in these models. Comparisons between rest and stress effective dose estimates revealed no significant difference. The average ‘adult’ effective dose for Rb-82 was found to be 0.00084 ± 0.00018 mSv/MBq. The highest dose organs were the lungs, kidneys and stomach wall. These dose estimates for Rb-82 are the first to be measured directly with PET/CT in humans, and are 4 times lower than previous ICRP 60 values based on a theoretical blood flow model. The total adult effective dose from a typical Rb-82 study including CT for attenuation correction and potential Sr-85 breakthrough is 1.5 ± 0.4 mSv.

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I'd like to thank Cecilia Ziadi and Judy Etele of the University of Ottawa Heart Institute for their hard work in recruiting patients and setting up the protocols, and generally making this whole project move smoothly on the patient side. I'd also like to thank Dr. Jeremy Hill of Draximage for his invaluable input on how to properly conduct dose calculations and statistical analysis, and his hard work in generating a *comprehensive report on the dosimetry of Rb-82*. Additionally I'd like to thank Dr. Rob Beanlands for his unwavering support for my research, as well as helping define all the medical protocols to ensure patient safety and the success of this project. Lastly, I'd especially like to thank my thesis advisor Dr. Rob deKemp for supporting both me and my research, and taking an active role in both the data analysis and formulation of protocols that ensured the highest quality data.

I'd like to thank the following financial institutions that contributed to my research, without whom this project would not have been possible: The Ontario Research Grant, The University of Ottawa Heart Institute, Draximage, and Carleton University.

Glossary

CT anatomic VOI - This is the VOI or ROI drawn to represent the true geometrical shape of the organ as defined by CT. A 3D model of this region will look like the actual organ.

Normal - In a radiopharmaceutical study, this is a subject with no expected symptoms of the disease that the radiopharmaceutical is used to help diagnose.

Radiation - In the context of this thesis it is exclusively ionizing radiation.

Spill-in - Partial volume averaging on a PET image that occurs near the boundary between two organs where activity from one organ is smeared over into the geometrical region of the other organ. This can cause the activity concentration in that organ to be higher than normal (e.g. spill in from the left ventricle into the heart wall).

Spill-out - Partial volume averaging that occurs near the edges of an organ where the activity from the organ is smeared over into adjacent regions, leading to an underestimate of the true activity concentration in the organ.

Tracer - A chemical that has been ‘tagged’ (chemically bonded to) with a radioactive element. This chemical has an important biological property that makes it

useful for investigating a metabolic process in a living organism.

VOI reduction technique - A partial volume correction technique for tissue thicknesses greater than twice the FWHM scanner resolution. Reduces the VOI from the anatomical VOI to avoid spill-out.

Dose coefficient - The ratio of the measured activity in an organ to the total injected activity in the patient.

List of Abbreviations

$\tilde{a}$ Residence Time

A Activity

Bq Becquerel

BGO Bismuth Germanate Oxide

CAD Coronary Artery Disease

CT Computed Tomography

D Absorbed Dose

DE Dose Equivalent

DF Distribution Factor

ED Effective Dose

EM Electro Magnetic

FWHM Full Width at Half Maximum

GI Gastro-Intestinal

Gy Gray

H Equivalent Dose

ICRP International Commission on Radiological Protection

LET_∞ Linear Energy Transfer

LLI Lower Large Intestine

MF Modifying Factor

MIRD Medical Internal Radiation Dose committee
OLINDA/EXM Organ Level Internal Dose Assessment/ EXponential Modelling
ORISE Oak Ridge Institute for Science and Education
PET Positron Emission Tomography
PMT Photo Multiplier Tube
PVA Partial Volume Averaging
PVE Partial Volume Effect
QF Quality Factor
RBE Relative Biological Effectiveness
rem Röntgen Equivalent in Man
ROI Region of Interest
S S-Parameter
SAF Specific Absorbed Fraction
SI Small Intestine
Sv Sievert
SPECT Single Photon Emission Computed Tomography
TAC Time Activity Curve
UB Urinary Bladder
ULI Upper Large Intestine
VOI Volume of Interest
VOI_{anatom} Anatomical Volume of Interest
 w_R Radiation Weighting Factor
 w_T Tissue Weighting Factor
X Exposure

Statement of Originality

The material presented here contains, to the best of my knowledge, previously unpublished results, and has not been submitted to any other university. Portions of this work were accepted to the 2010 Society of Nuclear Medicine (SNM) [1], the 2010 Canadian Organization of Medical Physicists (COMP) [2], and the 2010 Canadian Cardiovascular Society (CCS) annual meetings [3]. On June 8 2010, results from the rest dose estimates were presented as a poster at the SNM annual meeting. Results from the in-vivo to blood flow model comparison were presented as an oral presentation at the 2010 COMP annual scientific meeting in June 17, and selected for the J.R. Cunningham Young Investigators Award, where it was awarded third place. The rest stress comparison will be presented as a poster at the CCS annual meeting on October 23, 2010. The author's work involved analysing patient scans, developing correction/variability reduction techniques, performing dose estimates, and analysing all results. Posters and slides were prepared by the author and reviewed by the co-authors.

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Chapter 1

Introduction

1.1 Overview

Dosimetry is the study of how radiation deposits energy into a physical medium. It is concerned with the distribution, concentration, and penetration of this energy within the medium. The quantity that describes the deposition of energy in a tissue per unit mass of tissue is known as the absorbed dose. The unit of absorbed dose is the gray (Gy), defined in equation 1.1 as,

$$1 \text{ Gy} = 1 \text{ J/kg} \quad (1.1)$$

where: J is the SI unit of energy in joules, and kg is the SI unit of mass in kilograms. In diagnostic imaging the dosimetrists' goal is first to measure the absorbed dose in organs and tissues accurately and quantitatively, and second to translate the absorbed dose into an index of risk. Risk in radiation exposure is often expressed as the probability that an exposed person will develop a fatal cancer in their lifetime. The most common index currently used to quantify the risk to patients undergoing a procedure involving radiation is the effective dose (ED) (or effective dose equivalent (EDE) which is an older term), and is measured in units of sieverts (Sv). The risk

of fatal cancer also depends on the age at the time of exposure, and is a non-linear function. A reproduction of a graph published by Brenner and Elliston [13] in 2004 illustrates this, and is shown in Figure 1.1. Dosimetry is discussed in greater detail in Chapter 2.

Figure 1.1: Life long risks from radiation exposure.

Data from Brenner and Elliston [13].

A 55 year old person who receives a 10 mSv whole body dose will have a 0.06 % probability of developing a fatal cancer within their lifetime. The current issue in medical imaging is that the public dose from diagnostic medicine has risen 600% from 1980 to 2006 (per capita in the U. S.), largely due to an increase in the number of high-dose computed tomography (CT) scans. [14] For the purposes of public health and welfare, any diagnostic tool should be evaluated in terms of its safety versus diagnostic value. As with any diagnostic tool there is an associated risk, and this is also true of diagnostic tools that use radiation such as positron emission tomography (PET) imaging.

One of the uses of medical imaging is in myocardial perfusion imaging for aid in diagnosis of coronary artery disease (CAD). The incidence of CAD is expected to

rise within the next 15 years due to increased risk factors in an ageing population (obesity, diabetes etc). [15] While modern medicine offers treatment methods, it is widely reported in the literature that early detection of CAD can greatly improve the quality of CAD therapies, improve longevity of patients with CAD, and even prevent the disease from causing heart damage. [16] Early detection of CAD was not possible before the advent of modern medical imaging. Nuclear imaging offers cardiologists a non-invasive method of detection and medical treatment of patients with known or suspected CAD. These methods allow the detection of CAD much earlier than previously possible, and also allow a non-invasive method of monitoring the effectiveness of patient treatment methods.

Today we recognize the cause of CAD to be the thickening of plaques on the walls of the coronary arteries. These plaques restrict the flow of blood to the heart muscle (myocardium) and cause CAD. The goal of myocardial perfusion imaging is to measure blood flow to the heart muscle in order to try to determine where the arterial plaque is located in the coronary arteries, and help to direct treatment. This can be accomplished with either PET or single photon emission tomography (SPECT) imaging. Both PET and SPECT imaging rely on the chemistry of how the tracer is absorbed (uptake) into the myocardium, and the physical properties of nuclear decay. Radiation emissions from the tracer allow us to non-invasively track uptake and extraction of the tracer as a function of time. This information is then used to guess at where the arterial plaque is located in the coronary arteries by observing defects in uptake on the myocardium. PET imaging is discussed in greater detail in Chapter 3.

There are several radioactive isotopes used for perfusion imaging, including: Tl-201, Tc-99m for SPECT imaging; and N-13 ammonia, and O-15 water for PET imaging. [17] The PET imaging tracers N-13 and O-15, and the SPECT tracer Tl-201 are all cyclotron produced. Tc-99m is eluted from a (reactor produced) Mo-99

generator.

The tracer used in this study is Rb-82. Rb-82 is a radioactive isotope that decays by positron emission, and is used in PET imaging. With a 1.273 min half life, Rb-82 decays much faster than other currently used tracers, and Rb-82 is eluted from a Sr-82 generator (Sr-82 is cyclotron-produced and has a longer half life of 25.55 days). This makes Rb-82 an attractive tracer for PET centers that do not have access to a cyclotron. The history of the use of rubidium as a blood flow tracer begins around the 1950's. The section that follows is a historical overview of CAD and the use of rubidium as a blood flow tracer.

1.2 Historical Development of Rb-82 Perfusion Imaging

CAD is the leading cause of death among Canadians. [15] The first clinical observations of CAD symptoms were published by W. Heberden [18] in 1772. Heberden described the symptoms of CAD and coined the term 'angina pectoris', which comes from the Latin verb 'angere' meaning to choke or throttle, and the Latin noun 'pectus' meaning chest. Thus it literally translates to the choking or throttling of the chest. A quotation of some of the symptoms from Heberden's [18] original article is found below:

"Those, who are affected with it, are seized, while they are walking, and more particularly when they walk soon after eating, with a painful and most disagreeable sensation in the breast which seems as if it would take their life away, if it were to increase or to continue..."

Heberden did not link these symptoms to problems with the coronary arteries. However a patient allowed an anonymous physician to have his body autopsied after

his death and in 1772 the result of the autopsy was read to the College of Physicians; no pathology was found. The physician Edward Jenner [19] pointed out that the coronary arteries were not examined, and correctly hypothesized that they may be the cause of the pathology. It was not until many years after these observations that treatment methods for CAD became available.

The first breakthrough with respect to the use of Rb-82 as a blood flow tracer, was the discovery that rubidium was a potassium analogue. In 1883 Dr. Sydney Ringer [20] published a paper comparing the action of potassium with other similar chemical substances (including rubidium) on the ventricle of a frog's heart. This experiment was conducted using a perfusion tube placed in the groove separating the ventricles from the atria and employing a syphon technique to simulate blood flow. The results showed no difference in the action of the heart muscle between rubidium and potassium. The actual physiological function of potassium was unknown at this time. During the late part of the 19th century radioactivity was discovered (by Henri Becquerel [21]) and later started to be used in investigations into biological processes. In 1940 Noonan et. al. published their investigations on the distribution of radioactive potassium (K-42) in rats. In their article they pointed out that potassium is more or less distributed throughout the entire human body, but in certain locations like the heart, liver, kidney, and lung the uptake is higher and in other tissue like testes, erythrocytes, and brain the uptake is comparatively lower. [22]

Shortly thereafter, the same authors also investigated the role of potassium in muscle tissue using radioactive potassium. [23] This was conducted by electrical stimulation of the rats' hind leg muscles. After stimulation for 1-hour, the rat was sacrificed and the muscle was dissolved in nitric acid. The radioactivity in the remains was measured with a Geiger-Müller tube. Additionally a control group was used where the nerve to the muscle was cut so no stimulation of the muscle was possible. Their results showed a significantly higher concentration of potassium in the stimulated muscles

versus the control group, showing that indeed the muscle used potassium during its action. Additionally they showed that the level of uptake of potassium into muscle is directly proportional to blood flow, a fact we still use today as justification for rubidium studies for blood flow to the heart muscle to diagnose CAD.

One of the first reports of the use of rubidium (Rb-86) to detect CAD was in 1953 by Love et. al. [24] using canines. This study found that the rapid uptake of rubidium into the dog myocardium was comparable to that of potassium, and as such could be used as a tracer to investigate myocardial potassium exchange. Furthermore they found that most organs (excluding the myocardium) contained more rubidium relative to plasma than potassium, suggesting a slightly higher affinity of rubidium to those organs.

The first study on rubidium in man was conducted by Love et. al. [25] in 1957. At that time it was known that the interaction of rubidium was not identical in all biological processes but plasma ratios of rubidium and potassium were nearly identical in the myocardium. The purpose of this new study was to determine if the difference in uptake of rubidium in a healthy versus unhealthy heart was significant enough to detect heart disease, and thus was suitable as a diagnostic utility. It was found that cardiac patients had on average a 57 % increase in the concentration of rubidium in the plasma compared to healthy patients, meaning there was less uptake by systemic tissues. The methods used were first to locate areas of study by fluoroscopy, then blood samples were obtained in desired areas, and potassium concentrations were determined by a flame photometric technique. The concentration of K-86 was determined by a Geiger-Müller tube. The researchers could not isolate the heart wall in their study due to the limitations of these methods. However a marked decrease in the uptake of rubidium in all organs which normally have high uptake was measured. This decrease was attributed to a decrease of plasma flow to areas of high uptake (which were known to be the liver, lungs, heart and kidneys) and

redistribution to areas of lower uptake, and not a decrease in the way tissue extracts the tracer. Therefore, rubidium uptake is truly a quantitative measure of blood flow and not of tissue extraction efficiency.

One of the first instances of the use of Rb-82 to measure blood flow to the heart was in 1980 by Budinger et. al. [26] using canines and CAD patients. This was also one of the early uses of a positron emission tomograph (a Donner 280-Crystal device) for Rb-82. The canines were used as a control group by measuring rubidium uptake in the myocardium before and after ligation of the coronary arteries to simulate CAD in dogs. Methods included sequential transverse section imaging to obtain time activity curves of the myocardium and blood, and a constant infusion of Rb-82 to obtain equilibrium images for estimation of blood flow (by taking the ratio of uptake in the myocardium to left ventricle activity). Blood flow results from microsphere studies were used to validate their results. The study showed that Rb-82 quantifies blood flow well enough to compete with tracers like Tl-201, N-13 (ammonia) and K-38 for early detection of CAD. This study also pointed out some advantages of Rb-82 over other tracers, namely: its low dose, immediate availability, and short half-life. Since the publication of this study, the use of Rb-82 in medical diagnosis of CAD has increased, as is evident from the many publications that followed.

An additional validation study using Rb-82 was published in 1982 by Selwyn et. al. [27] using 6 canines and 10 humans (5 cardiac and 5 normals). The animal studies showed that any increase in the myocardial blood flow was accompanied by a smaller increase in the myocardial uptake. The normal human study showed a homogeneous uptake of Rb-82 both before (rest) and after work of 24,000 to 32,000 joules was performed by the volunteers (stress). It also showed a 16 ± 4 % increase in Rb-82 uptake in stress relative to rest. The work load of the cardiac patients was limited to 11,000 to 21,000 joules due to their condition, and stress tests showed obvious deficits of activity in diseased regions of the myocardium.

A more comprehensive analysis of myocardial perfusion imaging was conducted by Goldstein et. al. [28] in 1983. The study included 28 canines and measured blood flows with microspheres as well as Rb-82 PET imaging. It was determined that Rb-82 underestimated very low blood flow rates (≈ 0.1 ml/min/g), but blood flow measurements with Rb-82 had a linear relationship up to 2.5 ml/min/g. At higher flow rates, uptake increased non-linearly with flow, and underestimated the true blood flow. This result was important since patients with mild CAD may operate in this region under both rest and stress; thus diagnosis of their level of CAD may be limited. To compensate Goldstein et. al. [28] measured extraction as well as uptake (uptake is the product of flow and the extraction fraction). By correcting for first pass extraction (a large decrease in concentration of the tracer prior to systemic circulation), Goldstein was able to compensate for both the high and low flow rate discrepancies between Rb-82 and microsphere standard. This important result validated the use of Rb-82 as a myocardial blood flow tracer for a wide range of flow rates.

In 1986 Goldstein et. al. [29] conducted another study, this time on 32 humans, 18 cardiac patients and 14 control patients. The main goal of their research was to establish Rb-82 as a safe perfusion tracer for serial studies to track the progress of CAD treatment in patients. All cardiac patients were correctly diagnosed with CAD (confirmed by patient history and previous angiography) and normals (people determine not to have CAD) using Rb-82 except one cardiac patient where the lung activity obscured the heart activity in the image and prevented a diagnosis. In 1991 Stewart et. al. [30] compared the diagnostic accuracy of Rb-82 with Tl-201. Eighty-one patients were analyzed, 52 men and 29 women, and it was found that Rb-82 had 84 % sensitivity (portion of diseased patient correctly diagnosed), 88 % specificity (portion of normal patients found without disease) and 85 % accuracy (ability to determine the severity of the disease). By contrast Tl-201 had 84 % sensitivity, 53 % specificity and 79 % accuracy. Additionally there was no discernible difference

between pharmacological and physical stress testing.

The desire to use Rb-82 for myocardial perfusion imaging is not limited to diagnostic accuracy alone. The short half life of Rb-82 (76.4 seconds) allows for fast rest-stress studies which is desirable for patients, has a low dose compared to most tracers, and is generator produced from a longer lived (25.55 days) Sr-82 source. Additionally the Sr-82 source is a cyclotron produced isotope and thus was not subject to the shortage of reactor produced isotopes such as Mo-99. Two main methods of Sr-82 production are spallation of a molybdenum target with high energy (500-600 MeV) protons, and the irradiation of a RbCl (or Rb metal) target (natural rubidium). The second method produces a purer source of Sr-82; however the strontium yield is lower. [31] From the large number of papers on the use of Rb-82, and the obvious diagnostic usefulness of this radio-pharmaceutical, it is not surprising that, due to the recent shutdown of the Chalk River reactor, this isotope garnered a lot of attention.

To properly assess the risk of a procedure in nuclear medicine, accurate internal dosimetry information must be measured. Often animal studies are first performed, or blood flow models can be used to estimate the bio-distribution of a radioactive flow tracer. This information is then extrapolated to give information about where the tracer will concentrate. Combined with knowledge of the nuclear properties of the radioactive element, an effective dose estimate can be derived, as described in Chapter 2. However, an actual comprehensive measurement within a patient may provide a much better estimate of the dose to that patient. If dosimetry data is collected for several subjects, then one can generalize the effective dose estimate to the representative population. Current dose estimates for Rb-82 vary widely in the literature, and no comprehensive study in man has been conducted. The following section reports the currently published biodistribution and effective dose estimates.

1.3 Published Dose Estimates

There are four major sources of biodistribution data for Rb-82. Two of these sources are actual in-vivo measurements and the other two are theoretical blood flow models. The accuracy of the two in-vivo measurements listed below suffer from limitations. The first limitation is that the study by Ryan et. al. [32] only involved two subjects, and thus suffers from poor statistics. Additionally the study used a primitive method for tissue delineation, namely drawing regions of interest on planar images, based on knowledge of human anatomy. Since no CT scan of the patient was taken, the organ volume of interest (VOI) could only be approximated. The study by Kearfott [33] is limited by the fact that the results are based on an extrapolation from rats, and furthermore from Rb-86 not Rb-82. Therefore, the study by Kearfott is subject to uncertainties in rat extrapolations coupled with uncertainties in Rb-86 to Rb-82 extrapolations.

1.3.1 Published Residence Times

The first measured biodistribution data was a rat extrapolation by Kearfott [33] in 1982. This estimate used the biodistribution data from Rb-86 to estimate the biodistribution for Rb-82. Data were obtained using male Sprague-Dawley rats sacrificed at 1, 3, 10, 15, 20, 30, 60, 120, and 180 min, and recorded as radioactivity per gram of tissue i (A_i). These data were then extrapolated to humans using equation 1.2, and the organ masses (m_i) from the ICRP reference man [12] to give the fractional organ radioactivity concentration or percent of injected dose (% ID),

$$\% \text{ ID}_i(t) = A_i \times [m_i]_{\text{rat}} \times \left[\frac{m_p}{m_{TB}} \right]_{\text{human}} \quad (1.2)$$

where: m_{TB} is the total body mass of a rat or human respectively, and m_p is the plasma mass. The basic assumption with this type of rat extrapolation was that the

individual organ activity concentrations per whole body initial activity concentrations are the same in rats as in humans. In extrapolating these results, Kearfott [33] ignored any decay of Rb-82 during transit to the organs of uptake. The residence time (or appropriately named time integrated activity) was then obtained by numerical integration of the time activity curve; Kearfott did not elaborate on how this was accomplished. Final residence times from the Kearfott paper can be found in Table 1.1; the values presented here have been converted into SI units (MBq-h/MBq read as MBq hour per Mbq injected) from the original paper.

A theoretical blood flow model predicting the biodistribution of Rb-82 was published by the International Commission on Radiological Protection (ICRP) [8] in 1987. The model by Spector was based on fractional cardiac output leading to proportional blood flow to various organs. The ICRP acknowledged that these residence time estimates represented worst case estimates as given in Table 1.1.

The first human in-vivo biodistribution estimate for Rb-82 was published by Ryan et. al. [32] in 1986. Two healthy males were recruited (ages 23 and 27), and time activity curves were generated in five source organs. The activity in the organs was measured with an anger gamma camera with a tungsten collimator using a dynamic conjugate counting technique. It should be noted that the average age of cardiac patients is 55-65 years in this study, and it is unknown what effect patient age or heart condition may have on dosimetry. As no CT images of the subjects were acquired, the regions of interest (ROIs) were drawn around the anatomical region of the organ, based on the activity concentration of the planar images. Residence times for the five organs can be seen in Table 1.1.

A second blood flow model based on more modern data was proposed by Leggett and Williams [34] in 1995. This updated blood flow model has the advantage over the ICRP blood flow model in that it took into account tissue-dependent extraction of the tracer during a first pass circulation and decay in transit to various organs of

short lived isotopes. The Leggett and Williams model did not take into account the size and geometry of blood vessels and blood distribution throughout the organs. The residence times calculated by the Leggett and Williams blood flow model are shown in Table 1.1.

Table 1.1
Published organ residence times for Rb-82.

Organ	Ryan [32] MBq-hr/MBq	Leggett [34] MBq-hr/MBq	ICRP53 [8] MBq-hr/MBq	Kearfott [33] MBq-hr/MBq
Adrenals		5.56×10^{-5}	3.44×10^{-4}	
Brain		2.33×10^{-4}		1.10×10^{-4}
LLI		5.14×10^{-4}	7.17×10^{-4}	1.50×10^{-4}
SI		2.91×10^{-3}	2.83×10^{-3}	1.10×10^{-3}
Stomach		3.14×10^{-4}	6.58×10^{-4}	1.20×10^{-4}
ULI		6.81×10^{-4}	9.17×10^{-4}	1.90×10^{-4}
Heart Contents		1.67×10^{-3}		6.50×10^{-4}
Heart Wall	5.25×10^{-4}	7.25×10^{-4}	1.14×10^{-3}	1.40×10^{-3}
Kidneys	3.11×10^{-3}	3.30×10^{-3}	6.58×10^{-3}	2.00×10^{-3}
Liver	1.54×10^{-3}	1.79×10^{-3}	1.66×10^{-3}	1.30×10^{-3}
Lungs	1.95×10^{-3}	2.04×10^{-3}	2.78×10^{-3}	2.30×10^{-3}
Muscle		4.47×10^{-3}	4.67×10^{-3}	6.00×10^{-3}
Pancreas		3.03×10^{-4}	4.86×10^{-4}	6.10×10^{-5}
Red Marrow		7.31×10^{-4}	1.43×10^{-3}	
Cortical Bone		1.47×10^{-4}	1.14×10^{-3}	
Tabecular Bone		2.19×10^{-4}	2.86×10^{-4}	
Spleen		8.81×10^{-4}	1.00×10^{-3}	
Testes		1.19×10^{-5}		2.80×10^{-6}
Thyroid		2.42×10^{-4}	9.17×10^{-4}	
Urinary Bladder		1.25×10^{-5}		
Remainder	2.24×10^{-2}	4.96×10^{-3}	3.77×10^{-3}	1.59×10^{-2}

1.3.2 Published Dose Estimates

There are a limited number of dose estimates for Rb-82, partly due to the fact that the effective dose concepts introduced by the ICRP were not well established at the

time that Ryan et. al. [32] and Kearfott [33] published their biodistribution data. While some studies did not report the effective dose, a list of published organ doses (converted to modern SI units) can be found in Table 1.2.

Note that the Oak Ridge Institute for Science and Education (ORISE) [35] used the biodistribution data from the in-vivo study by Ryan et. al. [32], whereas the Bracco [36] values were derived from an unspecified combination of the biodistribution data from Ryan, and the rat extrapolation by Kearfott [33].

Additionally, several dose estimates have been published by various authors using the above values. A summary of all published effective dose estimates can be found in Table 1.3.

Note that the publications by Bracco [24] and Kearfott [19] both use a much older and out-of-date dosimetry system and quote the total body dose instead of the ED or EDE. The total body dose does not take into account inhomogeneities in tracer uptake. Also note that the paper by Stabin [37] used the biodistribution data from the publication by Ryan [32]. The paper by Einstein et. al. [38] used data from both the publication by Bracco and the ICRP biodistribution data (the biodistribution source is in brackets).

1.4 Research Objectives

Since Rb-82 is an internally deposited positron emitter (it is injected as a saline solution) the dose to organs comes from gamma and beta emissions which occur inside the subject. The goal of this research project was to accurately and quantitatively measure the effective dose of a Rb-82 study with dynamic PET/CT imaging in humans. This imaging modality produces 3D volumetric measurements of activity in the subject. The effective dose will be defined in the next chapter. This type of study has not been previously conducted in man with PET/CT. The large discrepancies

Table 1.2
Published organ doses for Rb-82.

Organ	ICRP53 [8] mGy/MBq	ORISE [35] mGy/MBq	Bracco [36] mGy/MBq	Kearfott [33] mGy/MBq	Leggett [34] mGy/MBq	Ryan [32] mGy/MBq
Adrenals	2.0×10^{-2}	4.4×10^{-4}	9.7×10^{-4}	5.4×10^{-4}	3.5×10^{-3}	
Bladder Wall	1.7×10^{-4}	3.6×10^{-4}		4.6×10^{-4}	3.1×10^{-4}	
Bone Surfaces	6.7×10^{-4}	3.3×10^{-4}			5.5×10^{-4}	
Brain		3.2×10^{-4}		6.8×10^{-5}	1.7×10^{-4}	
Breast	1.9×10^{-4}	3.3×10^{-4}				
Cortical Bone			4.1×10^{-6}	4.3×10^{-4}		
Eye				1.7×10^{-6}		
Fat				2.6×10^{-4}		
Gallbladder Wall		4.2×10^{-4}				
Stomach Wall	3.8×10^{-3}	3.8×10^{-4}	8.6×10^{-4}	5.7×10^{-4}	1.9×10^{-3}	
Small Intestine	3.9×10^{-3}	3.8×10^{-4}	1.4×10^{-3}	1.3×10^{-3}	3.9×10^{-3}	
Trabecular Bone			2.5×10^{-6}	4.3×10^{-4}		
ULI Wall	3.9×10^{-3}	3.8×10^{-4}	8.6×10^{-4}	6.8×10^{-4}	2.9×10^{-3}	
LLI Wall	3.9×10^{-3}	3.6×10^{-4}	8.6×10^{-4}	7.0×10^{-4}	2.8×10^{-3}	
Heart Wall	3.3×10^{-3}	1.8×10^{-3}	1.9×10^{-3}	3.5×10^{-3}	6.3×10^{-3}	2.0×10^{-3}
Kidneys	1.8×10^{-2}	9.0×10^{-3}	8.6×10^{-3}	5.1×10^{-3}	9.2×10^{-3}	8.4×10^{-3}
Liver	9.7×10^{-4}	8.3×10^{-4}	8.6×10^{-4}	7.3×10^{-4}	1.0×10^{-3}	8.1×10^{-4}
Lungs	2.4×10^{-3}	1.7×10^{-3}	1.7×10^{-3}	1.9×10^{-3}	2.5×10^{-3}	1.6×10^{-3}
Muscle		3.5×10^{-4}		2.6×10^{-4}	2.2×10^{-4}	
Ovaries	2.4×10^{-4}	3.7×10^{-4}	3.8×10^{-4}			3.2×10^{-4}
Pancreas	4.5×10^{-3}	4.2×10^{-4}	6.2×10^{-4}	6.2×10^{-4}	2.8×10^{-3}	
Red Marrow	9.9×10^{-4}	4.5×10^{-4}	3.8×10^{-4}	4.6×10^{-4}	5.7×10^{-4}	3.5×10^{-4}
Skin		3.2×10^{-4}		4.1×10^{-4}	5.3×10^{-4}	
Spleen	5.0×10^{-3}	4.1×10^{-4}		4.9×10^{-4}	4.4×10^{-3}	
Testes	1.3×10^{-4}	2.6×10^{-4}	3.0×10^{-4}	1.6×10^{-4}	3.4×10^{-4}	5.4×10^{-4}
Thymus		3.7×10^{-4}				
Thyroid	3.8×10^{-2}	3.4×10^{-4}		4.3×10^{-4}	1.0×10^{-2}	
Uterus	2.1×10^{-4}	3.7×10^{-4}				
Other Tissue	2.3×10^{-4}					

Table 1.3
Published dose estimates for Rb-82.

Author	Dosimetry System	Value	Units	Designation
ICRP	ICRP 26 [4]	4.8×10^{-3}	mSv/MBq	EDE
ICRP	ICRP 53 [8]	3.4×10^{-3}	mSv/MBq	ED
ORISE	ICRP 26 [4]	1.2×10^{-3}	mSv/MBq	EDE
Bracco [36]		4.3×10^{-4}	mGy/MBq	Total Body
Kearfott [33]		4.3×10^{-4}	mGy/MBq	Total Body
Stabin [37]	ICRP 60 [5]	7.9×10^{-4}	mSv/MBq	ED
	ICRP 26(ICRP) [4]	5.7×10^{-3}	mSv/MBq	EDE
	ICRP 60(ICRP) [5]	7.3×10^{-3}	mSv/MBq	ED
	ICRP 103(ICRP) [6]	6.9×10^{-3}	mSv/MBq	ED
Einstein et. al. [38]	ICRP 26(Bracco) [4]	1.7×10^{-3}	mSv/MBq	EDE
	ICRP 60(Bracco) [5]	1.6×10^{-3}	mSv/MBq	ED
	ICRP 103(Bracco) [6]	1.3×10^{-3}	mSv/MBq	ED

between current published dose estimates are highlighted in Figure 1.2.

The two ICRP values are the EDE published in ICRP 26 [4] and the ED published in ICRP 53 [8], both use the same biodistribution data published in ICRP 26 based on a theoretical blood flow model. The value from ORISE [35] is the EDE based on the published biodistribution data from Ryan et. al [32], and the value from Stabin [37] is a calculation of the ED also based on the Ryan biodistribution data. The data by Ryan et. al. were collected using a gamma camera and is a planar imaging technique, whereas the theoretical blood flow model is not a true measurement. Modern day PET/CT imaging enables a truly quantitative volumetric measurement of the activity concentration in the patient. The increase in usage of Rb-82 and the large discrepancies between the in-vivo measurements by Ryan et. al. [32] and the theoretical blood flow model by the ICRP [4] as shown in Figure 1.2 necessitate a study of this magnitude.

Figure 1.2: Published ED and EDE dose estimates.

1.5 Summary

The following is a summary of the content of the subsequent chapters:

Chapter 2 is on radiopharmaceutical dosimetry. This section gives a description of all internal dosimetry systems currently in use.

The principles and physics of PET imaging are presented in Chapter 3. Issues that limit resolution and accuracy of PET measurements are discussed.

Partial volume averaging corrections need to be performed because accurate determination of the activity concentration in source organs is essential, and if these corrections are not performed the activity concentrations will be underestimated. Techniques for partial volume averaging, GI-tract correction, and PET/CT co-registration misalignments are all discussed in chapter 4.

Chapter 5 reports the results from stress and rest dose calculations from this work. Furthermore, a comparison is made between the stress and abridged rest data, and

the breakthrough doses for Sr-82 and Sr-85 are given.

Chapter 6 compares and analyzes the results from the rest data using the effective dose calculated with the ICRP 103 tissue weighting factors.

Chapter 2

Radiopharmaceutical Dosimetry

2.1 Overview

In contrast to external beam dosimetry, the dosimetry of radiopharmaceuticals (internal emitters) is a more complicated problem. First, the dose depends on how the radiopharmaceutical concentrates within the subject. The concentration in organs will depend on the chemistry of the organ (biochemistry), and the transport of the isotope through the body (usually through the blood). This is also why the radioactive element is chosen and chemically bonded to form a “radio-tracer”. The tracer has a unique chemical property useful in imaging applications that relies on the biochemical interaction in the patient. A tracer with no unique chemical properties that is uniformly distributed throughout the patient would not be useful. However the uptake of a radiopharmaceutical into organs or tissues will be different for each patient. This is due to the fact that various factors relating to anatomy, age, and disease will alter the blood flow to each organ. Therefore, it is necessary to perform a dose assessment on a sample of subjects, and generalize the results to a larger population as a measure of the statistical probability that a subject would get a certain dose. A second complication comes from the fact that the activity concentrations in living tissue cannot always be measured directly. Typically, only in animal studies can samples of

organs be excised and directly measured. Animal to human extrapolations are not true representations of the dose within a human. Thus quantitative measurements in humans must be made when possible. This can be done with planar gamma cameras or with PET imaging. All the organs must be correctly identified and the activity in them properly quantified. PET/CT has the advantage that a CT scan of the patient is always taken along with the PET scan and can be used for anatomical definition of tissues as well as attenuation and scatter correction of the PET measurements.

Dosimetry information is used to assess the damage to biological tissues and to quantify the probabilistic (stochastic) risk of long term fatal cancer to a subject. This information is used for radiological protection of radiation workers and for environmental and public health and safety. With the increased use of ionizing radiation to help diagnose and treat patients, dosimetry information is essential for determining the risk versus benefit of any procedure used on a patient. Without this information it would be impossible to know if one imaging or treatment procedure is safer than another. Thus information on the dose for various techniques can be used to minimize the risk to patients and reduce the potential harm. Therefore, dosimetry is an essential method used to quantify and improve upon existing diagnostic or treatment procedures in medicine.

The “absorbed dose” in a medium is the amount of energy deposited by ionizing radiation per unit mass. The ionizing radiation may come from an internal source to the system (like a radiopharmaceutical) or from an external source like an x-ray beam. In the past the unit of absorbed dose was the rad ($0.01 \text{ joule kg}^{-1}$), but the modern-day SI unit is the gray (1 joule kg^{-1}). By comparison “Exposure” (X) is a quantitative assessment of the potential ability for the radiation to produce ionization in air. The specific unit of exposure is the Roentgen (R). [39] The unit of exposure is not often used in the dosimetry of internal emitters.

There can be two harmful effects when ionizing radiation interacts with biological

tissue. The first is direct damage to the tissue, like the destruction of sensitive cellular elements. Since this effect most often involves a threshold level of exposure, it is called a “deterministic effect”. [6] The other damaging effect of exposure to radiation is more long-term, usually as the result of genetic damage, which may not show up for years due to a latency period. This is therefore called a “stochastic effect” as it involves a probability of long-term damage. [6]

From 1970 onward, both the International Commission on Radiological Protection (ICRP) and the Medical Internal Radiation Dose (MIRD) committee developed independent systems for quantification and measurement of dose by internal emitters. Neither institution is a regulatory body, but both have been instrumental in helping to form radiation protection guidelines for the medical community to protect members of the public. Both institutions define procedures for the calculation of dose to a patient or radiation worker exposed to an internal emitter (originally inhaled radionuclides but expanded to include injected radionuclides). Until 2009 only the ICRP defined a method for determining the stochastic risk taking into account an inhomogeneous distribution of the radionuclide, as well as the relative sensitivity of the organs to radiation exposure. These will be defined in the following chapter as the effective dose equivalent (EDE) and the effective dose (ED).

2.2 A Brief History of The ICRP

In 1962 the concepts of the dose equivalent (DE), the radiation quality factor (QF) and the distribution factor (DF) were introduced by the ICRP. The distribution factor was introduced in order to quantify the biological effect of internal emitters that are not uniformly distributed within the body. The radiation quality factor was defined (on a common scale) to be the radiation incurred by an exposed person for all radiation types. The dose equivalent was measured in units of röntgen equivalent in man (rem)

and was calculated by the product of absorbed doses (D) with an appropriate QF, and DF as shown in equation 2.1. [40] Other factors were added in situations where the isotope had a very non-uniform distribution (which is why the dots are present in equation 2.1), such as in bone seeking isotopes. Dose Equivalent (DE) was an early attempt by the ICRP to quantify the stochastic risk of radiation exposure.

$$DE = D \times QF \times DF \times \dots \quad (2.1)$$

The quality factors were derived from the stopping power (the symbol used in 1962 was LET_{∞}) of radiation in tissue. This was defined by the ICRP as the energy loss per unit distance of charged particles originally set in motion by electro magnetic (EM) radiation, neutrons, or charged particles from a radiation source. From this, the quality factor of radiation was derived as shown in Table 2.1. [40] Neutrons are notably absent from Table 2.1, but are taken to have a quality factor of 10 if the precise neutron energy distribution is not known, and calculated values exist for known neutron energy distributions.

Table 2.1
Early radiation quality factors.

Radiation Type	QF
β^+ , β^- , Internal Conversion e^- , γ -rays, and x-rays	1.0
e^- radiations, β^+ , and β^- with maximum energies ≤ 0.03 MeV	1.7
α particles	10
Fission Fragments and recoil nuclei from alpha emissions	20

In 1965 the ICRP further determined that DE was directly proportional to the stochastic risk to a person from a radiation exposure. To truly quantify risk from radiation exposure, the absorbed organ doses must be weighted by a modifying factor that takes into account the radiation type and the spatial distribution of the absorbed dose, and the dose equivalent was used to accomplish this task. [39] So for a given

organ and modifying factors (MF) of radiation, the DE was defined by equation 2.2. These modifying factors include the QF, DF or any other factors necessary, and to account for an arbitrary number of modifying factors we denote the symbol ‘i’. [41]

$$DE = D \times MF_1 \times MF_2 \times \dots \times MF_i \quad (2.2)$$

At this point in time the radiation protection system was set up with a series of maximum permissible doses. The DE value was calculated for all critical organs and then compared with the maximum limits. The evolution of dosimetry within the ICRP naturally progressed to a single number used to quantify long term risk from radiation exposure.

2.3 The ICRP System for Dosimetry of Radionuclides

In 1977 the ICRP introduced the concept of “detriment”. This was a quantitative method of evaluating both the probability of harm incurred after exposure and also the severity of the effect. [4] At the same time they introduced the tissue weighting factors, and a short time later the effective dose equivalent (EDE). To better quantify the detriment of radiation exposure, the damaging potential of the radiation type must be considered. The absorbed dose by itself does not quantify the detriment; it is the dose equivalent which accomplishes this. The dose equivalent was redefined in 1977 as shown in equation 2.3. [4]

$$H = D \times Q \times N \quad (2.3)$$

where: D is the absorbed dose, Q is the quality factor, and N is the product of all other factors. At the time (in 1977) N was defined as unity (= 1). The “quality

factor” ‘Q’ is similar to the one defined in Section 2.2 (QF) and is a function of the collision stopping power. Its purpose is to quantify the effect of detriment by the microscopic distribution of the absorbed energy. For a spectrum of radiation, the ICRP recommended the effective quality factors $\bar{Q}$ given table 2.2. To differentiate between “dose equivalent” and “absorbed dose” the ICRP defined the unit for dose equivalent to be the sievert (defined as: $\text{Sv} = 1 \text{ joule kg}^{-1}$).

Table 2.2
Radiation quality factors in ICRP 26 [4].

Radiation Type	QF
x-rays, γ rays and electrons(β^+ , β^-)	1
Neutrons, protons and singly-charged particles of rest mass greater than one atomic mass unit of unknown energy	10
α -particles and multiply-charged particles (and particles of unknown charge), of unknown energy	20

In ICRP 60, the name “quality factor” was changed to “radiation weighting factor” (with the symbol w_R) and redefined as in Table 2.3. [5] The radiation quality factors from that point on, are derived from Relative Biological Effectiveness (RBE) values rather than the stopping power.

In ICRP 103, published in 2007, these were redefined again (but under the same name and symbol) as defined in Table 2.4.

The name “dose equivalent” was changed to “equivalent dose” in ICRP 60 [5], which was published 1991 (using the symbol H_T), and it is defined as in equation 2.4:

$$H_T = \sum_R w_R D_{T,R} \quad (2.4)$$

where: w_R is the radiation weighting factor, and $D_{T,R}$ is the absorbed dose to the tissue or organ T, due to radiation R. This definition continues to the present, and is used to calculate both the effective dose equivalent (EDE) and later the effective dose (ED).

Table 2.3
Radiation weighting factors in ICRP 60 [5].

Type and energy range	Radiation weighting factor, w_R
Photons, all energies	1
Electrons and muons, all energies	1
Neutrons, energy < 10 keV	5
10 keV to 100 keV	10
> 100 keV to 2MeV	20
> 2 MeV to 20 MeV	10
> 20 MeV	5
Protons, other than recoil protons, energy > 2 MeV	5
Alpha particles, fission fragments, heavy nuclei	20

(All values relate to the radiation incident on the body or, for internal sources, emitted from the source)

Table 2.4
Radiation weighting factors in ICRP 103 [6].

Radiation type	Radiation weighting factor, w_R
Photons	1
Electrons ^a and muons	1
Protons and charged pions	2
Alpha particles, fission fragments, heavy ions	20
Neutrons	A continuous function of neutron energy.

All values relate to the radiation incident on the body or, for internal radiation sources, emitted from the incorporated radionuclide(s).

2.3.1 The Effective Dose Equivalent

The effective dose equivalent is still used by some governmental regulatory authorities, and all of the early papers quote the EDE in their dose assessments. The concept of EDE was introduced in 1977 in ICRP publication 26 and 30, but was simply called the dose-equivalent limit for occupational exposure. The name was changed to effective dose equivalent in 1981 (ICRP publication 32) [7], and this terminology is in current use. The EDE (now denoted by H_E) is defined in equation 2.5.

$$H_E = \sum_T w_T H_T \quad (\text{with } \sum_T w_T = 1) \quad (2.5)$$

where: H_T is the mean dose equivalent in tissue T, and w_T is the tissue weighting factor. The tissue weighting factors are defined in Table 2.5, and represent the ratio of the stochastic risk from tissue T to the total risk from a uniform whole body irradiation. Thus the tissue weighting factors represent the risk factor of an organ, and the different values for organs are reflective of their relative sensitivities to radiation. The principle of this system is that the stochastic risk to an exposed person should be the same whether or not the whole body was uniformly irradiated, or the dose distribution was uneven throughout the body. If the dose distribution is uniform throughout an exposed person, the total risk factor is one. [42] Thus the tissue weighting factors always sum to unity.

Table 2.5
ICRP 32 tissue weighting factors [7].

Organ	w_T	$\sum w_T$
Remainder(total)	0.30	0.30
Gonads	0.25	0.25
Breast	0.15	0.15
Red bone marrow and Lungs	0.12	0.24
Thyroid and Bone Surfaces	0.03	0.06
Total		1.00

The “remainder” must further be explained as this is the most complicated and least understood part of the dosimetry protocol. The ICRP in publication 26 [4] recommends that each of the five organs or tissues considered part of the remainder which receive the highest dose equivalent should have a tissue weight of 0.06. The dose equivalent of all other remaining tissues is left out of the calculation (i.e. they are ignored). The list of organs considered part of the remainder has changed somewhat over the years. The gastro-intestinal (GI) tract is considered four separate organs for the purposes of radiation protection. The GI tract is split into the stomach, small intestine (SI), the upper large intestine (ULI), and the lower large intestine (LLI). The ULI is made up of the ascending and transverse colon, whereas the LLI is made up of the descending and sigmoid colon. ICRP 26 also mentions that the liver and salivary glands could also be considered as part of the remainder as there was some evidence at the time that cancer could be induced in these tissues at moderate doses. At the time it was not known if muscle or adipose tissue should be included, and the eye was considered a sensitive organ but not the skin. [4] In ICRP publication 30 [43] first the skin and lens of the eye were excluded as part of the remainder, and then in ICRP publication 32 [7] the hands, forearms, feet and ankles. Finally in 1987, the ICRP in publication 53 [8] (which also excluded the lens of the eye) provided the most recent list of tissues that should be considered for dosimetry purposes - see Table 2.6.

The target organs in Group 1 are defined as the organs for which the absorbed dose is always calculated. Group 2 represents a list of potential organs for consideration in dosimetry calculations. These organs would be of special interest due to radiation sensitivity, or would be expected to receive a significantly higher absorbed dose than the average to the rest of the body. This is either due to the organ having high uptake, thus the self dose is high; or it is near other organs of high uptake, and thus is a strongly irradiated target. To better assess the detriment, the EDE was changed to a slightly newer system, that being the “effective dose” (ED). Both methodologies

Table 2.6
Organs and tissues for which the absorbed dose is calculated [8].

Group 1	Group 2
Adrenals	Brain
Bone surfaces	Gallbladder wall
Breast	Heart
Gastrointestinal tract	Salivary glands
stomach wall	Spinal cord
small intestine wall	
upper large intestine wall	
lower large intestine wall	
Kidneys	
Liver	
Lungs	
Ovaries	
Pancreas	
Red bone marrow	
Spleen	
Testes	
Thyroid	
Urinary bladder wall	
Uterus	
Other tissues (e.g. muscle)	

use the same principles but are treated slightly differently and thus warrant different names.

2.3.2 The Effective Dose

The effective dose equivalent (EDE) was changed to the effective dose (ED) and was first introduced in 1991 by the ICRP in publication 60, as the term was considered simpler and EDE unnecessarily cumbersome. It is in principle the same as EDE but with the tissue weighting factors defined differently, and the remainder is also treated differently. The equivalent dose in tissue ‘T’ is still weighted by the tissue weighting factors ‘ w_T ’. However the values and distribution of these factors have changed - see Table 2.7. The tissue weighting factors are also explained as being the organ or tissue contribution to the total detriment due to whole body irradiation effects. To summarize, the effective dose is defined as the sum of all weighted equivalent doses for all organs listed by the ICRP, as shown in equation 2.6, [5]

$$E = \sum_T w_T \cdot H_T \quad (2.6)$$

where: H_T is the equivalent dose in tissue or organ T, and w_T is the tissue weighting factor for tissue T.

The ICRP introduced new tissue weighting factors in ICRP 60 [5], the values of which are listed in Table 2.7. Regarding these updated values, the ICRP did not rule out future changes (see Section 2.3.3). The tissue weighting factors depended on the current knowledge of radiobiology at the time, and as knowledge in these areas improved the tissue weighting factors changed. However, the definition of the equivalent dose and the effective dose were independent of the tissue weighting factor values and thus remain unchanged.

The ICRP made it a point to note that the remainder was to be calculated from

Table 2.7
ICRP 60 [5] tissue weighting factors.

Tissue or organ	w_T	$\sum w_T$
Gonads	0.20	0.20
Bone Marrow (red), Colon, Lungs, and Stomach	0.12	0.48
Bladder, Breasts, Liver, Oesophagus, Thyroid, and Remainder	0.05	0.30
Skin and Bone Surfaces	0.01	0.02
Total		1.00

biological data from equal numbers of both sexes over a wide age range and so could apply to either sex. The remainder is now defined as a specific set of organs and include: adrenals, brain, upper large intestine (ULI), small intestine (SI), kidney, muscle, pancreas, spleen, thymus, and uterus. At this time the ICRP reserved the right to include additional organs in the future if they were deemed radiologically sensitive. This specific list was compiled from the relative sensitivity of the organ, the organ's susceptibility to develop cancer, and its tendency to be selectively irradiated for various studies. The biggest change to the definition of the remainder comes from the so called "splitting rule", as stated in ICRP 60. [5] The splitting rule states that if one of the remainder tissue receives an equivalent dose which is greater than the highest dose of the twelve organs for which there is a specific tissue weighting factor, then that organ will have a 0.025 tissue weighting factor applied to it, and a tissue weighting factor of 0.025 will be applied to the average of the rest of the remainder equivalent doses. This definition has lead to much confusion in the published literature.

When the ICRP introduced this new dosimetry protocol in ICRP 60 [5], they did not mention how the colon was defined. However in ICRP 62 [44] (1991) the colon was defined as Lower Large Intestine (LLI), with the Upper Large Intestine (ULI) to be part of the remainder. This changed in ICRP 80 [45] where the ULI is removed

from the remainder and the equivalent dose to the colon H_{colon} is taken as the mass weighted average, as defined in equation 2.7,

$$H_{colon} = 0.57H_{ULI} + 0.43H_{LLI} \quad (2.7)$$

where: H_{ULI} and H_{LLI} are the equivalent doses in the walls of the ULI and LLI, respectively. This definition continues to the present ICRP 103 system to be discussed in Section 2.3.3.

With respect to the remainder, what is not mentioned in ICRP 60 [5] but later in ICRP 68 [46] is that the remainder is the “mass weighted average” of the equivalent doses. This applies whether or not the splitting rule is used. The equivalent dose (H) to the whole remainder requiring the splitting rule is given by equation 2.8,

$$H_{remainder} = \frac{\sum_{T=1}^{T=10} m_T H_T}{\sum_{T=1}^{T=10} m_T}, \quad \text{if } H_T \leq H_{max} \quad (2.8)$$

where: H_{max} , is the highest equivalent dose of the organs with explicit tissue weighting factors, and H_T is the equivalent dose to the remainder tissue T , and m_T is the mass of that tissue. If the splitting rule is applied for a tissue T' (whose dose is greater than the highest doses of the tissues with specific weighting factors), the equivalent dose must be calculated using equation 2.9,

$$H_{remainder} = 0.5 \frac{\sum_{T=1(T \neq T')}^{T=10} m_T H_T}{\sum_{T=1(T \neq T')} m_T} + 0.5H_{T'}, \quad \text{if } H_{T'} > H_{max} \quad (2.9)$$

where: $H_{T'}$ is the equivalent dose of the remainder tissue or organ which is greater than the highest equivalent dose of the organs with specific tissue weighting factors.

[46] The effective dose is then given by equation 2.10, [46]

$$E = \sum_{T=1}^{T=12} w_T H_T + w_{remainder} H_{remainder} \quad (2.10)$$

2.3.3 The Effective Dose Using ICRP Publication 103

In 2007 the ICRP using updated information revised their dosimetry system once again in publication 103. [6] Regarding the tissue weighting factors, ICRP 103 added new tissues as seen in Table 2.8, and redefined the remainder, thereby simplifying the calculation.

Table 2.8
ICRP 103 [6] tissue weighting factors.

Tissue	w_T	$\sum w_T$
Bone-marrow (red), Colon, Lung, Stomach,	0.12	0.72
Breast, Remainder tissues*		
Gonads	0.08	0.08
Bladder, Oesophagus, Liver, Thyroid	0.04	0.16
Bone surface, Brain, Salivary glands, Skin	0.01	0.04
Total		1.00

*Remainder tissues: Adrenals, Extrathoracic (ET) region, Gall bladder, Heart, Kidneys, Lymphatic nodes, Muscle, Oral mucosa, Pancreas, Prostate (σ), Small intestine, Spleen, Thy-mus, Uterus/cervix (φ).

The largest change to the newest system is that the so-called splitting rule was removed. Instead, the tissue weighting factor w_T for remainder tissues was divided equally among the 14 tissues listed as part of the remainder, or a weighting factor of 0.0086 each - for the adult (hermaphrodite) phantom. For the female or male phantoms, there are 13 organs each since there are 12 common organs or tissues and one specific organ to the male (the prostate) and one for the female (the uterus/cervix). Thus the tissue weighting factor is split into 0.0092 each. Each remainder tissue has

a tissue weighting factor which is less than the lowest tissue weighting factor (a value of 0.01). The important change was that in the previous system, when applying the splitting rule it was possible for a tissue to have a tissue weighting factor greater than a tissue with a specific tissue weighting factor assigned. This new system is reflective of a constant stochastic risk to an organ or tissue regardless of the dose to that organ or tissue. [6] Since organs in the remainder and organs with specific tissue weights always have the same weight, the system is additive. The older ICRP systems were not truly additive as organs could have been weighted differently (and often were) due to the splitting rule, meaning the stochastic risk was not equally weighted for each possible study. Additionally, the mass weighting of the remainder tissues was removed, although the colon is still defined as the mass weighted average of the ULI and LLI as in equation 2.7. The reason for this change is that organs with large differences in mass could lead to a bias of the effective dose towards heavier organs for some radionuclides (ICRP 103, 2007). In particular this leads to a bias towards the muscle tissue, which has a large mass, but is not very radiologically sensitive. The ICRP does not rule out adding more tissues to the remainder; however adipose tissue was judged to have negligible stochastic risk, and connective tissues are taken into account in the contribution to cancer of the named organs.

The current system recommends an arithmetic average of all 14 tissues in the remainder (13 for a sex specific case), and no longer a mass-weighted average. There is no explicit method specified by the ICRP when one of the tissue equivalent doses is unknown. However, there is a specific formula given in ICRP 103 [6] to calculate a gender-specific equivalent dose for the remainder as shown in equation 2.11.

$$H_{rmd}^M = \frac{1}{13} \sum_{T=1}^{13} H_T^M \quad \text{and} \quad H_{rmd}^F = \frac{1}{13} \sum_{T=1}^{13} H_T^F \quad (2.11)$$

where: H_{rmd}^M and H_{rmd}^F are the equivalent doses to the male and female remainder

respectively, and H_T^M and H_T^F are the equivalent doses to remainder tissue ‘T’ for the male and female respectively. To get the adult effective dose, equation 2.12 is used for this new protocol. [6]

$$E = \sum_T w_T \left[\frac{H_T^M + H_T^F}{2} \right] \quad (2.12)$$

Note that “T” in this case represents all tissues with specific weighting factors and the overall remainder as calculated by equation 2.11. It is important to remember that the tissue weighting factors are gender-averaged over all age groups. [6]

2.4 The MIRD System

In 1968 (and revised in 1976) the Medical Internal Radiation Dose (MIRD) Committee of the Society of Nuclear Medicine published MIRD pamphlet Number 1, which introduced calculation methods for absorbed dose to whole organs, subregions within a tissue, voxelized tissue structures, and individual cellular compartments from an internally deposited radionuclide. [47] The ICRP had independently developed a similar system, but used different terminology. The ICRP went further and defined an equivalent dose (weighted by radiation weighting factors) and an effective dose (weighted by tissue weighting factors) that the MIRD committee did not officially endorse until 2009 in MIRD pamphlet 21. [47] This pamphlet standardized the nomenclature and added the effective and equivalent doses to the MIRD system.

The absorbed dose to an organ from an internal emitter depends on the mass of the organ, its size and shape relative to any potential sources, as well as the organs and tissues between these sources and the target. The dose rate $\dot{D}$ (Gy/s) to tissue r_T from source r_S is given in equation 2.13,

$$\dot{D}(r_T, t) = \sum_{r_S} A(r_S, t) S(r_T \leftarrow r_S, t) \quad (2.13)$$

where $A(r_S, t)$ is the time dependent activity [Bq(t)] of the radionuclide in the source tissue r_S , and $S(r_T \leftarrow r_S, t)$ [Gy (Bq s)⁻¹] is the time dependent S-parameter which quantifies the dose rate to target tissue r_T from source tissue r_S at time t . [47]

These S-parameters are specific to the radionuclide, patient age, patient gender, and are calculated using Monte Carlo techniques from phantoms specifying the geometry and internal organ structure of a reference human. The source and target tissues could include a whole organ such as a liver, or a substructure of that organ or tissue such as the medulla and cortex of the kidney or the white and grey matter of the brain, etc. In either case the activity $A(r_s, t)$ is assumed to be uniformly distributed throughout the organ/tissue/substructure. Note that these quantities are referenced to a time ‘ t ’ after the activity has been administered. The mean absorbed dose to an organ or tissue is calculated by integration over a period T_D , and is given in equation 2.14. [47]

$$D(r_T, T_D) = \int_0^{T_D} \dot{D}(r_T, t) dt = \sum_{r_S} \int_0^{T_D} A(r_s, t) S(r_T \leftarrow r_S, t) dt \quad (2.14)$$

The dose integration period ‘ T_D ’ is taken to be infinity for long lived isotopes, but for short-lived isotopes (or ultra-short-lived such as Rb-82) it can be taken to be a multiple of the half-life that satisfies accuracy requirements. The “dose integration period” is sometimes called the “dose commitment period”. For the purposes of radiation protection the dose commitment period is 50 years for adults exposed at 20 years of age, and is variable up to 70 years for child, infant, or adolescent exposures. The absorbed dose coefficient given in equation 2.15 is used when the activity in the source organ $A(r_s, t)$ is normalized to a unit administered activity A_0 . The activity in the source organ $A(r_s, t)$ is divided by the administered activity and is the fraction

of administered activity in the source organ with the symbol $a(r_S, t)$. [47]

$$d(r_T, T_D) = \sum_{r_S} \int_0^{T_D} a(r_S, t) S(r_T \leftarrow r_S, t) dt \quad (2.15)$$

The S-parameters are calculated from absorbed fractions using Monte Carlo techniques from either stylized phantoms (such as the M. Cristy and K. F. Eckerman [48], or the MIRD phantom [49]), or a voxel-based phantom which describes the geometric and spatial effects of the dose distribution from the source to the target organs. These absorbed fraction values are usually tabulated data sets and are radionuclide specific. In any given nuclear transformation, there will be a number of possible nuclear emissions associated with transitions to different energy states of the nucleus. Each transition will emit a particle with some characteristic or average energy value. All the possible transitions and their probabilities must be taken into account when calculating the S-parameters. The S-parameter for a target tissue r_T from a source tissue r_S is calculated using equation 2.16. [47]

$$S(r_T \leftarrow r_S, t) = \frac{1}{M(r_t, t)} \sum_i E_i Y_i \phi(r_T \leftarrow r_S, E_i, t) \quad (2.16)$$

where: E_i is the mean energy of nuclear transition 'i', Y_i is the number of nuclear transitions per nuclear transformation, $M(r_t, t)$ is the time dependant mass of the target tissue, and $\phi(r_T \leftarrow r_S, E_i, t)$ is the absorbed fraction of radiated energy in the source tissue that is absorbed in the target tissue. The absorbed fraction is defined as unity (total absorption) for all beta ($\beta^{+/-}$) emissions whose range is short relative to the tissue size. It is calculated using the Monte Carlo technique for a specific phantom, and for a specific organ. However, these absorbed fractions are not radionuclide specific. For cases where there is a large variation of the absorbed fraction across the spectrum of nuclear transition energies (E_i), the sum must be replaced with an integral over the spectrum of energies. The quantities E_i and Y_i

are usually expressed as: $E_i Y_i = \Delta_i$, which is the mean energy of nuclear transition ‘i’. The specific absorbed fraction, as defined in equation 2.17, is the ratio of the absorbed fraction to the target organ mass. [47]

$$\Phi(r_T \leftarrow r_S, E_i, t) = \frac{\phi(r_T \leftarrow r_S, E_i, t)}{M(r_T, t)} \quad (2.17)$$

Using these definitions the final equation for the S-parameter is given by equation 2.18.

$$S(r_T \leftarrow r_S, t) = \sum_i \Delta_i \Phi(r_T \leftarrow r_S, E_i, t) \quad (2.18)$$

The equations presented so far have been the formulation of the general case for dosimetry of internally deposited radionuclides. While these equations are time-varying, the organ and target masses and overall structures are typically assumed to be time-independent. Thus the calculation of absorbed dose to a target tissue from a source tissue, which remains constant over a given time interval, is expressed in equation 2.19. [47]

$$D(r_T, T_D) = \sum_{r_S} \tilde{A}(r_S, T_D) S(r_T \leftarrow r_S) \quad (2.19)$$

The quantity $\tilde{A}(r_S, T_D)$ is the time integrated activity, or total number of nuclear transformations (Bq s) within the source organ, as shown in equation 2.20. Also $S(r_T \leftarrow r_S)$ is defined as the ratio of the time dependent rates in Equation 2.13.

$$\tilde{A}(r_S, T_D) = \int_0^{T_D} A(r_S, t) dt \quad (2.20)$$

Therefore, the time-independent absorbed dose coefficient is calculated as shown in equation 2.21.

$$d(r_T, T_D) = \sum_{r_S} \tilde{a}(r_S, T_D) S(r_T \leftarrow r_S) \quad (2.21)$$

The quantity $\tilde{a}(r_S, T_D)$ is the time-integrated activity coefficient as calculated in equation 2.22, also known as the residence time. The residence time represents a physical quantity specific to the biology of the patient, and it is this quantity that is fundamentally different between patients, and thereby leads to different dose estimates. Therefore, accurate determination of the residence times within patients is essential to an accurate determination of the effective dose (or effective dose estimate).

$$\tilde{a}(r_s, T_D) = \frac{1}{A_0} \int_0^{T_D} A(r_s, t) dt \quad (2.22)$$

The equivalent dose is the sum of all contributions to the absorbed dose in target tissue r_T by radiation type R , weighted by the radiation weighting factors w_R (defined in Table 2.4), as shown in equation 2.23. When the dose coefficients are used in place of the absorbed doses this formula give the equivalent dose coefficient $H(r_T, T_D)$.

$$H(r_T, T_D) = \sum_R w_R D_R(r_T, T_D) \quad (2.23)$$

For more information on the radiation weighting factors and the effective dose and equivalent dose please see Section 2.3.

2.4.1 Total Body Dose

Prior to the amalgamation of the effective dose as defined by the ICRP with the MIRD dosimetry method, the MIRD method for dosimetry used the total body dose to quantify stochastic risk. The total body dose specifies the total energy deposited in the whole body divided by the total body mass. It did not take into account inhomogeneities in tracer uptake throughout the body. Total body dose is typically

much lower than the effective dose using the same biodistribution information, and thus underestimates the dose to patients. [50] As a result, the total body dose is not as useful as the effective dose (or effective dose equivalent) in quantifying stochastic risk, and it will not be discussed further in this work.

2.5 The OLINDA/EXM Dosimetry Program

The Organ Level Internal Dose Assessment (OLINDA)/ EXponential Modeling (EXM) program is a de facto standard software program used for internal dosimetry calculations. This program was written in response to the Food and Drug Administration's (FDA) concern that the previous software program MIRDOSE was sometimes used in a manner that qualifies it to be a medical device under FDA guidelines. [51] The OLINDA/EXM program uses the MIRD method to calculate absorbed dose to various tissues, uses the ICRP 30 [43] tissue weighting factors to calculate the effective dose equivalent, and uses the ICRP 60 [5] tissue weighting factors to calculate the effective dose. The OLINDA/EXM program also introduced a newer dosimetry protocol, herein referred to as the RADAR method, named after their group. [51] The absorbed dose as defined by the RADAR method is given in equation 2.24,

$$D_T = \sum_S N_S \times DF_{T,S} \quad (2.24)$$

where: N_S is the total number of nuclear disintegrations which occur in the source organ per unit injected activity, S is the source organ index, $DF_{S,T}$ is the dose factor as defined in equation 2.25, and T is the target organ index. The N values are equivalent to the residence times as defined in the MIRD system, and are usually expressed in units of MBq-h/MBq. The dose factor given in equation 2.25, is mathematically equivalent to the S factors as defined in the MIRD system (see Section 2.4), and are

based on Monte Carlo calculated specific absorbed fractions (SAF) from the Cristy and Eckerman phantoms. [51]

$$DF_{T,S} = \frac{k \sum_i n_i E_i \phi_i}{m} \quad (2.25)$$

where: k is a proportionality constant used to standardize the units (usually k has units of Gy·kg/MBq·s·MeV), m is the target (T) organ mass, n_i is the number of nuclear transitions per nuclear transformation, E_i is the mean energy of nuclear transition 'i', and ϕ_i is the fraction of absorbed energy in the target (T) from emissions which occur in the source (S). All organ doses in this work were calculated using the OLINDA/EXM dose factors.

2.6 Consolidated Dosimetry System and Nomenclature

Every dosimetry study begins with the determination of the residence times $[\tilde{a}(r_s, T_D)]$ in important source organs. The residence times are calculated by integration of the time activity curve and division by the injected activity as shown in equation 2.22. An accurate determination of the residence times for all significant source tissues is essential to correctly determine the dose and thus the stochastic risk to patients. After the residence times in all important source organs have been determined, organ dose coefficients are calculated by summation over all source residence times multiplied by the respective S-parameters as shown in equation 2.21. It is common to express the organ dose as a ratio of the equivalent dose per unit injected activity in units of mSv/MBq, and is called the equivalent dose coefficient $h(r_T, T_D)$, or sometimes just equivalent dose. This is done using equation 2.23 with the dose coefficients $[d(r_T, T_D)]$ used in place of the absorbed doses $D_R(r_T, T_D)$. The final effective dose is calculated

by summation of all important tissues over the respective ICRP tissue weighting factor, and the effective dose is typically expressed as a ratio of the effective dose per unit injected activity (also in units of mSv/MBq). A summation of the procedure for a dose calculation with units is shown in Table 2.9.

Table 2.9
Effective dose calculation procedure.

Step	Procedure	Formula	Symbol	SI Unit
1	Determination of the residence time from the time activity curve.	2.22	$\tilde{a}(r_s, T_D)$	s
2	Calculation of the dose coefficients using the S-parameters and residence times.	2.21	$d(r_T, T_D)$	Gy/Bq
3	Calculation of the equivalent dose coefficients using radiation weighting factors and dose coefficients.	2.23	$h(r_T, T_D)$	Sv/Bq
4	Calculation of the effective dose (per unit injected activity) using the tissue weighting factors defined by the ICRP and the equivalent dose coefficients.	2.10	H/A_0	Sv/Bq

A summary of the various ICRP systems is also shown in Table 2.10.

Table 2.10
Summary of the ICRP dosimetry systems.

ICRP		w_r	w_t	Remainder	colon
System		(Table Numbers)			
26 [4]	EDE	2.2	3.2	5 Highest Organ Doses	N/A
60 [5]	ED	2.3	2.7	Splitting Rule + Mass Averaged	Taken as LLI
80 [45]	ED	2.3	2.7	Splitting Rule + Mass Averaged	Mass Averaging of ULI and LLI
103 [6]	ED	2.4	2.8	Arithmetic Average	Mass Averaging of ULI and LLI

Since it is imperative to determine accurate residence times, the methodology and equipment should be chosen that best accomplishes this task. PET/CT offers many advantages over other imaging modalities for accurate determination of the residence times. One of the primary advantages of PET/CT is in the absolute quantification

of the activity concentration within the field of view of the patient (usually measured in kBq/cc). PET/CT has accurate corrections for attenuation and scatter which lead to a more accurate representation of the activity concentrations. Additionally modern PET/CT systems can acquire data in a truly 3D acquisition, giving a high sensitivity and a volumetric measurement. One of the main advantages of PET/CT is the acquisition of the CT which is taken with every scan. While the primary purpose of the CT is for attenuation correction, it can also be used for delineation of tissue structures not easily definable on PET alone. This results in an accurate determination of the time activity curves for all visible organs.

Chapter 3

PET Imaging

3.1 Overview

Positron Emission Tomography (PET) is an imaging modality that takes advantage of the physics of positron annihilation. A positron annihilation event produces a coincident signal in the detectors used for PET imaging, the details of which will be presented in this chapter. The use of PET imaging started in the 1950's and has evolved into a fully 3D, quantitative, and volumetric measurement. Since the 1950's the use of PET imaging has risen due to improved technology of PET scanners and better production of PET isotopes, for instance between 1999 and 2006 the use of PET imaging to diagnose cancer rose 36-54%. [52] The main advantages PET has over other imaging modalities are high sensitivity and accurate attenuation correction. A PET scanner can measure activity concentration (Bq/cc) throughout the entire body of the patient. By defining a 3D Volume Of Interest (VOI) on the PET scan, a time activity curve can be produced (representing the change in Bq/cc over time). The determination of time activity curves is crucial for dosimetry purposes; an example of a time activity curve showing Rb-82 transit through the lungs is shown in Figure 3.1.

As described in Chapter 2, the critical step in dosimetry is to accurately determine

Figure 3.1: Time activity curve for Rb-82 transit through the lungs.

the total number of nuclear decays (residence time) in each organ considered a source. Sources are organs that have appreciable accumulation of the tracer above other organs in the body (see Chapter 2.2 for more details on dosimetry). Quantitative determination of the residence time for a source organ can be accomplished first through delineation of the VOI where the organ is located on the PET image to produce the time activity curve. Next, the time activity curve is integrated, then the integrand is multiplied by the organ volume, and the final result is divided by the total injected activity to give the residence time for the source organ. Since some organs are highly active early after injection (such as the blood in the left ventricle cavity), and other organs are only active after some time has passed (such as the heart wall) it is not sufficient to acquire a single time frame with all cumulated activity in it. Doing so would obscure the organ or tissue with delayed uptake due to spill-in (see Section 3.8 for details on spill-in and spill out) from adjacent early uptake regions. It is therefore recommended that the acquisition of data should be divided into separate time frames in order to differentiate the different regions as they become active. This is known as dynamic PET imaging. The total scanning time is split into time intervals specified by the user, and chosen to provide the best diagnostic images.

Time intervals in the early part of the scan are short due to the rapidly changing activity just after injection. Time intervals are longer later in the scan to compensate for significant tracer decay, and thus poorer counting statistics.

3.2 A Brief History of PET Imaging

The application of PET imaging was originally used in brain imaging. In 1951, Wrenn et. al. [53] published an article on the use of annihilation detection for the localization of brain tumors. The study used thallium-activated sodium iodide scintillation crystals, with photomultiplier tubes used for signal amplification. Calibration of the device involved observing coincident events on a commercial oscilloscope as oblique reflections. In 1952 the first clinical PET scanner was developed specifically for brain imaging. [54] This device used two gamma cameras rotated around the field of view. In 1971 Chelser [55] demonstrated the feasibility of a three dimensional PET reconstruction technique. Transmission scans from an external positron source were used to correct attenuation of the signal in the patient, and the effect of the number of projections was investigated. In 1972 the first PET system (PC-I) designed with 2 dimensional detector arrays was published. [54] This system used rotation and translation of the detector banks and incorporated interpolative motion to improve image quality. Data was stored on magnetic drums, but in 1973 Robertson et. al. [56] proposed a 32-ring detector and stored the PET raw data in the core memory of an XDS Sigma II digital computer. The coincidence timing resolution was narrowed to 40-100 ns, and any gamma rays not corresponding to the 511 keV spectrum peak could be suppressed. In 1976 the next generation (PC-II) was widely reported in the literature, and commercial development of the PET scanner began. [54] This device remained the only PET system available for human and animal studies for the next decade. Also in that same year Fill et. al. [57] made a comparison of the SPECT tracer

Tl-201 (73 hour half-life) to the PET tracer Rb-81 (4.7 hour half-life) for imaging of the myocardium. Images were obtained by PET imaging in 20 minutes (including the transmission image required for attenuation correction) compared to 60 minutes with SPECT. This was attributed to the fact that the PET scanner acquired all tomographic projections simultaneously, whereas they were acquired sequentially with Tl-201 SPECT. No other differences were noted between the two imaging modalities. Over the next several decades modern PET systems like the GE Discovery VCT (GE Healthcare) PET system were developed for commercial use, which was used in this research to measure the PET data. These systems employ multiple rows of ring detectors and are capable of either filtered back projection or iterative tomographic reconstruction. Additionally modern PET systems are carefully calibrated to correct for inhomogeneities of the scanner uniformity in the field of view as well as attenuation and noise modeling corrections.

3.3 Radioactive Decay and the Production of Positron Emitting Isotopes

Radiation is the emission of particles or electromagnetic energy and their transport through time and space. In the context of medical physics and radiation protection we are mainly interested in forms of radiation capable of freeing electrons from atomic nuclei or transferring energy to the atomic nucleus, and are called ionizing radiation. In PET imaging, radioactive isotopes that emit positrons are required.

3.3.1 Radioactive Decay

The existence of positrons was first postulated by Paul Dirac in his 1930 paper “A theory of electrons and protons” [58]. Dirac noticed that the solutions to the wave

equation could contain negative terms, and he made the argument that these negative terms would represent a particle which would be identical to an electron (β^-) but have the opposite Coulomb charge (β^-). [58] A radioactive element which has an excess of protons (i.e. is proton-rich) in the nucleus usually decays by positron (β^+) emission, but can also decay by electron capture and these two processes often compete with one another. Essentially the binding force of the nucleus is not high enough to stabilize the nucleus, and thus there is a probability the nucleus will self-stabilize by a nuclear transformation.

3.3.2 Electron Capture

Electron capture is the process whereby an electron (e^-) is absorbed into and combined with one of the protons in the nucleus. The formula for the process where a parent atom 'X' with 'Z' protons and 'A' nucleons is transformed by electron capture into a new daughter atom 'Y' with 'Z - 1' protons and 'A' nucleons is given by equation 3.1. The proton then transforms into a neutron (with emission of an neutrino (ν)) and thus the nucleus becomes more stable.

This process usually occurs in heavier nuclei since the electrons (usually) in the K or L shells (inner shells) experience a stronger Coulomb attraction from the positively charged protons in the nucleus. The removal of an electron from the shell in the atom leaves a hole in the respective shell. Consequently, the atom is in an unstable state which normalizes when an electron from one of the higher energy shells fills this hole resulting in an emission of a characteristic x ray. These characteristic x rays are typically of higher energies for larger atomic nuclei.

3.3.3 Positron Emission

In 1936 Carl Anderson was awarded the Nobel prize for experimentally demonstrating the existence of the positron. He did this by observing cosmic ray particles in cloud chamber photographs, and noticed that some of the particles behaved as if they were electrons but with a positive charge. Today positrons are used in PET imaging and the source is a radioactive isotope which decays by positron emission. Positron emission is the process whereby a proton in an atomic nucleus will transform into a neutron by emission of a positron (β^+). This process begins with a parent atom 'X' with 'A' nucleons and 'Z' protons which transforms into a new daughter atom 'Y' with 'A' nucleons and 'Z - 1' protons as shown in equation 3.2.

The mass energy difference ($E = mc^2$) between the parent atom and the daughter atom must be at least twice the rest mass of an electron or a positron (i.e., 1.022 MeV) for positron emission to be possible. The emission of the positron occurs with a spectrum of energies, and the maximum of this spectrum is given by equation 3.3. This occurs because the emission energy of the positron is shared with the neutrino.

$$E_{max} = E_{parent} - E_{daughter} - 1.022 MeV \quad (3.3)$$

The radiation yield (Y(i), number of emissions per second), and average energy of emission (E(i)) is given in Table 3.1 for Rb-82 (which decays to the stable isotope Krypton-82).

The process of positron emission is favoured by lighter elements on the periodic table, whereas heavier elements compete more with electron capture. The advantage of lighter elements for PET imaging is that these elements are mostly used within biological processes. Therefore, tracers can be labelled with positron emitters that are

Table 3.1
Important radiation emissions from Rb-82 decay [9].

	y(i)	E(i)
Radiation	(Bq-s) ⁻¹	MeV
β^+	0.116	1.157
β^+	0.833	1.523
γ	1.91	0.511
γ	0.134	0.777

close chemical analogues, or have exactly the same chemical structures and properties to naturally occurring molecules. These tracers are therefore useful for investigating biological processes. A table of common PET isotopes can be found in table 3.2,

Table 3.2
Common isotopes used in PET imaging [10].

Isotope	Isotope Source	Positron Fraction	E_{max} MeV	E_{mean} MeV	Half-life min	Range (RMS) mm
¹¹ C	Cyclotron	0.99	0.96	0.386	20.4	0.28
¹³ N	Cyclotron	1.00	1.19	0.492	9.96	0.45
¹⁵ O	Cyclotron	1.00	1.72	0.735	2.07	1.04
¹⁸ F	Cyclotron	0.97	0.64	0.250	109.8	0.22
⁶⁸ Ga	Cyclotron	0.89	1.90	0.83	67.7	1.35
⁸² Rb	Generator	0.96	3.35	1.40	1.274	2.6

where: the range of the positron is the mean distance the positron will travel prior to annihilation expressed as root mean square (RMS) distance in water, and E_{max} is the maximum energy of positron emission.

3.3.4 The Production of Positron Emitting Isotopes

Rb-82 is an ultra-short-lived isotope (half-life 1.273 min) that is produced when a longer lived (half-life 25.55 days) isotope, Sr-82 undergoes decay. A Sr-82/Rb-82 generator consists of a tin-oxide column that binds Sr, but not Rb. Sr-82 is loaded onto the column which is suspended in 0.9 % NaCl saline. When saline is flushed

through the column, Rb-82 activity is eluted from the column while Sr-82 activity remains bound. The elution process can be repeated every 5-10 min over the life of the generator.

There are no natural sources of Sr-82, and so it must be made artificially. The production of Sr-82 is usually accomplished with one of two methods: either spallation of a Molybdenum target or bombardment of natural Rubidium by protons. Sometimes proton beams of energies around 800 MeV were used for Molybdenum spallation (at the Los Alamos National Laboratory [59]) in the production of Sr-82 sources for research. [60] Production of Sr-82 can also be done using 500 MeV proton beams on natural rubidium (MDS Nordion [61] gets their supply from Vancouver), or 100 MeV proton bombardment of RbCl salt targets [62] (at a new facility at the Los Alamos National Laboratory [63]). The spallation process is quite complicated with multiple nuclear reactions. In addition to ^{82}Sr the process also produces ^{77}Br which is a useful SPECT tracer. The ^{77}Br isotope is usually removed first then the ^{82}Sr is removed from the residual material. Rubidium bombardment usually occurs as shown in equation 3.4. [64]

In either case impurities are also produced and must be removed so the desired isotope can be purified.

3.3.5 Positron Annihilation

Positrons and electrons are charged particles of equal magnitude but opposite polarity. In nature opposites attract and like charges repel, thus positrons and electrons are attracted to one another. When a high energy positron moves through a medium it has enough kinetic energy to overcome this force of attraction. As the positron

travels it undergoes collisions with electrons surrounding the atoms in the medium in a process known as Bhabha scattering. Since the electrons and positrons have the same mass the momentum transfer is large and the positron loses energy with each collision. Eventually the positron loses so much energy that it will no longer be able to overcome the Coulomb attraction of an electron and the two particles will combine. In 1942 Robert Beringer and C. G. Montgomery demonstrated that when a positron and an electron combine, they annihilate and produce two 511 keV gamma rays at 180° angles from one another, travelling in opposite directions. [65] They proved this with two fast rotating coincidence counters using an annihilation source (of activated copper atoms) at the center of rotation. Current measurements indicate that, due to conservation of angular momentum, there is a small distribution of angles close to 180° of about $\pm 0.25^\circ$ FWHM. [10] If detectors were placed on opposite sides of an annihilation event, both detectors would indicate a signal at roughly the same time, or in coincidence. The coincident detection of the annihilation photons is the principle upon which all PET imaging is based. A diagram illustrating positron annihilation is shown in Figure 3.2.

Figure 3.2: Diagram of positron annihilation.

3.4 Single Photon Detection

Annihilation photons used for PET imaging have an energy of 511 keV, a highly penetrating form of radiation. To detect such photons, a measurable amount of energy must be deposited into the detector. The number of photons (N) absorbed as a function of distance travelled through a uniform medium is given by equation 3.5,

$$N = N_o e^{-\mu x} \quad (3.5)$$

where: μ is the linear attenuation coefficient, N_o is the initial number of photons, and x is the depth in the medium. Since the linear attenuation coefficient is smaller for less dense materials the probability of photon absorption is lower. Therefore, the fraction of photons interacting (either partially or fully) (A) in a medium is given by equation 3.6. [11]

$$A = 1 - e^{-\mu x} \quad (3.6)$$

For a fixed length, the quantity that determines the number of interacting photons is the linear attenuation coefficient. Therefore, detectors are typically made from materials with a high linear attenuation coefficient. Detection of photons in PET imaging is accomplished using scintillators and photomultiplier tubes (PMT). In the early days of PET imaging photon detection was accomplished with thallium-doped sodium iodide (NaI[Ti]) scintillation crystals. Later on bismuth germanate or BGO ($\text{Bi}_4\text{Ge}_3\text{O}_{12}$) scintillation crystals were used. More modern scanners use cerium-doped lutetium oxyorthosilicate or LSO ($\text{Lu}_2\text{SiO}_5[\text{Ce}]$) scintillation crystals. [11]

Gamma rays which interact with the scintillation crystal can liberate low energy photoelectrons. As the photoelectrons travel through the crystal they excite atoms in the medium and lose energy in the form of heat, lattice vibrations, and photons. [66]

The photon output occurs as a spectrum and can include ultraviolet (UV) [67], visible [68], and infra red (IR) [69] radiations. The scintillation crystals in the GE Discovery VCT PET/CT system used in this study are LSO scintillation crystals. These crystals have a spectrum which peaks at 420 nm, or blue light but includes a very small (but negligible) amount of UV light. The PMT is usually constructed to respond to the peak of the spectrum, for instance the bialkali PMT is tuned to the LSO spectrum. [68] Light output from the scintillator liberates electrons in the photocathode of the PMT, and through a series of charged plates the electron signal is greatly amplified and converted into an electronic signal (pulse) and input into an electronic counting circuit.

In addition to the absorption of energy the scintillation crystals have an intrinsic efficiency. The efficiency of a scintillation crystal is given by equation 3.7. [70]

$$\eta = \beta SQ \quad (3.7)$$

where: β is conversion efficiency of the deposited γ -ray energy (E_γ) to electron hole-pairs, S is the transfer efficiency of the electron hole energy to the luminescent centers (the centers where the scintillation light is produced), and Q is the quantum efficiency of the luminescent centers. The quantity β can be calculated from the properties of the crystal, whereas Q and S are measured quantities. The speed of the transfer and emission process must also be addressed as this is a contributing factor to the detector “dead time”, which is a period of time during which the crystal cannot respond to a subsequent particle interaction. The speed of a scintillation crystal can be quantified by the quantity merit (M) as shown in equation 3.8. [70]

$$M = \frac{10^6 \beta S E_g}{2.3} \quad (3.8)$$

where: E_g is the bandgap energy which is a property of the crystal. A perfect scintillation crystal does not exist since there is often a trade-off of efficiency for speed or visa versa. In addition to speed and efficiency, light yield (the number of photons produced per interaction) is an important factor as it allows many scintillation crystals to be coupled to a single photomultiplier tube, since the crystals can be made physically smaller. These crystals are often high density and arranged into groups called ‘blocks’ coupled to photomultiplier tubes (PMT). [71] This allows for a reduction in the cost of a PET scanner. The spatial positions ‘X’ and ‘Y’, amplitude (energy), and time during scan are all recorded by a computer. For example in a 4 photomultiplier tube grid the ‘X’ and ‘Y’ positions of the detected event are calculated from the output ‘ P_i ’ of the four photomultiplier tubes according to equations 3.9 and 3.10.

$$X = \frac{P_1 + P_2 - P_3 - P_4}{P_1 + P_2 + P_3 + P_4} \quad (3.9)$$

$$Y = \frac{P_1 - P_2 + P_3 - P_4}{P_1 + P_2 + P_3 + P_4} \quad (3.10)$$

where: the subscript ‘i’ on ‘P’ is the identifier for the photomultiplier tubes (PMT) (i.e., i = 1, 2, 3, or 4). [10] Other factors that contribute to a good scintillation crystal are summarized in table 3.3.

3.5 Coincidence Detection

When an annihilation event occurs two photons are produced at approximately 180° travelling in opposite directions. Image formation begins by counting the total number of these events which occur within the field of view. This is accomplished by coincidence detection, which requires detectors placed on opposite sides of the field of view. Modern scanners use a ring of detectors arranged around the entire field

Table 3.3
Desirable characteristics of a PET scintillation crystal [11].

Crystal Characteristic	Benefit
High η	High γ -ray detection efficiency
Short decay time & High M	Good coincidence timing
High light output	Large number of crystals per PMT
Good energy resolution	Full identification of energy events
Emission wavelength near PMT response	Good PMT response
Transparent at emission wavelength	Good transport of light output to PMT
Same n as PMT	Good optical coupling to PMT
Radiation hard	Stable response over time
Nonhygroscopic	Easier to package crystals
Rugged	Easier to produce smaller crystal elements

of view. An annihilation that produces two photons travelling towards a pair of detectors will produce a signal in opposing detectors at nearly the same time, i.e., in coincidence. A line of response (LOR) can be drawn between both detectors and somewhere along this line the annihilation event is assumed to occur. Some uncertainty in the LOR will result from the fact that the detectors have a finite width, and thus there are a finite number of angles based on various detector locations along the possible path representing the line of response. This effect contributes to the intrinsic resolution of the scanner. [10] Figure 3.3 illustrates coincident photon detection with a ring detector (annihilation event originates at the blue star), and the resultant line of response.

Photons travel at the speed of light $c = 3 \times 10^8$ m/s, and thus a photon only takes 2 ns to cross the entire field of view, for a field of view size of 60 cm. In practice the coincidence time difference will be shorter since the annihilation events take place near the center of the field of view (i.e. inside the patient) and thus a photon emitted during an annihilation event will not have to cross the distance of the entire field of view. Since the annihilation events could occur at any location along the line of response (i.e., not necessarily in the center) there could be a small time delay between the

Figure 3.3: Line of response between two detectors.

detected signals even though both photons were emitted simultaneously. Additionally there may be differences in the timing of when the scintillation detectors produce a signal from a photon, and differences in the electronic circuits used to analyze the output from the scintillation detectors. Both of these contribute to delays between detection of the two simultaneously emitted photons. To account for this, a finite coincidence timing window is used to determine when two detected signals should be counted as a simultaneous event. A typical coincidence timing window is in the nanosecond range. Figure 3.4 is an example of how the electronics of coincidence detection are set up.

Figure 3.4: Coincidence detection circuitry.

Derived from "Handbook of Biomedical Image Analysis", Koon-Pong Wong [10].

Since characteristic x rays may also be produced by Compton interactions during a scan, it is necessary to use an energy window to filter out photons which do not originate from an annihilation event. Therefore, the pulse generator produces a square pulse for all detected pulses above a threshold voltage (V_T). Figure 3.5 shows two pulses with different amplitudes generated by two PMT's. [10] Since both pulses shown are above the minimum threshold they will both produce pulses from the pulse generators.

Figure 3.5: Illustration of coincidence pulses from a PMT.

Derived from "Handbook of Biomedical Image Analysis", Koon-Pong Wong [10].

In addition to energy differences, there may also be differences in the amplitude of the detected photon signal due to variations in the deposition of energy in the scintillation detectors. This is caused by partial deposition of energy by the photons and also variations in the detector's efficiency. Therefore, the energy window must have some finite width to account for variances in energies deposited by annihilation events. Therefore, the gate pulse generator takes the square wave pulse inputs, and produces another square wave pulse with the pulse width of the coincidence timing window (2τ) added. The logic unit has a logical AND function and registers a coincidence if the two gate pulses overlap. Figure 3.6 shows two sets of gate pulses; set A represents a coincident event, set B does not. [10]

A valid coincidence event requires: a valid acceptance angle, a valid coincidence

Figure 3.6: Gate pulses: (A) represents coincident pulses, (B) does not.

Derived from “Handbook of Biomedical Image Analysis”, Koon-Pong Wong [10].

time, and a valid energy of deposition. When all three criteria are met a coincidence event is recorded defining a line of response within the field of view, these events are known as prompt events.

3.5.1 Data Acquisition

PET images are described by a plane of activity $f(x, y)$ throughout a cylindrical field of view ω of radius $R_\omega < R$, where R represents the physical radius of the scanner. [72] The LOR has an associated orientation angle through the field of view and a displacement from the center of the field of view. A single point in the field of view defines a set of LOR’s corresponding to a displacement from the center of the field of view as a function of the angle of the LOR. The plot would look like half a sine wave and is therefore called a sinogram. An illustration of this is shown in Figure 3.7 [71]. Acquired data are always stored in a sinogram, which stores all counts as the projection angle versus the radial distance from the center of the field of view.

Modern PET systems use multiple detector rings operating in tandem. Detector rings can be separated by a highly absorbing material called septa for 2D acquisitions, or removed for fully 3D volumetric acquisitions as shown in figure 3.8 [10].

Figure 3.7: Illustration of a sinogram with various lines of response.

Reproduced from “Data Acquisition in PET Imaging”, Frederic H. Fahey [71].

Figure 3.8: Data acquisition: (A) septa in place - 2D, (B) septa removed - 3D.

Reproduced from “Handbook of Biomedical Image Analysis”, Koon-Pong Wong [10].

In 2D acquisitions, counts only come from the plane of the detector rings. In 3D acquisitions, the septa are removed and oblique angles between planes are allowed, thus counts can be recorded in one ring, and coincident events can be recorded in counts that occur in two different detector rings. If all values for a given angle in the sinogram are combined what results is a 1D projection of the sinogram called a line integral. Mathematically the 3D line integral is given by equation 3.11 [72].

$$p(s, \phi, z, \delta) = \int f(s \cos \phi - t \sin \phi, s \sin \phi + t \cos \phi, z + t\delta) dt \quad (3.11)$$

where: ϕ is the angle between the projection and the y-axis, $\delta = \tan \Phi$ is the ring difference ($\delta \neq 0$ for oblique sinograms), Φ is the angle between the LOR and the transaxial plane, t is defined to be along the LOR projection, and z is the midpoint between two detectors. If a PET scanner has N rings and data are acquired in 3D mode the resultant data set will have N^2 sinograms (including N direct sinograms and $N(N - 1)$ oblique sinograms). [72] Data can be acquired in 3D and converted into an equivalent stack of 2D data sets using a process known as Fourier re-binning (FORE). The 2D Fourier transform of the 3D sinograms is given by equation 3.12 [72].

$$P(\omega, k, z, \delta) = \int_0^{2\pi} \int_{-R_\Omega}^{R_\Omega} p(s, \phi, z, \delta) e^{-ik\phi - i\omega s} ds d\phi \quad (3.12)$$

where: ω is the radial frequency, and k is the Fourier index. Using the Taylor expansion of the exact Fourier rebinning formula leads us to formula 3.13 [72].

$$P(\omega, k, z, \delta) \approx P\left(\omega, k, z - \frac{\delta k}{\omega}, 0\right) \quad (3.13)$$

Using this method the oblique angles are translated into the 2D plane equivalent, on which a 2D reconstruction algorithm can be used.

3.6 Reconstruction

The accumulation of coincidence events as a function of radii and angles around the field of view forms a sinogram, which is a plot of the recorded data on a 2D plane. The sinogram contains the information needed to form the image, but it must be reconstructed onto a Cartesian plane. Additionally, the raw data is distorted due to three main effects which include: scatter events, random events, and attenuation.

3.6.1 Scatter Correction

An annihilation photon can undergo Compton scattering in the medium and create a line of response that does not pass through the true location of the annihilation event. This increases the noise level and decreases the contrast of the image. To minimize Compton interactions in the scintillation crystal, high density scintillation crystals are used to maximize photoelectric absorption. In a patient however, the Compton events are unavoidable. The scatter effect is rather moderate for 2D PET imaging. However for 3D PET imaging scattered events can account for 35-80 % of detected events, and accurate correction techniques must be used.

Scatter correction can be accomplished by direct measurement of the differences in counts with the septa in place versus removed. Additionally analytic functions can be fit to the scatter tails outside the object in projection space. A technique employing multiple energy windows can also be used. This technique measures the scatter events by choosing an energy level such that only scattered photons are recorded. These events can then be removed. Some techniques also use convolution or deconvolution methods that model the scatter distribution with an integral transformation of the projection data recorded in the photo-peak window. Finally the true amount of scatter can be simulated using Monte Carlo techniques then subtracted to correct the final image. However, any bias in the subtraction can lead to meaningless negative

values in the activity concentration on the PET image.

3.6.2 Random Event Correction

It is possible for two photons generated by separate annihilation events to each be detected by crystals within the timing and energy window criteria. In this case a false coincident event is recorded in the line of response defined by the crystals. The rate ' R ' at which this occurs for a given pair of detectors ' i ' and ' j ' is calculated from the coincidence timing window ' 2τ ' and the rate of single events ' S ' which occurs for each detector as shown in equation 3.14 [10].

$$R_{ij} = 2\tau \times S_i \times S_j \quad (3.14)$$

Thus the random rate increases as the square of the single event rates. To correct for this the timing window of one of the detectors can be delayed. The delay on the second detector's timing window causes all the true events to be rejected and only records the random events. The true number of events between any two detectors is then calculated from the difference between the first timing window (prompt events) and the second (delayed events). However these windows record different numbers of events due to their different timing characteristics and thus some statistical noise is still present. As with scatter correction, the subtraction can lead to meaningless negative values in the activity concentration on the PET image.

3.6.3 Attenuation Correction

Attenuation of signal from an emitter inside a medium causes a loss of photons and thus a loss of the measured activity concentration in the patient. To recover the true amount of activity this attenuation must be corrected. The fraction of photons ' ϕ ' that passes through a medium consisting of many different materials (like in a

patient) is given by equation 3.15 [10].

$$\phi = e^{(-\sum_i \mu_i x_i)} \quad (3.15)$$

where: μ_i and x_i are the linear attenuation coefficient and thickness of tissue ‘ i ’ respectively. If N_0 is the total number of true events in the source and N is the total number of measured events, then the measured events in the detector can be calculated using equation 3.16. The situation can be somewhat simplified by assuming the object is a homogeneous attenuating medium with linear attenuation coefficient μ having thickness D . An annihilation event occurring at depth x in the object has the probability of $e^{(-\mu x)}$ of one photon being detected, and the probability of the other photon to be detected is $e^{(-\mu[D-x])}$. Therefore, the total probability for detection of a coincident event will be the multiplication of these two probabilities $e^{(-\mu x)} \times e^{(-\mu[D-x])} = e^{-\mu D}$ [10].

$$N = N_0 \times e^{(-\int_0^D \mu(x) dx)} \quad (3.16)$$

where: $\mu(x)$ is the depth dependent attenuation coefficient which describes the variation of material through the medium, and D is the total thickness of the attenuating medium. Therefore, the probability of detection is independent of where the annihilation event occurred in the medium, even if the annihilation event occurred outside the medium itself.

Since the attenuation thickness is independent of the source location one can use a rotating positron source (typically ^{68}Ge) outside the object being imaged. Two scans are acquired; one blank scan with nothing in the field of view, and one scan with the patient present in the field of view and with no activity injected into the patient. Attenuation correction factors are determined by the pixel by pixel ratio of the measured projection to blank scan.

X-ray CT has replaced the use of external positron sources for attenuation correction in current systems. [73] An attenuation map is generated from a co-registered CT image that is adjusted to attenuation of 511 keV photons.

3.6.4 Iterative Reconstruction

Iterative reconstruction works by making a series of successively better guesses as to the true activity concentration distribution. Typically the first guess is just a uniform data set, i.e. all points are set to the same value. Each guess is forward projected using a model of the detection process, and a sinogram of the guess is simulated. The assumed image is updated by taking the difference in measured sinogram to simulated sinogram, and a new estimate on the sinogram is made by back projecting the new assumed image. This process is repeated until the desired error is reached. This process is known as the maximum likelihood expectation maximization (MLEM) method. Additionally scatter, and random events can be added to the simulation, thereby eliminating the need to subtract randoms and scatter from the image which can lead to negative activity concentration values. Attenuation, and non-uniform detector response can also be added into the simulation algorithm, and thus correct for these effects during reconstruction. For a given simulation image ' I ' the iterative technique can be accomplished by equation 3.17 [74].

$$I_j^{k+1} = I_j^k \times \frac{1}{\sum_i \left(p_{i,j} \frac{1}{n_i a_i} \right)} \sum_i \left[p_{i,j} \frac{S_i}{(\sum_i p_{i,j} I_j^k) + a_i (r_i n_i + c_i)} \right] \quad (3.17)$$

where: I_j^{k+1} is the image of the next iteration, I_j^k is the image of the current iteration, $p_{i,j}$ is the probability matrix that sinogram bin i contributes to image voxel j , S_i is the

sinogram for bin i , n_i is the normalization for bin i which corrects for non-uniform detector response, a_i is the attenuation correction for bin i , r_i is the randoms correction for bin i , and c_i is the scatter correction for bin i . MLEM tries to maximize the $p_{i,j}$ probabilities, and has the advantage that the image solution can be constrained to be positive valued, which is consistent with the known physical property of radioactivity. When these values sum to unity, no further iteration will improve the reconstruction of the image.

The biggest drawback to this method is its computational requirements, which can take a significant amount of time to complete compared to filtered back-projection. The straight application of this method would require the projection and comparison of all angles. The computation requirements of each are equivalent to a full back-projection reconstruction. To simplify the problem and thus speed up the convergence time, a subset of projections can be used for each iteration. This process is called accelerated expectation maximization (EM) using ordered subsets or OSEM. [74]

3.7 Spatial Resolution

There are various physical factors that limit the resolution of PET. The first is positron range. The positron range is the average distance that positrons of a certain energy will travel prior to annihilation, and higher energy positrons have a larger positron range. The positron range creates a blurring effect which becomes worse with increasing energy. This is due to the fact that, in PET imaging, we wish to quantify where the activity is in the subject; i.e., where the annihilation events originate. Since the site of annihilation does not correspond to the point of decay, the image looks blurred. This blurring effect can be modelled with an exponential function. Rb-82 has a positron range blurring factor of about 2-3 mm RMS due to its high energy positrons, see Table 3.1 for details on the spectrum from Rb-82 decay. [10]

In addition to the positron range, there is an angular distribution in the emitted annihilation photons from positron decay. Positron annihilation events produce two opposite travelling photons at $180^\circ \pm 0.5^\circ$. [65] This distribution of angles also leads to a blurring effect on the PET images. The projection data also have an intrinsic resolution related to the detector size. For instance a single array of detectors of detector width D will have a triangular point spread function with a spatial resolution of approximately $D/2$. Therefore, a smaller detector size results in a sharper point spread function and thus a sharper image. The scintillation crystals used in PET imaging have a high stopping power to absorb the 511 keV photons. The intrinsic image resolution of the GE Discovery Rx/VCT is 6 mm (FWHM). If an 8 mm Hann filter is applied to the reconstructed image, the final image would have a resolution of 10 mm (FWHM) using this scanner.

3.8 Partial Volume Averaging

Partial volume effects occur due to limited spatial resolution of the PET imaging scanner. Additionally motion can blur the image since the accumulation of counts is taken over a finite period of time, and motion of the source in the patient can occur during this time interval. This has the effect of smearing the true activity over a region of interest and can lead to an over or underestimate of the true activity concentration in small objects. The mathematical representation of the scanner imaging response is a convolution of the point spread function (PSF) representing the resolution of the scanner with the physical profile of the tissue or organ under study. The PSF mathematically describes the system response to an input delta function signal. The PSF of the scanner can be approximated as a 3D Gaussian function. This is an approximation as motion blurring may not be perfectly Gaussian (symmetric and periodic), which the PSF does not include. Also characteristics of the scanner may

not be perfectly symmetric. For instance near the edges of the field of view lines of response tend to be biased in one axis over another leading to a non symmetric distribution. Partial volume averaging leads to two effects, spill-in and spill-out. Spill-in causes activity to be smeared into an adjacent region, causing an increase in the apparent activity concentration in that region, leading to possible overestimates of the true activity concentration. Spill-out causes the measured activity concentration in a region to be lower than the true activity concentration, leading to possible underestimates of the true activity concentration. A 1D illustration of spill-in and spill-out is shown in Figure 3.9, where the point spread function has a FWHM equal to the dimension of rectangular organ structures imaged.

Figure 3.9: Partial volume averaging example of spill-in and spill-out.

Figure 3.9-A: shows the result of the convolution of two tissues (shown as square functions) close to each other with the PSF of the scanner. As shown in Figure 3.9-A: spill-out leads to a large increase in the activity concentration into the space between the tissues and a decrease in the activity concentration inside the tissue region. The curve in Figure 3.9-B: shows the activity concentration as it would appear on the PET image.

The rectangular function represents the true activity concentration inside the organ or tissue in the patient, whereas the curve (convolution curve, representing the result of the convolution) represents the PET image profile through the organ. Notice that there is a difference in the peak activity between the convolution curve and the rectangular function, whereby the peak of the convolution curve is always lower. The peak underestimation is greater for smaller tissue thickness, and thus for smaller tissues the partial volume losses are more severe. If these effects are not corrected, the underestimate of the activity concentration could be as high as 30-40% for tissue thicknesses equal to the FWHM of the scanner (assuming FWHM = 10 mm). Corrections for the partial volume effects are described in more detail in Chapter 4.

3.9 PET/CT Co-Registration

Since the CT and PET images are acquired sequentially, the alignment between the two may not be perfect. For instance the patient position may shift during the scan; in addition, cardiac and respiratory motion can cause misalignments. Imaging technologists must use the known characteristics of the PET image to align it with the anatomical information from the CT image. For example it is known that there is high uptake of Rb-82 in the heart wall, and it is visible as a high contrast signal of activity above background in later time frames on the PET image. This can be aligned with the CT image of the heart, since the anatomy of the heart with respect to the heart wall is well known. However since PET uses low dose/no contrast CT for attenuation correction, the exact location of the heart wall is not known and there could still be small alignment issues between the PET and CT images.

3.10 Calibration of the PET System

Careful phantom studies have been carried out on the GE Discovery RX system. Findings indicate that the attenuation and scatter correction methods used provide an accurate reconstruction of the true activity concentration. [75] However for dosimetry purposes, absolute quantification of the activity concentration is required. The system is initially calibrated with F-18, and studies with the GE Discovery RX system indicate an absolute accuracy of $> 90\%$. [76] To accurately measure Rb-82 concentrations, conversion from F-18 to Rb-82 was accomplished by taking into account the half-life of Rb-82 compared to F-18. However to test the validity of these conversions a calibration with Rb-82 was performed.

To verify the calibration accuracy with Rb-82, a cylindrical phantom of known volume was used. A known amount of Rb-82 was eluted and accurately measured with a dose calibrator specifically designed to measure activity from positron emitting isotopes. This activity was injected into the phantom, which was filled with water, and mixed so the activity concentration was uniformly distributed throughout. Accurate timing between the elution and the start of the PET scan was performed in order to determine the true activity concentration at the beginning of the PET acquisition. After acquiring PET data, the measured activity concentration from the PET scan was found to be within 5% of the true activity concentration.

3.11 PET/CT Imaging for the Purposes of Dosimetry

It is important to accurately define the important organs or tissues under investigation. This is accomplished by acquiring dynamic PET data, and a low dose CT scan mainly for attenuation correction. The CT scan can be used for anatomical

definition, while the dynamic data show important regions as they become active or inactive such as the heart wall of the left ventricle. Figure 3.10 is an example of a dynamic image series of the chest with the heart in the center of the image. The top frames are fused PET/CT images and the bottom frames are PET images alone.

Figure 3.10: Dynamic PET imaging of Rb-82 (Elapsed Time) showing transit through the right atrium/ventricle, lungs, left atrium/ventricle, and uptake in the heart muscle.

At first the heart wall is not perceivable, but early on the ventricles and atria are visible as large high contrast areas in the middle of the field of view. Especially notable are the active regions of the left ventricle and atrium after an elapsed time of 50 s. After an elapsed time of 120 s the heart wall starts to become clearly visible, and after 360 s there is almost no left ventricle cavity activity, whereas the heart wall is an active region.

Activity concentration in a tissue is measured by defining a VOI which encompasses the organ under investigation. VOI's are defined by drawing regions of interest (ROI's) on each slice where the desired tissue is located. An example of a ROI in lung is shown in figure 3.11.

Figure 3.11: Example of a VOI drawn on lungs.

The sagittal, coronal, and transaxial slices are all shown, but the ROI's are drawn on the transaxial slices to form the VOI.

3.12 Summary

After each VOI is defined, average values of the dynamic PET data within the VOI are calculated to form a time activity curve as shown previously in Section 3.1. These average values are in units of activity concentration (kBq/cc), and it is by integration of these time activity curves that the residence times are calculated, and thereby a dose is calculated. The following chapter describes the use of PET/CT to measure Rb-82 dosimetry in humans.

Chapter 4

Methods

4.1 Overview

This chapter describes the demographics of the patient population, the PET/CT imaging protocol, the VOI analysis, and the dosimetry methodology.

4.2 Study Design

Dosimetry information was determined from human in-vivo Rb-82 PET-CT studies using both clinical cardiac patients, and normal subjects with no expected cardiac disease. A rest study and a stress study were conducted. The rest study included 30 subjects, 12 female and 18 male (this includes 1 female normal and 3 male normals), while the stress study included 25 subjects, 10 female and 15 male (1 normal). A list of the patient population with injected activities, scan regions (biodistribution (BD), and chest), body weight, and ages is given in table 4.1.

Injected activities to patients were given based on the patient's weight at 10 MBq/kg over 30 s. Chest PET/CT scans were obtained in all patients. For the rest tests only, one extra scan was performed in a different biological region for each patient called the biodistribution (BD) region. The BD scan region was either the

Table 4.1
Patient demographics and injected activities.

Patient	Injected Activity		Weight	Age	
	Chest				BD
	Rest	Stress			
	MBq	MBq	MBq		
1	822.4	-	839.5	70	74
2	1034.2	1033.8	1026.8	99	70
3	1102.4	1149.7	1075.4	100	72
4	783.2	794.4	773.3	66	58
5	1142.4	1142.1	1121.5	104	67
6	979.1	-	982.1	94	45
7	1034.3	1013.1	1030.7	98	64
8	869.9	871.8	892.8	70	68
9	869.1	861.8	861.4	84	75
10	893.4	876.6	896.4	73	82
11	880.4	-	881.1	82	61
12	1431.6	1430.5	1436.7	136	68
13	1133.5	-	1145.7	106	40
14	1012.4	968	962.4	95	69
15	694.7	691	686.5	63	67
16	1352.3	1353.7	1369	132	49
17	1178.7	1178.8	1208	118	57
18	762.4	761.4	766.2	75	49
19	985.1	980.9	984.6	99	60
20	911.4	913.6	914.5	73	59
21	838.7	829.9	831.3	79	65
22	1078.6	1083.1	1074.6	103	63
23	863.7	-	871.1	82	29
24	668	668.6	661.5	63	66
25	1290.8	1267.6	1345.1	122	55
26	967.8	673.2	686.1	59	32
27	1360.3	1368.9	1382.7	122	47
28	943.6	953.6	932	82	40
29	1254.1	1264.8	1257.4	113	54
30	834.7	830	812.9	70	63
Average	999.1	998.4	990.3	91.1	58.9
±SD	200.1	223.8	215.0	21.6	12.8

head, thigh, neck, pelvis, or abdomen. From the chest scans the heart wall, heart contents, liver, stomach, spleen, and lungs were always measured. Occasionally the ULI, pancreas, and gallbladder were also visible and measured. From the pelvis scan the gonads, muscle, and sometimes bone marrow were measured. From the thigh scan the muscle and marrow were measured. From the abdomen scan the kidneys, ULI, LLI, and SI were measured. Finally from the neck scan the thyroid was measured. An example of the biodistribution regions can be found in Appendix D, Figure D.1. There were no biodistribution scans for the stress tests. The breakdown of the sample size measured in each organ is listed in Table 4.2.

4.3 PET Imaging Protocol

Subjects were positioned on the PET scanner with their arms out of the field of view (FOV). Dynamic PET scans of the chest were acquired at rest on a 3D PET system (GE Discovery Rx/VCT). First a scout scan was performed to confirm patient position, then a low dose CT scan was performed for attenuation correction. The total scanning time of 10 minutes was split into the following time intervals, 9×10 s, 3×30 s, 1×60 s, 1×120 s, and 1×240 s. After Fourier re-binning (FORE) of the 3D projection data, the images were reconstructed using a 2 dimensional OSEM iterative reconstruction algorithm (4 iterations with 21 subsets) followed by an 8 mm Hann filter. The intrinsic resolution of the scanner was 6 mm. Therefore the reconstructed images had a resolution of ~ 10 mm. All correction methods were enabled, but decay correction was turned off since dosimetry relies on measurement of the tissue clearance including radioactive decay for estimation of the residence time. The imaging procedure was repeated for the BD regions. Pharmacological stress testing was conducted using the vasodilator Dipyridamole at 0.70 mg/kg. Then dynamic PET images of the chest at stress were acquired using the time intervals

Table 4.2
Organ sample sizes by gender.

Organ	Rest			Stress		
	Total	Male	Female	Total	Male	Female
Adrenals	4	2	2			
Brain	7	5	2			
Breasts	12		12	11		11
Gall Bladder	5	4	1	3	3	
LLI	7	4	3			
SI	4	2	2			
Stomach	30	18	12	25	14	11
ULI	9	6	3			
Heart Contents	30	18	12	25	14	11
Heart Wall	30	18	12	25	14	11
Kidneys	4	2	2			
Liver	30	18	12	25	14	11
Lungs	30	18	12	25	14	11
Muscle	11	9	2			
Ovaries	4		4			
Pancreas	12	8	4	7	4	3
Red Marrow	7	6	1			
Spleen	30	18	12	25	14	11
Testes	5	5				
Thyroid	4	2	2			
Bladder	4		4			
Uterus	4		4			

previously specified. A final CT image of the subject was acquired for attenuation correction of the stress images. Mean Rb-82 residence times were determined in the 20 source organs for rest, and 9 source organs for stress, using volumes-of-interest (VOI) drawn on the fused PET/CT images, as described in the next section.

4.4 Organ VOI Analysis

After identification of the organs on the fused PET/CT images, VOI's were drawn with the software program PMOD version 3.0. An example of a lung VOI can be seen in Figure 3.11, and of the stomach and pancreas in Figure 4.1.

Figure 4.1: Example of a CT anatomic VOI drawn on stomach and pancreas.

4.4.1 Summary of Organ VOI's

The VOI definition method chosen for all source organs is shown in Table 4.3. Imaging modality lists the main method by which the organ VOI was defined. Also listed is either the surrogate organ used, or if another imaging modality was used to help guide VOI selection. Furthermore, the methods used to correct for partial volume losses for each organ are listed, and explained in the section that follows.

Sometimes PET or CT was used to help delineate an organ which is mainly defined with the other imaging modality. For example PET was sometimes used to delineate

Table 4.3
Organ VOI delineation methods.

Organ	Imaging Modality		PVE Correction
Adrenals	N/A	Kidneys used as surrogate	N/A
Brain	CT	-	VOI reduction
Breasts	CT	-	VOI reduction
Gall Bladder	CT	-	none
LLI	CT	-	none
SI	CT	-	none
Stomach	CT	PET used as guide	VOI reduction
ULI	CT	-	none
Heart Contents	PET	CT not useful	VOI reduction
Heart Wall	PET	CT used as guide	40-80
Kidneys	PET	CT used as guide	40-80
Liver	CT	-	VOI reduction
Lungs	CT	-	VOI reduction
Muscle	CT	-	VOI reduction
Ovaries	N/A	Uterus used as surrogate	N/A
Pancreas	CT	PET used as guide	VOI reduction
Red Marrow	CT	-	none
Spleen	CT	PET used as guide	VOI reduction
Testes	CT	PET used as guide	none
Thyroid	PET	-	40-80
Bladder	CT	CT used as guide	VOI Reduction
Uterus	CT	PET used as guide	none

an anatomical VOI, and sometimes CT is used to help delineate a PET threshold VOI. This occurs for some CT measurements where delineation between tissues in low-dose CT is difficult due to similar densities surrounding the organ of interest. In particular, this problem is worse for younger patients, due to a smaller barrier of fat between organs. In such cases, if there is some uptake of Rb-82 in the tissue, the PET data can be used as a guide to help delineate the organ on CT from other surrounding organs. A similar situation exists for organs with high uptake that must be analysed on PET only. Spill-in from organs close to the organ under investigation can make it difficult to delineate the true region where the organ is located. In these cases, the CT can sometimes be used as an anatomical guide by delineating the offending organ (the one causing the spill-in). Thus the CT is used as a guide to separate the desired organ PET activity from the offending organ PET activity.

4.4.2 CT Anatomic VOI

Partial volume correction in large organs was accomplished by reducing the size of the anatomical VOI (VOI_{anatom}) to avoid partial volume losses which occur near the edges (spill-out). Some corrections for PET/CT co-registration misalignments are also required which also involve a reduction of the VOI size. Therefore, this method is herein referred to as the VOI-Reduction technique. This procedure can be used on organs thicker than $2 \times$ FWHM of the PSF of the scanner. Since the FWHM of the PSF of the scanner is 10 mm, the limitation of this method is that the organ must be at least 20 mm thick. The VOI_{anatom} is a VOI defined on CT only, and is drawn to represent the true organ dimension. This was used where the exact delineation of an organ could be made on CT, but where the PET uptake was not high enough above background to apply an appropriate threshold, or where the PET activity was very non-uniform such that an accurate threshold could not be determined. A 1D illustration of the VOI reduction method is shown in Figure 4.2.

Figure 4.2: Illustration of the VOI reduction method.

Figure: 4.2 (A): illustrates the VOI reduction method with a thickness of 40 mm, Figure 4.2 (B): illustrates the VOI reduction method with a thickness of 20 mm. The filled area represents the reduced VOI in which the average activity concentration was calculated.

Additional errors can occur due to PET/CT misalignments. Co-registration is the alignment of the PET tomographic image with the CT image in the 3D volume representing the field of view. This is necessary due to the fact that there are few landmarks of anatomy in PET, and so to quantify activity in a particular organ correctly the CT image must be used for some organs. In the thorax this is usually done by the radiologists by aligning the heart wall activity with the CT of the heart, or in the case of the kidneys alignment of the activity in both kidneys with the cortex of the kidney on CT. In either case the alignment is not necessarily perfect and there could be unquantifiable misalignments between the two tomographic images. Since we must reduce the VOI to avoid partial volume losses from spill-out, any misalignments could mean that a further reduction in VOI size would be necessary to avoid the PET/CT co-Registration misalignment. To accomplish this, the VOI_{anatom} was reduced in incremental steps of 10 mm diameter. At each step the residence time

was calculated as shown in figure 4.3, using the lung as an example.

Figure 4.3: Plot of lung residence time v.s. reduction of VOI diameter from $\text{VOI}_{\text{anatom}}$.

This demonstrates that there is a VOI small enough for which no further reduction in VOI size will increase the residence time. The combination of co-registration and spill-out effects can make a reduction of more than 20 mm in diameter necessary to reach the plateau region of the curve. Thus by selecting a VOI in the plateau region of this curve we can avoid both spill-out and the PET/CT co-registration issues. This procedure was used in every instance of the VOI reduction technique. For all organs, a plateau region could easily be determined. However, for some organs a non-linear behaviour was seen due to noise when the VOI volume approached a few pixels. Therefore, only VOIs of an appropriately large size (at least 4 cc) were used to determine the residence times.

Large organs such as the stomach, liver, brain, spleen, breasts, lungs, muscle (from the thigh or pelvis), bladder, and pancreas were all corrected using the VOI reduction method. See figure D.2 for an example of the VOI for the brain; Figure D.4 for an example of the VOI for the pancreas, stomach, liver, spleen, breasts, and lungs; Figure D.9 for an example of a VOI for the bladder; and Figure D.11 for an example of the VOI for muscle. Since the whole organ was not within the scanner field of view, the organ volumes were taken from ICRP Publication 110 [77].

4.4.3 PET Threshold VOI

Tissues thinner than 20 mm, with high uptake, and completely within the field of view, can be corrected for partial volume losses by use of the 40-80 method (see Appendix A.1.2 for details). A threshold VOI is a VOI drawn such that all pixel values above a threshold value are included. A VOI is defined first at 40 % of the maximum organ activity. Next, a threshold VOI is defined at a threshold of 80 %. The volume from the 40 % threshold VOI is multiplied by the average activity concentration of the 80 % threshold VOI. This method is illustrated in Figure 4.4, where the 40% and 80% thresholds are highlighted.

Figure 4.4: Example of the 40-80 method (40% shown in red, 80% shown in green).

For a detailed mathematical description of this method and its justification, see Appendix A.1.2. This method was used to correct partial volume losses in the kidneys, heart, and thyroid. See figures D.3, D.4, and D.5 for an example of the 40-80 regions defined for thyroid, heart wall, and kidney respectively.

4.4.4 Organs Without Partial Volume Correction

Explicit partial volume corrections were not performed on the following organs: the red marrow, right atrium (heart contents), uterus, LLI, ULI, SI, gallbladder, and

testes. The red marrow, uterus, LLI, ULI, SI, and gallbladder were too small to use VOI reduction and did not have high enough uptake of Rb-82 above background to use the 40-80 method. The areas of the Testes were visible on PET but were close to background and had relatively non-uniform uptake. Furthermore a VOI_{anatom} cannot be defined for the testes. Therefore, an approximate VOI based on the PET activity was used to approximate the average activity concentration for the testes. See Figure D.4 for an example of gallbladder; Figures D.6, D.7, and D.8 for examples of the ULI, LLI, and SI respectively; Figure D.9 for an example of uterus; Figure D.10 for an example of testes; and Figure D.11 for an example of red marrow.

4.4.5 Surrogate Organs

The following organs were in the field of view but could not be clearly identified on PET or CT: the male breast, adrenals, and ovaries. The adrenal activity concentration was estimated based on the activity concentration of the kidneys. The activity concentration of the ovaries was estimated from the activity concentration of the uterus. The female breast residence times were used as the male breast residence times. No partial volume correction techniques were used for these organs.

4.5 Residence Time Calculations

The organ time activity curves were generated using PMOD version 3.0 [78]. This is accomplished by averaging the activity concentration in the VOI for all time intervals; final measurements are in units of kBq/cc. Time activity curves were then integrated by multiplying the average activity concentrations by the respective time interval for all points in the time activity curve, and summation of the result. The outcome from the integration is then used to determine the residence time by multiplication by the organ volume and division by the injected activity. An example of the time activity

curve for the lungs is found in Figure 3.1, and of the heart contents in Figure 4.5.

Figure 4.5: Example of a time activity curve for heart contents.

4.5.1 Estimation of Remainder Residence Time

Since the half-life ($t_{1/2}$) of Rb-82 (1.273 min) is so short, after a scanning time of 10 min there will be no Rb-82 left in the patient. It would be unreasonable to expect appreciable excretion of the tracer during such a short time interval. Therefore, all activity injected into a subject is assumed to decay within the subject. The decay of a radioactive isotope is given by equation 4.1.

$$A(t) = A_0 \times e^{-t\lambda} \quad (4.1)$$

where: $A(t)$ is the activity at time t , A_0 is the initial (injected) activity, and $\lambda = \frac{\ln 2}{t_{1/2}} = 32.7 \text{ h}^{-1}$ is the decay constant for Rb-82. From this formula we can get the total body the residence time ($\tilde{a}$) by integration over all time as shown in equation 2.22, and the results for Rb-82 in equation 4.2.

$$\tilde{a} = A_0 \times \frac{1}{A_0} \int_0^\infty A(t) dt = \frac{A_0}{A_0} \int_0^\infty e^{-t\lambda} dt = \frac{1}{\lambda} = 3.16 \times 10^{-2} \text{ h} \quad (4.2)$$

Therefore, to calculate the remainder residence time (the residence time which

assumes the rest of the activity is uniformly distributed throughout the rest of the body) the values from all measured organs were subtracted from equation 4.2.

4.6 Effective Dose Calculations

Equivalent dose calculations for each organ were done with OLINDA/EXM (from the RADAR group) [51] using the organ residence times as described previously in section 2.5. These equivalent doses were then used to calculate the ED, using the ICRP 60 [5], 80 [45], and 103 [6] tissue weighting factors.

4.6.1 Gastrointestinal Tract Correction Method

For hollow organs in the gastrointestinal tract (GI Tract) the dose factors in OLINDA assume all the absorbed dose comes from activity within the contents. These organs include the stomach, small intestine, and the upper and lower large intestines. However Rb-82 is very short lived and its uptake is primarily in the wall of these organs due to nutrient blood flow, and not within the contents. The specific absorbed fraction in the wall by emissions in the contents is given by equation 4.3.

$$\Phi(Wall \leftarrow Contents) = \frac{1}{2 \times m_{Contents}} \quad (4.3)$$

Therefore, a correction has been suggested by Stabin [79] and Parsey et. al. [80] to take the specific absorbed fraction specified by equation 4.3 and change it to the one specified by equation 4.4.

$$\Phi(Wall \leftarrow Wall) = \frac{1}{m_{Contents}} \quad (4.4)$$

This effectively doubles the self dose to the GI tract organs. Thus the organ doses from OLINDA/EXM were tabulated, but the GI tract was recalculated using these

new dose factors to correct the GI-tract. This correction was applied to the Stomach, Upper Large Intestine (ULI), Lower Large Intestine (LLI), and Small Intestine (SI). The corresponding effective dose was then recalculated based on the new GI-tract total dose estimates.

4.6.2 Adjustment of ICRP 103 Effective Doses

Adjustment of the ICRP 103 ED values must be done since there are no published dose factors for some of the organs listed in ICRP 103 [6]. Essentially there is a deficit of dose using this system with OLINDA, since those organs have been excluded from the calculation. Conversion to ICRP 103 is accomplished by increasing the overall effective dose by the proportion of tissue weighting factor missing from the analysis (as per a recommendation by M. Stabin [81] during a personal communication). The female organs were removed from the adult phantom calculation, and the adult dose is taken to be the male dose. The missing organs for the male are the oesophagus, salivary glands, extrathoracic region, lymphatic nodes, oral mucosa, and the prostate; corresponding to a total tissue weighting factor of 0.0869 or 8.69%. The missing female organs are the oesophagus, salivary glands, extrathoracic region, lymphatic nodes, and the oral mucosa; corresponding to a total tissue weighting factor of 0.0777 or 7.77%. The final effective dose after applying the ICRP 103 [6] tissue weighting factors was increased by 8.69% for the male and 7.77% for the female to compensate for the missing organ dose factors.

4.7 Error Analysis

After integration of the organ TACs and calculation of the residence times, average organ residence times (over all subjects) for each organ were calculated. The associated error on these values is the sample standard deviation. Next, equivalent doses

were calculated using equation 2.24, where the dose factors were assumed to have zero error. The error on the equivalent dose is thereby given by equation 4.5,

$$\sigma_{H_T} = \sqrt{\sum_S (\sigma_N \times DF)^2} \quad (4.5)$$

where: σ_{H_T} is the error on the equivalent dose H_T , S is the source organ index, σ_N is the error on the residence time, and DF is the dose factor (or S-parameter). The effective dose is calculated using equation 2.6. The error on the effective dose (ED) is given by equation 4.6,

$$\sigma_{ED} = \sqrt{\sum_T (w_T \times \sigma_{H_T})^2} \quad (4.6)$$

where: σ_{ED} is the error on the effective dose, T is the organ index for organs with specific tissue weighting factors, and w_T is the tissue weighting factor of tissue T.

Chapter 5

Results

5.1 Overview

Organ time activity curves, residence times, equivalent doses, and effective dose estimates from the rest and stress studies are all presented in this chapter. In addition, effective dose estimates are calculated for Sr-82 and Sr-85, which are potential ‘break-through’ impurities contained within the Rb-82 chloride eluate.

5.2 Time Activity Curves and Residence Times for Rest

Average time activity curves for the 6 organs with the highest residence times are shown in Figure 5.1. The first organ to reach peak activity was the heart contents which peaked after an elapsed time of ~ 40 s. The next organ to reach peak activity was the lungs (~ 50 s), followed by the heart wall (~ 60 s), liver (~ 80 s), and kidneys (~ 80 s). The peaks are expected in this order since after the Rb-82 chloride solution is injected into the blood, it first travels to the right atrium of the heart (heart contents), then gets pumped to the lungs, and is transported back to the heart for

general circulation to the rest of the body.

Figure 5.1: Time activity curves for selected organs (rest).

Estimates of the organ residence times for each subject were calculated from the average time activity concentration curves within the VOI for each subject's organ. The average organ residence times were then calculated by averaging across all subjects. The average organ residence times are shown in table 5.1. The organ with the highest residence time was the muscle, followed by the lungs, kidneys, heart contents, liver, heart wall, SI, spleen, stomach, pancreas, brain, adrenals, red marrow, LLI, breasts, bladder, uterus, gallbladder, thyroid, ovaries, and testes.

A bar graph of the residence times can be found in Figure 5.2, with the sample standard deviation shown as error bars.

5.2.1 Equivalent Doses and Effective Dose Estimates

The output from OLINDA/EXM was GI-corrected using methods described in Section 4.6.1, and using the tissue weighting factors (w_T) from the ICRP Publication 60 system. [82] Additionally, OLINDA/EXM uses a hermaphrodite adult phantom which has both male and female sex organs. To convert to a male phantom ED, the female sex organ equivalent doses from the adult phantom were removed from the

Table 5.1
Organ residence times for Rb-82 (rest).

Organ	Residence Time	
	(MBq-hr/MBq)	$\pm$ SD
Adrenals	7.74×10^{-5}	9.9×10^{-6}
Brain	1.22×10^{-4}	4.1×10^{-5}
Breasts	4.51×10^{-5}	2.4×10^{-5}
Gallbladder	2.17×10^{-5}	2.6×10^{-6}
LLI	4.49×10^{-5}	2.2×10^{-5}
SI	2.63×10^{-4}	7.9×10^{-5}
Stomach	1.75×10^{-4}	6.2×10^{-5}
ULI	6.26×10^{-5}	1.8×10^{-5}
Heart - Contents	1.01×10^{-3}	3.0×10^{-4}
Heart - Wall	5.10×10^{-4}	1.6×10^{-4}
Kidneys	1.64×10^{-3}	1.9×10^{-4}
Liver	9.75×10^{-4}	2.0×10^{-4}
Lungs	2.16×10^{-3}	6.9×10^{-4}
Muscle	2.75×10^{-3}	1.5×10^{-3}
Ovaries	1.97×10^{-6}	2.2×10^{-7}
Pancreas	1.72×10^{-4}	4.6×10^{-5}
Red Marrow	5.75×10^{-5}	2.7×10^{-5}
Spleen	1.97×10^{-4}	5.7×10^{-5}
Testes	3.56×10^{-6}	6.6×10^{-7}
Thyroid	1.84×10^{-5}	7.9×10^{-6}
Bladder	3.82×10^{-5}	2.3×10^{-5}
Uterus	3.58×10^{-5}	4.0×10^{-6}
Remainder	2.02×10^{-2}	1.7×10^{-3}

Figure 5.2: Organ residence times for Rb-82 (rest).

calculation. The equivalent doses and the resultant ED estimates for the male and female phantoms are given in Table 5.2. The effective dose using the ICRP 103 [6] tissue weighting factors was done in the manner prescribed by Section 4.6.2.

5.3 Time Activity Curves and Residence Times for Stress

Time activity curves for organs with the highest residence times are shown in Figure 5.3. The order in which the organs reached their peak activity is the same in stress as in rest.

Average residence times for all organs are summarized in table 5.3, and were calculated from the 25 individual subject residence times as described in the rest analysis.

A bar graph of the residence times can be found in Figure 5.4, with the sample standard deviation shown as error bars. The organ with the highest residence time was the lungs, followed by the liver, heart contents, heart wall, stomach, pancreas,

Table 5.2
Equivalent doses and effective dose estimates (rest).

Organ	Phantom			
	Male		Female	
	Fraction $\pm$ SD (mSv/MBq)		Fraction $\pm$ SD (mSv/MBq)	
Adrenals	3.76×10^{-3}	4.6×10^{-4}	4.37×10^{-3}	5.3×10^{-4}
Brain	1.14×10^{-4}	2.7×10^{-5}	1.37×10^{-4}	3.2×10^{-5}
Breasts	1.74×10^{-4}	5.7×10^{-5}	1.85×10^{-4}	5.6×10^{-5}
Gallbladder	5.11×10^{-4}	1.9×10^{-5}	6.09×10^{-4}	2.2×10^{-5}
LLI	5.88×10^{-4}	1.2×10^{-4}	6.94×10^{-4}	1.3×10^{-4}
SI	8.53×10^{-4}	1.5×10^{-4}	1.01×10^{-3}	1.8×10^{-4}
Stomach	9.19×10^{-4}	2.0×10^{-4}	1.09×10^{-3}	2.3×10^{-4}
ULI	5.74×10^{-4}	6.6×10^{-5}	6.92×10^{-4}	7.3×10^{-5}
Heart Wall	2.47×10^{-3}	5.3×10^{-4}	3.04×10^{-3}	6.6×10^{-4}
Kidneys	4.66×10^{-3}	5.4×10^{-4}	5.06×10^{-3}	5.8×10^{-4}
Liver	5.57×10^{-4}	9.8×10^{-5}	7.47×10^{-4}	1.3×10^{-4}
Lungs	1.92×10^{-3}	5.9×10^{-4}	2.36×10^{-3}	7.2×10^{-4}
Muscle	1.69×10^{-4}	4.8×10^{-5}	2.41×10^{-4}	7.7×10^{-5}
Ovaries	-	-	2.42×10^{-4}	1.7×10^{-5}
Pancreas	1.62×10^{-3}	4.0×10^{-4}	1.81×10^{-3}	4.4×10^{-4}
Red Marrow	2.83×10^{-4}	1.0×10^{-5}	3.33×10^{-4}	1.0×10^{-5}
Osteogenic	4.34×10^{-4}	7.3×10^{-6}	5.93×10^{-4}	9.5×10^{-6}
Skin	2.84×10^{-4}	3.2×10^{-6}	3.62×10^{-4}	3.8×10^{-6}
Spleen	1.02×10^{-3}	2.6×10^{-4}	1.24×10^{-3}	3.2×10^{-4}
Testes	1.37×10^{-4}	1.4×10^{-5}	-	-
Thymus	3.53×10^{-4}	1.1×10^{-5}	4.49×10^{-4}	2.9×10^{-5}
Thyroid	7.66×10^{-4}	3.0×10^{-4}	9.20×10^{-4}	5.7×10^{-6}
Bladder	3.95×10^{-4}	5.0×10^{-5}	4.69×10^{-4}	2.3×10^{-5}
Uterus	-	-	4.26×10^{-4}	2.4×10^{-4}
ED(ICRP 60 w_T) [5]	7.37×10^{-4}	7.52×10^{-5}	8.64×10^{-4}	8.98×10^{-5}
ED(ICRP 80 w_T) [45]	7.18×10^{-4}	7.53×10^{-5}	8.45×10^{-4}	8.98×10^{-5}
ED(ICRP 103 w_T) [6]	7.62×10^{-4}	7.43×10^{-5}	9.15×10^{-4}	8.93×10^{-5}

Figure 5.3: Time activity curves for selected organs (stress).

Table 5.3
Organ residence times for Rb-82 (stress).

Organ	Residence Time	
	(MBq-hr/MBq)	$\pm$ SD
Breasts	3.87×10^{-5}	2.45×10^{-5}
Gallbladder	3.02×10^{-5}	6.62×10^{-6}
Stomach	1.98×10^{-4}	7.60×10^{-5}
Heart Contents	9.61×10^{-4}	2.38×10^{-4}
Heart Wall	6.67×10^{-4}	1.48×10^{-4}
Liver	1.12×10^{-3}	2.24×10^{-4}
Lungs	2.15×10^{-3}	5.75×10^{-4}
Pancreas	1.48×10^{-4}	5.72×10^{-5}
Spleen	1.15×10^{-4}	3.72×10^{-5}
Remainder	2.52×10^{-2}	1.05×10^{-3}

spleen, breasts, and gallbladder.

Figure 5.4: Organ residence times for Rb-82 (stress).

5.3.1 Equivalent Doses and Effective Dose Estimates

The Equivalent Doses from OLINDA/EXM for the male and female phantoms are given in Table 5.4 along with the effective dose estimates.

5.4 Abridged Rest Results

There are no published biodistribution values for Rb-82 under conditions of cardiac stress imaging, and therefore the results can only be compared with the rest data. However, since the rest data have a significantly greater number of organs (including those in the BD regions) the rest analysis should be modified to correspond to the stress analysis. Only subjects with both stress and rest data were compared, this included 25 subjects. Also, all organs from the BD regions were removed in this analysis since they were not measured at stress. Therefore, this data set is called the abridged rest data set. The recalculated average residence times are found in Table 5.5, and the recalculated equivalent doses and effective doses for the rest data are

Table 5.4
Equivalent doses and effective dose estimates (Stress).

Organ	Phantom			
	Male		Female	
	Fraction $\pm$ SD (mSv/MBq)		Fraction $\pm$ SD (mSv/MBq)	
Adrenals	4.07×10^{-4}	9.86×10^{-5}	5.19×10^{-4}	1.24×10^{-4}
Brain	3.34×10^{-4}	6.46×10^{-5}	4.29×10^{-4}	8.03×10^{-5}
Breasts	1.60×10^{-4}	1.10×10^{-4}	1.63×10^{-4}	1.17×10^{-4}
Gallbladder	4.04×10^{-4}	4.38×10^{-4}	5.04×10^{-4}	5.33×10^{-4}
LLI	3.72×10^{-4}	3.81×10^{-4}	4.75×10^{-4}	4.86×10^{-4}
SI	3.80×10^{-4}	3.83×10^{-4}	4.68×10^{-4}	4.73×10^{-4}
Stomach	1.04×10^{-3}	7.42×10^{-4}	1.24×10^{-3}	6.00×10^{-4}
ULI	3.79×10^{-4}	3.81×10^{-4}	4.84×10^{-4}	4.86×10^{-4}
Heart Wall	3.07×10^{-3}	2.04×10^{-3}	3.81×10^{-3}	2.60×10^{-3}
Kidneys	3.78×10^{-4}	9.07×10^{-5}	4.82×10^{-4}	1.11×10^{-4}
Liver	7.64×10^{-4}	5.49×10^{-4}	1.03×10^{-3}	7.39×10^{-4}
Lungs	2.40×10^{-3}	1.83×10^{-3}	2.93×10^{-3}	2.24×10^{-3}
Muscle	3.57×10^{-4}	7.62×10^{-5}	4.56×10^{-4}	9.20×10^{-5}
Ovaries	-	-	4.78×10^{-4}	1.26×10^{-4}
Pancreas	1.42×10^{-3}	1.27×10^{-3}	1.59×10^{-3}	1.41×10^{-3}
Red Marrow	2.89×10^{-4}	2.79×10^{-4}	3.51×10^{-4}	3.39×10^{-4}
Osteogenic Cells	4.71×10^{-4}	4.75×10^{-4}	6.56×10^{-4}	6.09×10^{-4}
Skin	3.25×10^{-4}	3.30×10^{-4}	4.15×10^{-4}	4.22×10^{-4}
Spleen	8.76×10^{-4}	5.34×10^{-4}	1.07×10^{-3}	6.48×10^{-4}
Testes	3.45×10^{-4}	7.59×10^{-5}	-	-
Thymus	4.05×10^{-4}	3.63×10^{-4}	5.13×10^{-4}	4.68×10^{-4}
Thyroid	3.59×10^{-4}	8.23×10^{-5}	4.48×10^{-4}	8.96×10^{-5}
Bladder	3.69×10^{-4}	3.79×10^{-4}	4.42×10^{-4}	4.54×10^{-4}
Uterus	-	-	4.76×10^{-4}	1.24×10^{-4}
ED(ICRP 103 w_T) [6]	6.94×10^{-4}	2.61×10^{-4}	8.46×10^{-4}	3.17×10^{-4}

given in Table 5.6. All abridged rest subjects had the same organ list as the stress subjects.

Table 5.5
Abridged organ residence times for Rb-82 (rest).

Organ	Residence Time	
	(MBq-hr/MBq)	$\pm$ SD
Lungs	2.24E-03	7.12E-04
Liver	9.98E-04	2.08E-04
Spleen	2.01E-04	5.23E-05
Pancreas	6.19E-05	8.84E-05
Gallbladder	3.23E-06	6.65E-06
Stomach	1.75E-04	6.455E-05
Breasts	1.89E-05	2.82E-05
Heart Contents	1.04E-03	3.07E-04
Heart Wall	5.04E-04	1.67E-04
Remainder	2.54E-02	8.35E-04

5.5 Comparison of Stress Versus Rest Dosimetry

5.5.1 Residence Times

An analysis of the stress residence times was carried out by calculation of the relative difference with respect to the rest residence times as shown in Table 5.7. Notable differences ($> 50\%$) include the spleen, gallbladder, pancreas, and breasts.

A two-tailed t-test was performed for all residence times to test for the equivalence of means. Significant differences ($P < 0.05$) were found in the liver, spleen, pancreas, gallbladder, breast, and heart wall, but not in the right atrium, remainder, or lungs.

Table 5.6
Abridged equivalent doses for Rb-82 (rest).

Organ	Phantom			
	Male		Female	
	Fraction $\pm$ SD (mSv/MBq)		Fraction $\pm$ SD (mSv/MBq)	
Adrenals	4.13E-04	9.91E-05	5.28E-04	1.24E-04
Brain	3.52E-04	6.51E-05	4.52E-04	8.09E-05
Breasts	4.25E-04	7.53E-05	1.25E-04	8.70E-05
Gallbladder	4.25E-04	3.88E-04	5.27E-04	4.84E-04
LLI	6.80E-04	3.84E-04	7.95E-04	4.89E-04
SI	3.51E-04	3.86E-04	4.34E-04	4.77E-04
Stomach	9.70E-04	4.72E-04	1.16E-03	5.79E-04
ULI	5.55E-04	3.84E-04	6.73E-04	4.90E-04
Heart Wall	2.48E-03	1.71E-03	3.05E-03	2.13E-03
Kidneys	3.91E-04	9.13E-05	4.99E-04	1.12E-04
Liver	5.58E-04	4.90E-04	7.50E-04	6.60E-04
Lungs	2.00E-03	1.91E-03	2.44E-03	2.33E-03
Muscle	3.73E-04	7.68E-05	4.75E-04	9.27E-05
Ovaries	-	-	5.02E-04	1.27E-04
Pancreas	6.61E-04	5.43E-04	7.47E-04	6.05E-04
Red Marrow	2.99E-04	2.81E-04	3.64E-04	3.42E-04
Osteogenic Cells	4.93E-04	4.79E-04	6.87E-04	6.14E-04
Skin	3.41E-04	3.32E-04	4.35E-04	4.26E-04
Spleen	1.01E-03	9.22E-04	1.23E-03	1.12E-03
Testes	3.63E-04	7.64E-05	-	-
Thymus	4.13E-04	3.66E-04	5.25E-04	4.72E-04
Thyroid	3.77E-04	8.30E-05	4.69E-04	9.03E-05
Bladder	3.89E-04	3.82E-04	4.65E-04	4.58E-04
Uterus	-	-	5.01E-04	1.25E-04
ED(ICRP 103 w_T) [6]	7.29E-04	2.68E-04	8.38E-04	3.26E-04

Table 5.7
Relative difference of residence times at stress versus rest.

Organ	% Difference	± SD
Lungs	-4	
Liver	12	
Spleen	-54	
Pancreas	82	
Gallbladder	161	
Stomach	12	
Breasts	69	
Heart Contents	-8	
Heart Wall	28	
Remainder	-1	

5.5.2 Effective Dose Estimates

The effective dose contributions were analysed by taking the % difference from stress relative to rest. The results of this comparison are shown in Table 5.8. Notable differences ($> 25\%$) include the spleen, gallbladder, pancreas, and breasts. Final effective dose estimates are shown in Table 5.9, with the relative differences indicated versus rest.

In males only, the breasts, LLI, and pancreas were significantly ($P < 0.05$) different, and in females only the LLI and pancreas differed significantly. No significant difference was found for the rest of the organs or the effective dose estimates at rest versus stress.

A students t-test was also performed for the effective dose results. No significant differences were found.

Table 5.8
Relative difference of effective dose contributions at stress versus rest.

Organ	% Difference	
	Male	Female
Adrenals	0	0
Brain	-1	-1
Breasts	-91	32
Gallbladder	35	32
LLI	-54	-46
SI	12	12
Stomach	-31	-30
ULI	-34	-29
Heart Wall	14	15
Kidneys	-1	0
Liver	10	10
Lungs	-4	-3
Muscle	-1	0
Ovaries		-1
Pancreas	68	66
Red Marrow	0	-1
Osteogenic Cells	-1	-1
Skin	-1	0
Spleen	-48	-47
Testes	-1	
Thymus	0	0
Thyroid	-1	-1
Bladder	-1	-1
Uterus		-1

Table 5.9
Relative difference of effective dose from stress.

	Male		Female	
	mSv $\pm$ SD		mSv $\pm$ SD	
Stress	6.94E-04	$\pm$ 2.61E-04	8.46E-04	$\pm$ 3.17E-04
Rest	7.29E-04	$\pm$ 2.68E-04	8.38E-04	$\pm$ 3.26E-04
% Difference	5		1	

5.6 The Effective Dose Contributions From Sr-82/85 Breakthrough

Potential impurities in the Rb-82 chloride eluate must be taken into consideration. During the spallation process Sr-85 is produced as a by-product, and some Sr-85 will be present in the Sr-82 source within the Rb-82 generator. Additionally the elution process is not perfect and some Sr-82 and Sr-85 may leak into the injected Rb-82 chloride. Often this is expressed as the breakthrough, which is the ratio of the activity of the impurity divided by the eluted activity of the desired isotope (in this case Rb-82). The upper limit on the Sr-82 and Sr-85 breakthroughs are given by Alvarez-Diez et. al. [83] as shown in equations 5.1 and 5.2.

$$\frac{\text{Sr-82}}{\text{Rb-82}} < 0.02 \times 10^{-3} \quad (5.1)$$

$$\frac{\text{Sr-85}}{\text{Rb-85}} < 0.2 \times 10^{-3} \quad (5.2)$$

Based on these limits, and using the average injected activity of 1.0 ± 0.2 GBq, the maximum breakthrough injected activities of Sr-82 and Sr-85 are 20 ± 4 kBq and 200 ± 40 kBq respectively. From ICRP 80 [45] the effective dose from Sr-85 is 0.79 mSv/MBq. Therefore, the maximum dose from Sr-85 breakthrough would be 0.16 ± 0.03 mSv.

There are no published dose estimates for Sr-82. Therefore, the estimate for the dose from Sr-82 was derived from the biodistribution of Sr-85, Sr-87m, and Sr-89 published in ICRP 53 [8]. This was done through linear interpolation of the cortical and trabecular bone structures, and log interpolation of the rest of the organs - see appendix C for greater details. From OLINDA/EXM the effective dose from Sr-82

would be 4.53 mSv/MBq to the male and 5.57 mSv/MBq to the female. Assuming the worst case and taking the higher estimate, the maximum dose from Sr-82 breakthrough would be 0.11 ± 0.02 mSv.

5.7 Summary

Using the procedure outlined in Section 2.3.3, without the breakthrough doses the gender averaged (adult) ED for all subjects would be $8.4 \times 10^{-4} \pm 0.81 \times 10^{-4}$ mSv/MBq. The effective dose was 0.84 ± 0.18 mSv to the adult population from the Rb-82 (per scan) with 3D PET, using the average injected activity of 1.0 ± 0.2 GBq from this study. The adult CT effective dose in this study was 0.5 ± 0.4 mSv, which were derived from the dose length products using the conversion factors in ICRP 102 [84]. The breakthrough effective dose from Sr-82 was 0.11 ± 0.02 mSv, and the breakthrough effective dose from Sr-85 was 0.16 ± 0.03 mSv. The total effective dose to all subjects in this study from Rb-82 (either rest or stress) including CT and breakthroughs was 1.61 ± 0.53 mSv to an adult. By comparison the ICRP effective dose to an adult would be 4.3 ± 0.8 mSv, and the yearly background radiation dose in Canada [85] is ≈ 2 mSv. The final effective dose estimates to subjects in this study for Rb-82 are summarised in Table 5.10. The variability in the values shown in Table 5.10 are primarily due to the variability in the injected dose ($\pm 20\%$), which reflects the variability in the patient masses for the 30 subjects used in this study (the variability in the effective doses quoted in mSv/MBq are $\pm 10\%$).

Table 5.10
Effective dose estimates for 30 subjects for Rb-82 using ICRP 103 [6].

	Phantom					
	Male		Female		Adult	
	(mSv)		(mSv)		(mSv)	
Rb-82	0.76	± 0.17	0.92	± 0.20	0.84	± 0.18
Sr-85	0.16	± 0.03	0.16	± 0.03	0.16	± 0.03
Sr-82	0.11	± 0.02	0.11	± 0.02	0.11	± 0.02
CT (Chest)	0.5	± 0.3	0.5	± 0.5	0.5	± 0.4
Total	1.53	± 0.35	1.69	± 0.54	1.61	± 0.53

Values are calculated using an average injected activity of 1.0 ± 0.2 GBq.

Chapter 6

Discussion

6.1 Overview

The results from this study show little difference between stress and rest, although the kidneys were not measured in the stress data. This study shows a large difference in dose estimates between in-vivo studies (namely this study, Ryan et. al. [32], and Kearfott [33]), and the blood flow models by the ICRP [8] and Leggett and Williams [34]. These differences are presented and discussed using the ICRP tissue weighting factors and the dose factors from OLINDA/EXM. Only comparisons of the published residence times from the original sources were used (no combined data).

6.2 Published Dose Estimates

It is important to note that published dose estimates use a dosimetric phantom different from the one used in this study. It is unknown what effect the different dose factors from these phantoms may have on a dose estimate. It is clear however that differences do exist, as is evident from the differences in recalculated values when compared with the published values. Additionally, no published dose estimates for the Leggett and Williams [34] blood flow model exist. To properly compare these data

to other studies, only the effect of the difference in biodistribution is required (i.e., the residence times), since only the residence times are measured quantities. To eliminate a possible bias towards a particular phantom it is appropriate to recalculate the published biodistribution data using the same dosimetric system for a ‘fair comparison’ (i.e., one where a single dependant variable is compared between two data sets). These recalculations are based on the current dose factors from OLINDA/EXM, and the ICRP 103 tissue weighting factors. For the published residence times please refer to Section 1.3. Tables 6.1 and 6.2 list the equivalent doses for the published data, and the corresponding effective doses (ED) using the ICRP 103 [6] tissue weighting factors.

6.3 Dosimetry of Rb-82 at Rest

6.3.1 Comparison of Residence Times

Comparisons between the residence times of different studies highlight the differences in measured or assumed tracer biodistribution. The total body residence time is the sum of all organ residence times including the remainder. This quantity should therefore be the total number of nuclear decays per unit injected activity in the whole body. To compare studies the relative distribution of the total residence times was calculated, as shown in Table 6.3. The results show that the main source organs (> 5%) for the ICRP blood flow model are the kidneys, muscle, lung, and SI; for the Leggett blood flow model the main source organs were SI, heart contents, kidneys, liver, lungs, and muscle; for the study by Ryan et. al. the main source organs were the kidneys and lungs; for the estimate by Kearfott the main source organs were the kidney, lungs, and muscle; and for this study the main source organs were the muscle and lungs. Additionally, to highlight the differences in magnitude between this and

Table 6.1
Equivalent dose derived from blood flow models.

	ICRP53 [8]		Leggett [34]	
	Male	Female	Male	Female
	(mSv/MBq)	(mSv/MBq)	(mSv/MBq)	(mSv/MBq)
Adrenals	1.63E-02	1.89E-02	2.79E-03	3.25E-03
Brain	7.64E-05	9.16E-05	1.67E-04	1.96E-04
Breasts	1.09E-04	1.36E-04	1.22E-04	1.53E-04
Gallbladder	2.75E-04	3.30E-04	2.44E-04	2.98E-04
LLI	4.24E-03	2.37E-03	3.09E-03	1.76E-03
SI	2.95E-03	3.41E-03	3.00E-03	3.46E-03
Stomach	1.28E-03	1.47E-03	7.01E-04	8.18E-04
ULI	1.89E-03	2.13E-03	1.46E-03	1.65E-03
Heart	3.21E-03	4.20E-03	3.69E-03	4.52E-03
Kidneys	1.85E-02	2.01E-02	9.34E-03	1.01E-02
Liver	9.31E-04	1.24E-03	9.60E-04	1.29E-03
Lungs	2.45E-03	3.00E-03	1.82E-03	2.23E-03
Muscle	2.29E-04	3.39E-04	2.08E-04	3.11E-04
Ovaries		2.84E-04	2.18E-04	2.74E-04
Pancreas	4.44E-03	4.94E-03	2.80E-03	3.11E-03
Red	6.87E-04	6.69E-04	4.24E-04	4.25E-04
Osteogenic	7.00E-04	9.34E-04	3.72E-04	4.98E-04
Skin	9.06E-05	1.14E-04	9.69E-05	1.22E-04
Spleen	4.78E-03	5.81E-03	4.16E-03	5.05E-03
Testes	8.29E-05		2.78E-04	
Thymus	1.38E-04	1.70E-04	1.69E-04	2.05E-04
Thyroid	3.43E-02	4.14E-02	9.09E-03	1.10E-02
Urinary	1.21E-04	1.44E-04	1.53E-04	1.83E-04
Uterus		2.32E-04	1.90E-04	2.37E-04
ED (ICRP 103 w_T)	3.04E-03	3.45E-03	1.42E-03	1.57E-03

Table 6.2
Equivalent dose derived from in-vivo data.

	Kearfott [33]		Ryan [32]	
	Male	Female	Male	Female
	(mSv/MBq)	(mSv/MBq)	(mSv/MBq)	(mSv/MBq)
Adrenals	3.44E-04	4.37E-04	4.27E-04	5.49E-04
Brain	1.02E-04	1.22E-04	3.10E-04	3.98E-04
Breasts	2.65E-04	3.35E-04	3.21E-04	4.12E-04
Gallbladder	3.24E-04	3.94E-04	4.06E-04	5.00E-04
LLI	1.14E-03	4.27E-04	3.45E-04	4.41E-04
SI	2.44E-03	8.41E-04	3.66E-04	4.54E-04
Stomach	6.94E-04	1.59E-03	3.71E-04	4.72E-04
ULI	1.00E-03	6.12E-04	3.67E-04	4.67E-04
Heart	4.53E-03	5.82E-03	1.53E-03	2.01E-03
Kidneys	5.68E-03	6.17E-03	8.78E-03	9.54E-03
Liver	7.16E-04	9.61E-04	8.30E-04	1.11E-03
Lungs	2.05E-03	2.51E-03	1.74E-03	2.13E-03
Muscle	2.63E-04	3.96E-04	3.36E-04	4.28E-04
Ovaries	-	3.56E-04	3.56E-04	4.51E-04
Pancreas	6.71E-04	7.59E-04	4.10E-04	5.18E-04
Red	2.30E-04	2.76E-04	2.78E-04	3.38E-04
Osteogenic	3.46E-04	4.73E-04	4.41E-04	6.15E-04
Skin	2.32E-04	2.96E-04	3.04E-04	3.89E-04
Spleen	3.18E-04	4.03E-04	4.01E-04	5.11E-04
Testes	1.18E-04	-	3.20E-04	
Thymus	3.09E-04	3.90E-04	3.51E-04	4.50E-04
Thyroid	2.60E-04	3.23E-04	3.31E-04	4.13E-04
Urinary	2.73E-04	3.19E-04	3.45E-04	4.13E-04
Uterus	-	3.54E-04	3.57E-04	4.48E-04
ED (ICRP 103 w_T)	7.88E-04	9.52E-04	7.26E-04	8.72E-04

other studies, the relative difference of the residence time from this study was taken with respect to published residence times as shown in Table 6.4.

Table 6.3
Relative distribution of residence times to the total body residence time.

Organ	ICRP53 [8]	Leggett [34]	Kearfott [33]	Ryan [32]	This Study	
	%	%	%	%	%	$\pm$ SD
SI	9	11	4	0	1	± 3
Heart Contents	0	6	2	0	3	± 3
Kidneys	21	13	6	11	5	± 3
Liver	5	7	4	5	3	± 3
Lungs	9	8	7	7	7	± 3
Muscle	15	17	19	0	9	± 3
Red Marrow	5	3	0	0	0	± 3
Remainder	12	19	51	76	66	± 4
Thyroid	1	1			0.1	± 3

6.3.2 Comparison of Effective Dose Estimates With Other Dosimetry Studies

Table 6.5 shows the relative contribution to the effective dose for various published estimates. Most notable were the differences in thyroid and lungs for the in-vivo measurements which were much lower than predicted by the blood flow models.

Of particular note is that the lungs contribute $\approx 30\%$ to the effective dose for all in-vivo measurements, whereas the blood flow models from the ICRP, and Leggett and Williams were lower at 10% and 15% respectively. The thyroid contributes $< 4\%$ for the in-vivo measurements, whereas the blood flow models from the ICRP, and Leggett and Williams were 45% and 25% respectively. The reasons for these differences are not known at this time. Final effective doses are found in Table 6.6, with the relative differences from this study also given.

Table 6.4
Relative difference in residence times from published studies.

Organ	Ryan [32]		Leggett [34]		ICRP53 [8]		Kearfott [33]	
	%	± SD	%	± SD	%	± SD	%	± SD
Adrenals	39	18	78	3				
Brain	48	18			11	38		
LLI	91	4	94	3	70	14		
SI	91	3	91	3	76	7		
Stomach	44	20	73	9	46	52		
ULI	91	3	93	2	67	10		
Heart Contents	39	18			56	46		
Heart Wall	30	22	55	14	64	12	3	31
Kidneys	50	6	75	3	18	10	47	6
Liver	45	11	41	12	25	16	37	13
Lungs	6	34	22	25	6	30	11	36
Muscle	38	33	41	32	54	25		
Pancreas	43	15	65	9	181	76		
Red Marrow	92	4	96	2				
Spleen	78	7	80	6				
Testes	70	6			27	24		
Thyroid	92	3	98	1				
Urinary Bladder	206	188						
Remainder	308	34	437	45	27	11	10	8

Table 6.5
Relative contributions (> 5%) to the effective dose.

Organ	% Contribution					
	This Study $\pm$ SD		Kearfott [33]	Ryan [32]	Leggett [34]	ICRP53 [8]
Lungs	30	± 9	31	33	15	10
Stomach	14	± 2	11	7	6	5
Colon	9.0	± 0.3	16	7	18	11
Kidneys	6	± 1	7	13	6	6
Adrenals	5	± 1	< 1	1	2	5
Red Marrow	4.0	± 0.2	4	5	4	3
Thyroid	4	± 2	1	2	25	45
Heart Wall	3	± 1	5	2	2	1
Breasts	3	± 1	4	6	1	< 1
Liver	3	± 1	4	5	3	1

Table 6.6
Comparison of the effective dose for various estimates.

		ICRP53 [8]	Leggett [34]	Kearfott [33]	Ryan [32]	This Study	$\pm$ SD
		mSv/MBq	mSv/MBq	mSv/MBq	mSv/MBq	mSv/MBq	mSv/MBq
Male	ED	3.04E-03	1.42E-03	7.88E-04	7.26E-04	7.62E-04	7.43E-05
	%Diff	75	46	3	5	-	
Female	ED	3.45E-03	1.57E-03	9.52E-04	8.72E-04	9.15E-04	8.93E-05
	%Diff	74	42	4	5	-	

6.4 Summary and Conclusion

The remainder tissues accounted for 66 % of the total number of decays in the body. This is much higher than the two blood flow model predictions of 12 % for ICRP and 19 % for Leggett, but is in relative agreement with the study by Ryan (76 %), and Kearfott (51 %). The organs with the highest residence times were: the muscle (9 %), lungs (7 %), kidneys (5 %), liver (3 %) and heart (3 % each). The total body relative residence time in the kidneys is half that of the Leggett and Ryan estimates and a quarter of the ICRP estimate, but agrees with the Kearfott estimate. The total number of decays for the muscle is a little less than half that for Leggett, ICRP, and Kearfott. The residence time in the liver and heart contents is in close agreement with Kearfott, Ryan, and ICRP but is half that of the Leggett estimate. The reason for these discrepancies is not known at this time.

The final effective dose is a quarter of the current ICRP estimate, slightly less than half the Leggett estimate, and about 20% higher than the Ryan estimate. The organs with the highest equivalent dose were the kidneys, followed by the adrenals, heart wall, lungs, pancreas, and spleen. For ICRP the organ with the highest total dose was estimated as the thyroid, followed by the kidneys, adrenals, spleen, pancreas, and LLI. For the Leggett blood flow model the organ with the highest total dose was the kidneys, followed by the thyroid, spleen, heart wall, LLI, and SI. For the Ryan estimate the organ with the highest total dose was the kidneys, followed by the lungs, heart wall, liver, Bone Surfaces, and adrenals. Finally for the Kearfott rat extrapolation the organ with the highest total dose was the kidneys, heart wall, SI, lungs, and colon. Kearfott, Ryan, and Leggett all agree closely with regards to the kidney effective dose estimates, but the thyroid was reported to have the highest equivalent dose by the ICRP estimate contrary to other estimates. Most of the highest organs were in agreement with other models except for the thyroid for the two blood

flow models, the bone surfaces for the Ryan estimate, and the Colon and SI for the Kearfott estimate. The total order of magnitude is variable between all models. The reason for this discrepancy is not known.

The lungs accounted for 31 % of the effective dose estimate, followed by the stomach at 15 %, the colon at 10 % and the kidneys at 5 %. A plot of the time activity curves in units of measured activity per unit injected activity (Relative TAC) for the four critical organs for dosimetry can be found in figures 6.1 and 6.2. There is excellent agreement with Kearfott for the Lungs (31 %), Colon (16 %), stomach (11 %), and kidneys (5 %). For the Ryan estimate the lungs accounted for 35 % of the total effective dose, giving good agreement with this estimate. However the lungs only accounted for 10 % in ICRP and 15 % in the Leggett blood flow models for the total effective dose, which is less than half the value of the estimate in this work. The stomach values for ICRP, Leggett, and Ryan were all lower by 5 %, 6 %, and 7 % respectively. The Ryan and Leggett estimates for the colon at 7 % and 11 % respectively gave good agreement with the estimate of this work, but the ICRP blood flow model is almost double at 18 %. The kidneys were in agreement with the two blood flow models and the Kearfott measurements, but differed from the Ryan estimate by a factor of three (14 %) this estimate. A summary comparing the relative contributions to the effective dose for the various estimates is found in table 6.5.

Figure 6.1: Relative time activity curve for the kidneys and lungs.

Figure 6.2: Relative time activity curve for the stomach and colon.

The many similarities with the data from this study and the Ryan and Kearfott estimate was encouraging since both studies agree that the critical organ for dosimetry is the lungs whereas the blood flow models predict the thyroid to be the critical organ. Also the kidneys were predicted to be the highest dose organ for Ryan, Leggett, Kearfott, and this estimate, whereas the ICRP estimate predicts that the thyroid receives the highest equivalent dose. The largest difference between this study and the Ryan estimate seems to be in the magnitude of the kidney and lung contributions to the dose estimate. The general agreement with the Kearfott estimate is very good for most organs, with minor differences between the colon and stomach doses. These differences may simply be due to using higher precision measuring equipment and more up to date techniques.

The stress results showed little difference in the effective dose compared to rest, despite the significant changes to many of the organ residence times. Most notable was a marked decrease in the spleen residence time from stress relative to rest. The reason for this decrease is unknown.

These dose estimates for Rb-82 are the first to be measured directly with PET/CT in humans. They are one quarter of the current ICRP estimate, and about half the estimate by Leggett. They agree within 20 % of the human in-vivo estimate by Ryan et. al., and within 5 % of the Kearfott estimate extrapolated from rats. The

agreement with the estimate by Ryan and Kearfott indicates that the two blood flow models may be overly conservative. As previously described in Chapter 5.6, the total adult effective dose to the subjects used in this study from Rb-82 (either stress or rest) including CT and potential Sr breakthrough is 1.6 ± 0.5 mSv. By contrast the ICRP adult effective dose would be 4.3 ± 0.8 mSv and the yearly background radiation dose in Canada [85] is ≈ 2 mSv.

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Appendix A

Proof of the 40-80 Method

A.1 Overview

As previously mentioned, for this analysis it is assumed the point spread function of the scanner is a Gaussian function with a FWHM of 10 mm, while noise is ignored.

To fully describe these effects, and the correction techniques that follow, it is useful to define: baseline activity (or just ‘baseline’), an anatomical volume of interest ($\text{VOI}_{\text{anatom}}$), and also the definition of a threshold VOI. The baseline activity is a general level of activity which is systemic within the patient. This activity acts as a background and limits the minimum threshold level attainable for a tissue above baseline. The $\text{VOI}_{\text{anatom}}$ is defined by the VOI drawn from CT data only, and is drawn to represent the true organ dimension. A threshold VOI is drawn such that it encompasses all PET pixel values above some threshold pixel value. The threshold value is always a fraction of the peak activity concentration (average of the highest 5 pixels) within an anatomic VOI. A non uniform PET image is defined where the PET activity is not uniformly distributed across the $\text{VOI}_{\text{anatom}}$. This could be caused by spill-in from adjacent regions, where the biological blood flow regions are complicated, or where the Rb-82 activity is so low that a threshold VOI can not be defined above baseline activity.

In addition to PVA there are possible issues with the alignment of the PET scan with the CT scan. Corrections for this effect are described in Section 4.4.

A.1.1 PVE Simulation Methods

The methods presented in this chapter are based on mathematical simulations of the physical system. The simulations were carried out according to equation A.1.

$$f(x, y, z) = AVG (VOI * PSF) \quad (A.1)$$

where: $f(x, y, z)$ represents the simulated 3D distribution of activity across the field of view for a particular VOI, AVG denotes the average value of the function, VOI is the VOI described by VOI_{anatom} , and $*$ denotes the convolution.

Since a PET image is defined by the mathematics of the convolution of the PSF of the scanner with the tissue structure a review of the mathematics of the convolution is given in Appendix B.3. Also the PSF of the scanner is assumed to be described by a Gaussian function, and therefore a review of the mathematics of Gaussian functions is given in Appendix B.1. Additionally, what is measured within the VOI is the average activity concentration throughout its volume (i.e. measurements of kBq/cc). Therefore, to understand the behaviour of such systems we need to take the average value of the convolution of the PSF with the organ VOI. A mathematical description of function averages is found in Appendix B.2.

A.1.2 The 40-80 Simulations

Tissues thinner than the theoretical minimum, with high uptake, can be corrected by use of the 40-80 method. The following section describes this method, which is used to correct partial volume losses in the kidneys, heart, and thyroid. The kidneys are composed of two long cylindrical structures, the cortex and medula. The heart

is composed of different regions: the atria, ventricles, and the heart wall (primarily located around the left ventricle). The Thyroid is composed of two lobes connected by a layer of thin tissue called the Isthmus. The Isthmus is barely visible in PET due to partial volume losses in the anteroposterior direction and is normally obscured by normal background activity. Since the Isthmus is not visible above background the lobes of the Thyroid are used to define the activity concentration in this region. Since the heart wall and kidneys are long approximately cylindrical structures, partial volume averaging along the length of the organ is minimal. The thyroid is very large in two of its three spatial dimensions, and therefore partial volume losses are significant in the anteroposterior direction only. Therefore partial volume averaging for the thyroid, heart wall, and kidney is only significant in one of its three spatial dimensions, and simulations done herein use a 1D version of equation A.1. A list of organ structures for the kidneys, heart wall, and thyroid are given in Table A.1.

Table A.1 Thicknesses of tissues requiring the 40-80 method [12].				
Heart Region	Min	Max		
L and R Atria	0.5 mm	3.5 mm		
RV	5 mm	7 mm		
LV	11 mm	14 mm		
Kidney Region	Min	Max		
Medula	16 mm	19 mm		
Cortex	4 mm	13 mm		
Thyroid Region	Min/Max	Transverse	Vertical	Anteroposterior
Each Lobe	min	20 mm	50 mm	10 mm
	max	40 mm	80 mm	25 mm
Isthmus	min	20 mm	20 mm	2 mm
	max	-	-	6 mm

Simulations of important tissue thicknesses are shown in table A.2 where: P_{max} is the peak value of the 1D simulation using equation A.1, $\%P_{max}$ is the peak value of the 1D simulation after multiplication by a fraction, $\pm X$ -Values are the x coordinates

corresponding to the x values of the 1D simulation that correspond to the $\%P_{max}$ value, and Average is the average value of the 1D simulation over the $\pm X$ -Value. An example diagram for the 11 mm thickness is shown in Figure A.1 with 10%, 40%, and 80% thresholds displayed.

Table A.2
Convolution simulation values.

Width mm	P_{max} kBq/mm	Quantity	Units	Fraction of P_{max}						
				10%	20%	30%	40%	70%	80%	90%
0.5	0.047	$\%P_{max}$	kBq/mm	0.0047	0.0094	0.0141	0.0188	0.0329	0.0376	0.0423
		$\pm X$ -Value	mm	9.25	7.50	6.63	5.75	3.63	2.75	1.88
		Average	kBq/mm	0.026	0.031	0.033	0.036	0.042	0.044	0.045
3.5	0.3199	$\%P_{max}$	kBq/mm	0.0320	0.0640	0.0960	0.1280	0.2239	0.2559	0.2879
		$\pm X$ -Value	mm	9.50	7.88	6.88	5.88	3.63	2.75	2.13
		Average	kBq/mm	0.179	0.206	0.225	0.245	0.287	0.300	0.308
5	0.4442	$\%P_{max}$	kBq/mm	0.0444	0.0888	0.1333	0.1777	0.3109	0.3554	0.3998
		$\pm X$ -Value	mm	9.75	8.00	6.88	6.00	3.75	2.88	1.88
		Average	kBq/mm	0.249	0.289	0.318	0.341	0.398	0.416	0.431
7	0.5885	$\%P_{max}$	kBq/mm	0.0589	0.1177	0.1766	0.2354	0.4120	0.4708	0.5297
		$\pm X$ -Value	mm	10.25	8.50	7.25	6.50	4.00	3.25	2.13
		Average	kBq/mm	0.332	0.383	0.423	0.448	0.528	0.547	0.571
11	0.8025	$\%P_{max}$	kBq/mm	0.080	0.161	0.241	0.321	0.562	0.642	0.722
		$\pm X$ -Value	mm	11.38	9.63	8.38	7.38	4.63	3.88	2.50
		Average	kBq/mm	0.469	0.532	0.581	0.621	0.723	0.746	0.780
14	0.9012	$\%P_{max}$	kBq/mm	0.090	0.180	0.270	0.360	0.631	0.721	0.811
		$\pm X$ -Value	mm	12.50	10.88	9.63	8.50	5.50	4.38	3.00
		Average	kBq/mm	0.544	0.605	0.655	0.700	0.810	0.842	0.873
20	0.9788	$\%P_{max}$	kBq/mm	0.098	0.196	0.294	0.392	0.685	0.783	0.881
		$\pm X$ -Value	mm	15.63	13.63	12.25	11.13	7.88	6.63	4.88
		Average	kBq/mm	0.628	0.700	0.751	0.792	0.893	0.922	0.952

Each threshold in Figure A.1 has an associated VOI, and is therefore called a threshold VOI (VOI_{thresh}). Geometries of VOI_{thresh} are different for different tissue thicknesses, and always correspond to the VOI defined at the threshold of P_{max} .

Assuming a true activity concentration of 1 kBq/cc for all simulations, results

Figure A.1: Geometry of simulation data.

from various thresholds of P_{max} can be found in Table A.3. The following values are shown in the table: $P_{max} * Vol$ is the multiplication of P_{max} times the volume of the specified VOI_{thresh} , $Avg * Vol$ is the average activity concentration of the specified VOI_{thresh} multiplied by the volume of the specified VOI_{thresh} , $Avg(80) * Vol$ is the average activity concentration of the VOI_{thresh} defined at the 80% threshold multiplied by the volume of the specified VOI_{thresh} , and $Avg(90) * Vol$ is the average activity concentration of the VOI_{thresh} defined at the 90% threshold multiplied by the volume of the specified VOI_{thresh} .

A.1.3 Conclusion from 40-80 Simulations

As shown from the tabulated values, using 'Avg * Vol' consistently underestimates the true activity concentration. The activity concentration is also underestimated in all tests for threshold values above 40%. For tests $P_{max} * Vol$, $Avg(80) * Vol$, and $Avg(90) * Vol$, the activity concentration is overestimated for threshold values below 40%. The optimum method is to use $Avg(80) * Vol$ at a 40% threshold volume, and therefore this method is aptly named the 40-80 method. One of the advantages of using this method is that it relies solely on the PET data, and is therefore not prone to PET/CT co-registration issues.

Table A.3
Convolution simulation results for various thresholds.

Tissue Thickness mm	Test	Fraction of P_{max}							True Value kBq
		10% kBq	20% kBq	30% kBq	40% kBq	70% kBq	80% kBq	90% kBq	
0.5	Avg * Vol	0.49	0.46	0.44	0.41	0.30	0.24	0.17	0.50
	P_{max} * Vol	0.87	0.71	0.62	0.54	0.34	0.26	0.18	
	Avg(80)*Vol	0.81	0.66	0.58	0.50	0.32	0.24	0.16	
	Avg(90)*Vol	0.84	0.68	0.60	0.52	0.33	0.25	0.17	
3.5	Avg * Vol	3.40	3.24	3.09	2.88	2.08	1.65	1.31	3.50
	P_{max} * Vol	6.08	5.04	4.40	3.76	2.32	1.76	1.36	
	Avg(80)*Vol	5.70	4.73	4.13	3.53	2.18	1.65	1.28	
	Avg(90)*Vol	5.85	4.85	4.24	3.62	2.23	1.69	1.31	
5	Avg * Vol	4.86	4.62	4.37	4.09	2.99	2.39	1.62	5.00
	P_{max} * Vol	8.66	7.11	6.11	5.33	3.33	2.55	1.67	
	Avg(80)*Vol	8.11	6.66	5.72	4.99	3.12	2.39	1.56	
	Avg(90)*Vol	8.40	6.90	5.93	5.17	3.23	2.48	1.62	
7	Avg * Vol	6.81	6.51	6.13	5.82	4.22	3.56	2.43	7.00
	P_{max} * Vol	12.06	10.00	8.53	7.65	4.71	3.83	2.51	
	Avg(80)*Vol	11.21	9.30	7.93	7.11	4.38	3.56	2.33	
	Avg(90)*Vol	11.71	9.71	8.28	7.42	4.57	3.71	2.43	
11	Avg * Vol	10.67	10.25	9.74	9.17	6.69	5.79	3.90	11.00
	P_{max} * Vol	18.26	15.46	13.45	11.84	7.43	6.23	4.01	
	Avg(80)*Vol	16.98	14.37	12.50	11.01	6.91	5.79	3.73	
	Avg(90)*Vol	17.75	15.02	13.07	11.51	7.22	6.05	3.90	
14	Avg * Vol	13.60	13.16	12.62	11.90	8.91	7.38	5.24	14.00
	P_{max} * Vol	22.53	19.61	17.36	15.32	9.91	7.89	5.41	
	Avg(80)*Vol	21.05	18.32	16.22	14.31	9.26	7.38	5.05	
	Avg(90)*Vol	21.83	19.00	16.81	14.84	9.60	7.65	5.24	
20	Avg * Vol	19.63	19.08	18.40	17.63	14.07	12.23	9.29	20.00
	P_{max} * Vol	30.60	26.68	23.98	21.79	15.43	12.98	9.55	
	Avg(80)*Vol	28.82	25.13	22.59	20.52	14.53	12.23	9.00	
	Avg(90)*Vol	29.76	25.95	23.32	21.19	15.00	12.62	9.29	

To implement this method a threshold technique is used by drawing a VOI based on a threshold value. A general knowledge of anatomy of the organ is required to do a preliminary analysis in order to determine what the peak activity in the area is. Once the peak is determined, a VOI can be drawn around a percentage of the maximum peak activity. Therefore, to use this method two VOI's must be drawn, one at 40% of P_{max} , and another at 80% of P_{max} . The average activity concentration at 80% of P_{max} is calculated and multiplied by the volume of the VOI at 40% of P_{max} . The limitation of this method is that the whole organ at the 40 % threshold value must be within in the scan, partial volume averaging effects can only be significant in one dimension, and the 40% threshold volume must be well defined and separable from other organs. As a result, this method is often best used in later time frames when the background is sufficiently below the areas of high uptake.

Appendix B

Mathematical Background Information

B.1 General Notes On Gaussian Functions

Any PET image can be represented as a convolution of the true activity concentration with the point spread function of our PET system. Contributions to the point spread function include the intrinsic resolution of the scanner and any image filtering which is done. The point spread function of a PET imaging system is approximately Gaussian and thus a Gaussian function of the form shown in equation B.1 will be used in this analysis.

$$g(x) = \frac{1}{\sqrt{2\pi\sigma^2}} e^{-(x-\mu)^2/(2\sigma^2)} \quad (\text{B.1})$$

Where: σ is the standard deviation of the Gaussian distribution and μ is the mean value of the Gaussian distribution (i.e. where the function is centered). For the purposes of this analysis it is assumed the Gaussian is centered at zero ($\therefore \mu = 0$), since making it non-zero is not meaningful. Therefore equation B.1 simplifies to equation B.2, and it is this equation that will be used to represent the point spread function of the PET imaging system.

$$g(x) = \frac{1}{\sqrt{2\pi\sigma^2}} e^{-x^2/(2\sigma^2)} \quad (\text{B.2})$$

The intrinsic resolution of the scanner as specified and measured by the manufacturer is 6 mm, and the PET image is reconstructed using an 8 mm Hann filter. Since the system is Gaussian the overall full width at half maximum (FWHM) will be an addition in quadrature of all contributions to the FWHM (we assume they both have a Gaussian distribution) or $FWHM = \sqrt{6^2 + 8^2} = 10$. A plot of a Gaussian function is shown in figure B.1, with a FWHM of 10 mm.

Figure B.1: Plot of a Gaussian function.

B.1.1 Relating FWHM to σ

It is very useful to relate the full width at half maximum (FWHM) of the scanner to the standard deviation σ of the Gaussian distribution which represents the scanner resolution for the purposes of calculation. In other words, we would like to choose the standard deviation which represents the FWHM of the scanner. The derivation of this is very simple. What we want is to pick an x value (x_m) which maximizes $g(x)$ and take half this value for the FWHM points, therefore:

$$\frac{1}{2}g(x_m) = \frac{1}{\sqrt{2\pi\sigma^2}}e^{-x^2/(2\sigma^2)} \quad (\text{B.3})$$

Since the exponential involves an $-x^2$, the larger this value the smaller $g(x)$ is, thus to maximize $g(x)$ we set $x_m = 0$ therefore:

$$\frac{1}{2}g(0) = \frac{1}{2} \frac{1}{\sqrt{2\pi\sigma^2}} = \frac{1}{\sqrt{2\pi\sigma^2}}e^{-x^2/(2\sigma^2)} \quad (\text{B.4})$$

$$\therefore e^{-x^2/(2\sigma^2)} = \frac{1}{2} \quad (\text{B.5})$$

Now we solve for x :

$$\frac{-x^2}{2\sigma^2} = \ln\left(\frac{1}{2}\right) \quad (\text{B.6})$$

$$\therefore -x^2 = -\ln(2) 2\sigma^2 \quad (\text{B.7})$$

$$\therefore x^2 = \ln(2) 2\sigma^2 \quad (\text{B.8})$$

$$\therefore x = \pm\sqrt{\ln(2) 2\sigma^2} = \pm\sigma\sqrt{\ln(2) 2} \quad (\text{B.9})$$

So the FWHM points occur at $x_p = \sigma\sqrt{\ln(2) 2}$ and $x_n = -\sigma\sqrt{\ln(2) 2}$, so the width is given by:

$$x_p - x_n = \sigma\sqrt{\ln(2) 2} - (-\sigma\sqrt{\ln(2) 2}) = \sigma\sqrt{\ln(2) 2} + \sigma\sqrt{\ln(2) 2} = 2\sigma\sqrt{\ln(2) 2} = \text{FWHM} \quad (\text{B.10})$$

Therefore we pick the standard deviation as follows:

$$\sigma = \frac{\text{FWHM}}{2\sqrt{2\ln(2)}} \quad (\text{B.11})$$

For example, for a FWHM = 10 mm we get:

$$\sigma = \frac{10}{2\sqrt{2\ln(2)}} = 4.24661 \text{ mm} \quad (\text{B.12})$$

B.2 Average Value of a Function

A volume of interest (VOI) or region of interest (ROI) defines an anatomical region where the activity concentration within the organ is supposed to be. Due to the nature of the measurement some noise will always be present and thus it is appropriate to take the average value within this region of the activity concentration to average out any variations within the ROI or VOI. Mathematically you would therefore be taking the average value of the convolution of the point spread function of the scanner with the function which best represents your tissue. The average value of a function over an interval a to b is defined to be:

$$f(x)_{\text{avg}} = \frac{1}{b-a} \int_a^b f(x) \, dx \quad (\text{B.13})$$

Therefore if $a = -b$, i.e. if the function is symmetric like a Gaussian function:

$$f(x)_{\text{avg}} = \frac{1}{b - (-b)} \int_{-b}^b f(x) \, dx = \frac{1}{2b} \int_{-b}^b f(x) \, dx \quad (\text{B.14})$$

The average value of a normalized Gaussian distribution would be calculated as follows:

$$g(x)_{\text{avg}} = \frac{1}{\infty - (-\infty)} \int_{-\infty}^{\infty} g(x) \, dx = \frac{1}{2\infty} = 0 \quad (\text{B.15})$$

Thus to be useful we want the average value within a confined space near the mean of our Gaussian. A measurement at infinity would not be physically possible as we would need an infinitely large field of view, but the mathematical principle still

applies that the larger the VOI or ROI is, the lower the average value of the activity concentration within the VOI or ROI will be. So our first criterion for drawing the region of interest is the rather qualitative and obvious statement that it must be drawn in such a way as to give a non-zero average value. The main implication is that due to the fact that our ROI must have a finite size these integrals cannot be solved analytically as they involve the integral of a Gaussian, so they will be solved numerically in this analysis.

B.3 Convolution Of The Gaussian

A PET image is not a perfect representation of the activity concentration within the field of view. There are physical restrictions placed on any imaging system which cause the activity to be spread out spatially from its true location. Two effects to be discussed are the intrinsic resolution of the PET system and the partial volume effect. For more information on the causes of these effects please see Chapter 3. In this section the mathematical representation of these issues and their solutions are developed.

The convolution is defined in the following way:

$$f(x) * g(x) = \int_{-\infty}^{\infty} f(u)g(x-u)du \quad (\text{B.16})$$

A rectangular function will be used to represent the tissue density profile for reasons that will be explained later. A rectangular function is defined in equation B.17

$$\Pi(x) = f(x) = \begin{cases} 1 & \text{for } |x| < \frac{W}{2} \\ 0 & \text{for } |x| > \frac{W}{2} \end{cases} \quad (\text{B.17})$$

where: W is the tissue thickness. Thus when we convolve the rectangular function with the Gaussian we get equation B.18, which will be solved numerically.

$$f(x) * g(x) = \Pi(x) * g(x) = \int_{-\infty}^{\infty} \Pi(u)g(x-u)du = \int_{-\frac{W}{2}}^{\frac{W}{2}} g(x-u)du \quad (\text{B.18})$$

The final form of the equation we must solve is given by equation B.19.

$$\Pi(x) * g(x) = \int_{-\frac{W}{2}}^{\frac{W}{2}} g(u)du = \frac{1}{\sqrt{2\pi\sigma^2}} \int_{-\frac{W}{2}}^{\frac{W}{2}} e^{-(x-u)^2/(2\sigma^2)} du \quad (\text{B.19})$$

This equation gives the mathematical representation of the PET image, but what we actually calculate is the spatial average of this within some ROI or VOI as shown in equation B.20. If we take the spatial average of the actual tissue dimensions then for reasons explained later we will always underestimate the true activity concentration within the tissue or organ we are investigating.

$$\frac{1}{2b} \int_{-b}^b \Pi(x) * g(x)dx = \frac{1}{2b} \int_{-b}^b \left(\frac{1}{\sqrt{2\pi\sigma^2}} \int_{-\frac{W}{2}}^{\frac{W}{2}} e^{-(x-u)^2/(2\sigma^2)} du \right) dx \quad (\text{B.20})$$

In this case 'b' is the ROI or VOI dimension and not necessarily the tissue or organ dimension, i.e. the ROI or VOI is usually less than the actual tissue dimension. As a general rule of thumb if a tissue has a thickness twice the scanner resolution (FWHM) then the partial volume effect (PVE) can be compensated for by a small enough region of interest. This technique is herein called the VOI reduction technique, since it involves shrinking the VOI from the baseline VOI. The first case considered will be a tissue with a thickness of 20 mm; this will represent the theoretical minimum tissue thickness required to use the VOI reduction technique. For smaller organs (organs that are smaller than twice the scanner resolution) partial volume losses can

be significant. These would include the kidneys, heart wall and thyroid. To correct for partial volume losses, a region of interest could be drawn around the 1-2% threshold of maximum peak (in the organ) and multiplied by the average activity concentration, which results in about 97% recovery of the true activity. However due to spillover from adjacent organs and a high general baseline activity a minimum threshold of 30% or higher must be used, which results in losses of up to 15-20%. Therefore a different method was chosen to correct for partial volume losses in small organs with a relative high uptake. Since the heart wall is a cylindrical structure partial volume losses only occur in 1 dimension. Thus a convolution with a 1D rectangular function is needed to represent this structure.

Appendix C

Biodistribution of Sr-82

C.1 The Biodistribution of Various Strontium Isotopes

Since there are no published residence times for Sr-82 the biodistribution was estimated from the biodistribution of Sr-87m, Sr-89, and Sr-85. Since radioactivity does not affect the chemistry of an isotope, the uptake and extraction in organs is expected to be similar. However, for longer lived isotopes the impact of the additional biological process of excretion through sweat, the urinary tract, and the digestive tract cannot be known. The published strontium isotopes have half lives ranging from 2 hours to 65 hours (see Table C.1), and Sr-82 has a half life in between the range of these isotopes. Therefore the impact of excretion on the residence times is assumed to be in between the values of the published isotopes used in this analysis. The published residence times (and their associated half-lives) for strontium are taken from ICRP 53 [8], and are shown in Table C.1 along with the interpolated values of Sr-82.

Table C.1
Biodistribution and half-life of various strontium isotopes.

	Isotope			
	Sr-87m	Sr-82*	Sr-89	Sr-85
Half Life (days)	2.805	25.55	50.5	64.84
Residence Times	MBq-h/MBq	MBq-h/MBq	MBq-h/MBq	MBq-h/MBq
Remainder	2.687	120	156	170
Cortical Bone	0.533	77.0	166	202
Trabecular Bone	0.500	62.1	134	161
SI - contents	0.018	0.444	0.60	0.60
ULI - contents	0.014	1.432	1.90	2.00
LLI - contents	0.004	2.601	3.50	3.60
Bladder	0.050	0.819	1.08	1.12
Total Body	97	884.7	1749	2245

*Quantity derived from biodistribution of Sr-87m, Sr-89, and Sr-85.

C.2 Interpolation of Sr-82 Biodistribution

To interpolate to Sr-82 the organ residence times were plotted versus the total body residence time, and a line of best fit using either linear or log interpolation was used, see figure C.2. The total body residence time was used rather than the remainder since the total body residence time is independent of excretion, whereas the remainder and organ residence times may not be. Therefore, by using the organ residence times with the total body residence times we are assured only one dependant variable, and thus a fair interpolation between the isotopes.

From OLINDA/EXM [82] the effective doses using the ICRP 103 [6] tissue weighting factors are 0.0197 mSv/MBq and 0.0265 mSv/MBq to the male and female respectively. However, Sr-82 decays into the positron emitter Rb-82 which this dose assessment does not account for. To calculate the dose from the Rb-82 daughter product of Sr-82, the effective dose of Rb-82 was calculated using the same biodistribution as Sr-82. This is an approximation since the chemistry of Rb-82 is similar

to potassium, whereas the chemistry of Sr-82 is similar to calcium. Therefore, we expect some Rb-82 to diffuse out of high calcium regions into low potassium regions. It is important to note that Sr-82 is primarily taken up by bone and blood flow to these regions are not high, also Rb-82 has a very short half life. Therefore, we expect that most of the Rb-82 daughter products will decay in the same tissues as Sr-82. Using the OLINDA/EXM dose factors the effective doses for the Rb-82 daughter products using the ICRP 103 [6] tissue weighting factors are 4.51 mSv/MBq and 5.54 mSv/MBq to the male and female respectively. Therefore, the total effective dose from Sr-82 including all daughter products is 4.53 mSv/MBq and 5.57 mSv/MBq to the male and female respectively.

(a) Plot of bladder residence time v.s. total body residence time for various strontium isotopes.

(b) Plot of cortical bone residence time v.s. total body residence time for various strontium isotopes.

(c) Plot of LLI residence time v.s. total body residence time for various strontium isotopes.

(d) Plot of SI residence time v.s. total body residence time for various strontium isotopes.

(e) Plot of trabecular bone residence time v.s. total body residence time for various strontium isotopes.

(f) Plot of ULI residence time v.s. total body residence time for various strontium isotopes.

(g) Plot of remainder residence time v.s. total body residence time for various strontium isotopes.

Figure C.1: Interpolation graphs for Sr-82 biodistribution.

Interpolated points for Sr-82 are circled for all organs.

Appendix D

Extra Figures

The following appendix shows examples of PET/CT images from the various biodistribution regions. Slices are shown along the coronal plane (long axis - across the subject from left to right and head to toe), and the sagittal plane (long axis - bisecting the middle of the subject from head to toe).

D.1 All Biodistribution Regions

Figure D.1: All bio-distribution regions - coronal slices.

D.2 Individual Biodistribution Regions

Figure D.2: Fused PET/CT for the head - sagittal and coronal.

Figure D.3: Fused PET/CT for the neck - sagittal and coronal.

Figure D.4: Fused PET/CT for the chest - sagittal and coronal.

Figure D.5: Fused PET/CT for the kidneys - sagittal and coronal.

Figure D.6: Fused PET/CT for the ULI - sagittal and coronal.

Figure D.7: Fused PET/CT for the LLI - sagittal and coronal.

Figure D.8: Fused PET/CT for the SI - sagittal and coronal.

Figure D.9: Fused PET/CT for the female pelvis - sagittal and coronal.

Figure D.10: Fused PET/CT for the male pelvis - sagittal and coronal.

Figure D.11: Fused PET/CT for the thighs - sagittal and coronal.