DOSIMETRY TO EVALUATE THE EFFECT OF PHOSPHOROMIDON ON LU-177-RM2

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by

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Dosimetry to Evaluate the Effect of Phosporomidon on Lu-177-RM2

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Introduction

Cancer

The human body is comprised of trillions of cells. In the healthy case, human cells divide naturally in a controlled manner in order to replace cells as needed. The process in which the body's cells divide continually in an unregulated fashion and thereby spread into surrounding tissues is known as cancer. Since the entire body is made up of cells, it is possible for this condition to occur anywhere in the body. The chance of an individual having this condition is related to their genetics as well as other factors.

These tumor cells being formed will eventually combine to form larger cellular masses or “tumors.” These tumors are split into two main categories known as “malignant” and “benign.” Benign tumors do not spread into nearby tissue and can generally be easily removed. Malignant tumors or “cancerous tumors” can spread into nearby tissue and distant organs ultimately resulting in patient mortality. Once the cancer spreads from one region of the body to another it is called metastatic cancer because the process of transfer is known as metastasis. There are over 100 different forms of cancer. [7] The focus of this discussion will be prostate cancer.

Prostate cancer is the most prevalent cancer among men. Approximately a quarter of all new male cancer cases will be cancer of the prostate. An estimated 27,540 die from this terrible disease every year in the United States [3]. However, research is currently underway to decrease these numbers. These treatments are

differing in nature, expense, and effectiveness, which drives the need for more research. [7]

Broad Cancer Treatment

There are many approaches to eradicating the human body of cancer. These different treatments can be surgery, chemotherapy, or radiotherapy. These all have both positive and negative characteristics that will be discussed. Each patient will present individual needs that only one or a combination of treatments will be able to treat.

The most obvious of these approaches is to perform surgery that removes the cancerous tumor. Surgery can be used in early stage cancers or as part of a broader treatment plan. However, the patient must be in good health for this approach.

Another approach is a drug-based treatment commonly known as chemotherapy. Chemotherapy is effective at destroying cells that are dividing. However, this treatment kills all cells undergoing division, even the beneficial cells that cannot be classified as cancer. Chemotherapy involves directly injecting specific drug(s) into the blood stream. This is highly effective for cancers such as testicular and Hodgkin's lymphoma. [6] Chemotherapy is primarily used in conjunction with other treatments, as a part of a treatment plan.

Radiotherapy works by destroying the cancer cells as well as the healthy cells in a certain area by exposing the cancerous tumor to a radioactive material or source. Since the healthy cells are much better at repairing themselves as compared with the

cancerous cells, radiation can be a very effective treatment. Obviously, it is better to reduce the amount of radiation given to the healthy cells and increase the amount of radiation given to the cancer cells. Radiation is generally given as part of a treatment plan. Radio immunotherapy is a radiotherapy treatment and will be outlined later. [6]

Cancer Targeting Therapy

Radio immunotherapy

Radio immunotherapy (RIT) is one way to deliver a highly-targeted dose of radiation to the cancer cells while lowering the dosage to the surrounding healthy cells. One form of RIT uses engineered antibodies. These antibodies target a specific antigen that is abundant on the surface of tumor cells while not being found in high number on the surface of healthy cells. Generally, this antigen is found in excess of 100,000 sites per cell. The selection of the radionuclide is very important and is based on tumor mass, the overall pharmacokinetics of the RIT conjugate, the drug-tumor residence time, as well as other factors. Beta particles have a longer distance traveled than alpha particles which allows for a larger dispersion of radioactivity at the target site. This is an advantage for killing adjacent tumor cells or very large tumor masses. Alpha particles typically have a much shorter distance traveled and can have a much larger energy but based on their LET typically their cell killing effect is confined to a much smaller radius from the site of deposition. Due to the high LET, more energy is dispersed in a smaller range, of alpha particles, much less radioactive material is required to affect the same cell. When applying this in vivo the bio distribution should not have a large uptake in normal tissue and organs like the liver, spleen, and kidney. [24] This is shown in the graphs in the Appendix and explained in the Results section. [12]

The effects of radio immunotherapy fall under the classification of internal exposure. Before sufficient research into radioactive effects had been accomplished, many common everyday products contained unsafe amounts of radioactive isotopes.

As a historical example, paint containing radium was used in the manufacturing of some wristwatches. The factory workers had a habit of wetting the brushes with their lips. This led to large activities of radium being taken orally by these individuals. The internal radioactivity led 50 of 2,000 women at a certain plant to die of cancer due to these unsafe working conditions. [14] However, since that time, a plethora of researchers have taken it upon themselves to determine how to manipulate these dangerous radioactive isotopes to work for the benefit the health of a patient. These researchers were successful in their attempts, making radiation a strong defense of the patient from cancer. One of these beneficial ways to use radioactive material is through the use of radio immunotherapy.

Radio immunotherapy can be a very effective treatment plan. While it is very beneficial, researchers and doctors must keep the overall safety of the patient as the priority during the development and administration of these drugs. Even among differing parts of the body, the same amount of radiation can have different levels of effects. This is because the overall effect of radiation is dependent upon the amount of radiation absorbed by the respective tissue. For instance, due to the often-prolonged residence time and clearance of RIT agents through the renal system, the kidney often has a high absorption of dose so this can result in the kidney being the dose-limiting organ. The dose limiting organ means that the amount of radiation that this organ can absorb before possibly doing negative effects to the body is lower than the other organs in the body. This would not be prudent to allow the body to undergo exposure to radiation levels that would negatively affect the kidneys, even if it takes longer for the tumor to shrink. The main effect of radiation is the inhibition of mitosis by affecting the

DNA in the nucleus of cells. These effects are shown by observing unrepaired single and double DNA strand breaks in the nucleus. This is obviously beneficial when it comes to destroying tumors as a result of tumor targeted cell kill. Researchers have been looking into RIT because of its ability to take the radioactive isotope directly to the tumor, which limits the exposure of the healthy tissue to radiation. [12]

Perhaps the best way to judge the safety effects of the RIT bio distribution is to use the Tumor to Kidney Dose Ratio. This ratio will show how much more radiation the tumor is absorbing than the kidney. The kidney is chosen to compare to the tumor because the kidney is often the main dose-limiting organ. [5]

Radio immunotherapy of human tumors

Radio immunotherapy uses whole antibodies or antibody fragments conjugated to a radio metal to carry radioactivity as a targeted therapeutic agent. RIT agents are created in a lab and intravenously injected. Immediately after injection, the RIT agent is carried by the blood flow to the antigen-binding site on the tumor cells. Upon binding to the antigen binding site, the attached radioactive isotope then irradiates the tumor mass and the surrounding tissue. This process is frequently used for radiosensitive neoplasms including leukemia and lymphomas. RIT can be used for solid tumors; however, these tumors require five to ten times the amount of radiation for tumor growth ablation. Recent research into using this therapy for prostate cancer has shown promising results, specifically the research taking place in the labs of Memorial Sloan Kettering. [24] Other limiting factors that require more radiation be delivered to tumor

tissue to achieve the same therapeutic response are hypoxia and the ability to repair radiation induced damages. [24] The main goal of RIT is to safely deliver a high radiation dose to a tumor while not killing the surrounding healthy cells.

Features of the RIT approach

The RIT approach can be much more convenient for the patient when compared to external beam radiotherapy as it is applied as a single intravenous injection of radioactivity with the resulting dose delivered to the tumor, which is subsequently irradiated over time. Dependent on the radioisotope utilized, irradiation of the tumor can occur over a period of minutes to several days. In the case of ^{177}Lu which is the focus of this report, the radioactive half-life is 6.73 days. Following injection, the patient can typically be released and additional visits for treatment are often not necessary.

Another type of targeted radiotherapy, peptide receptor radionuclide therapy (PRRT) utilizes targeting of peptide receptors expressed on the surface of tumor cells. [24] Like RIT, PRRT targets cell surface expressed receptors on tumor cells. The perfect receptor or antigen is one that is found only on the tumor cells and not the surrounding healthy cells. Like RIT where the radioactive metal is being carried by the antibody to the antigen, in PRRT, the radioactive metal is carried to the cell surface receptor via a peptide. Once this journey is completed the radioactive isotope will be adjacent or inside the tumor. The radiation delivered from the therapeutic isotope will kill the tumor cells by damaging the DNA found in the nucleus beyond repair. The choice for the radioactive isotope is an important one as the different isotopes have

varying practical characteristics making them available to use against different tumors. [24]

RIT with prostate cancer

RIT and PRRT treatments are being shown to be viable options when confronting metastatic prostate cancer. [25] Prostate cancer is radio responsive and often appears as many small-volume sites of metastatic disease that contain high levels of antibodies Prostate cancer as has prostate specific membrane antigen (PSMA). Serum prostate specific antigen (PSA) monitoring, which can signal progression or recurrence of prostate cancer, can be used as a diagnostic indicator of disease status. [25] The radioisotope most commonly associated with Radioimmunology pertaining to prostate cancer involving is Lutetium-177 due to its many applicable physical properties.

Summary of Radiation

History

The study of radiation began with Wilhelm Rontgen detecting the x-ray in the 1890s. [15] In the next several years, other scientists discovered radioactivity and applications for this newfound notion. [15] Perhaps the most important application to humanity is the one pertaining to imaging and therapy of cancers.

Ionizing Radiation

Anything that can ionize atoms when it interacts with them is called ionizing radiation. Specifically, ionizing radiation is defined as a form of radiation that sends 4-25 eV of energy into an atom and cause a valence electron to escape. For gamma rays or electric magnetic radiation from a nucleus or annihilation, it is governed by the equation:

$$E = \frac{hc}{\lambda} \qquad \text{Eq. 1}$$

E is the Energy

h is Planck's constant

c is the Speed of light

λ is the wavelength

Common ionizing electromagnetic radiations are x-rays and gamma rays. X-rays and gamma radiation are similar in the regards that they are both electromagnetic radiation, the only difference is how they are created. Gamma radiation comes from

inside the nucleus, while x-rays come from energy transitions of orbital electrons. Fast electrons are another source of ionizing radiation. They can be positrons, which are positively charged electrons, or Beta particles, which are negative electrons. Another form of ionizing radiation is heavy charged particles. Many particles fall under the classification of heavy charged particles, but the main one is the alpha particle. The alpha particle is simply a helium nucleus. The final ionizing radiation discussed is the neutron. While neutrons are present in almost every nucleus, a nuclear reaction has to occur to cause one or more of these neutrons to be released. [15]

Radiation Physics

Radiation Dosimetry

This is the quantitative assessment of absorbed radiation dose per unit of mass of biological tissue. The mathematics outlined involve evaluating the kinetics, the distribution, and the residence time of a radiopharmaceutical in a biological system (in our case the mouse) and converting it to a general model of a human. The areas that hold the most importance to perform these calculations are the kidneys, liver, and tumors. While this paper performs, the general calculations needed to prove that the drug being tested, Lu-177-RM2, is safe and effective; calculations will have to be done for each individual patient. This is because mass is an aspect that has to be accounted for due to equation 1, and mass varies in every patient. [10]

A radiopharmaceutical is simply a radioactive drug. This is used for either diagnostic or therapeutic applications. The main application in regards to therapy is the treatment of tumors. Diagnostic applications revolve around imaging of the body. Since therapeutic and diagnostic applications differ, it follows that the radioactive elements required are different as well. For instance, a therapeutic radioactive isotope is ^{177}Lu due to its physical properties. A diagnostic radioactive isotope would be ^{99m}Tc since it has a lower energy and much shorter half-life. [26, 30]

Absorbed Dose

The absorbed dose is the best method of quantification of the biological radiation dose based on many books and papers for this method of irradiation. [28,18,20,25] The

absorbed dose most accurately predicts the radiation effects that will happen when biological tissue is exposed to energy that is delivered to matter by ionizing radiation. [28,18] This quantification is expressed by equation 2, below.

$$D = \frac{dE}{dm} \qquad \text{Eq.2}$$

dE is average energy delivered to matter by ionizing radiation

dM is the mass of matter imparted with energy

Linear Energy Transfer

Linear Energy Transfer (LET) deals with the microscopic spatial distribution of the events that deposit energy by ionizing radiation. The factors that determine LET are: mass, charge, and energy of the charged particles. The equation governing the prediction of LET is equation 3.

$$LET = \frac{dE}{dl} \qquad \text{Eq.3}$$

dE is energy lost by radiation during travel

dl is the distance traveled

Activity of Radiation

To calculate the amount of radiation present, or activity present, there must be many calculations done. The first step is to find the time-activity function. The time-activity function is found by plotting amount of radioactivity versus time. By performing an exponential or exponential decay fit to this data one can find a helpful expression of how activity changes over time. This fit will be in the form of equation 4.

$$A(t) = ae^{-\lambda t} \qquad \text{Eq.4}$$

a is initial amount of activity present

A(t) is amount of activity present after time (t)

λ is the decay constant

To find the amount of activity present in an area throughout the whole experiment, an integration must be performed. This integral is expressed as equation 5.

$$A = \int A\,(t) * dt \qquad \text{Eq.5}$$

A is total number of decays during time (t)

A(t) is amount of activity present after time (t)

These were calculated with the help of the program “KaleidaGragh” to assure accurate results as it can be used to verify the calculations. The main equation utilized in calculating dose is labeled as equation 6.

$$D = \frac{k\,\tilde{A}\sum_i n_i E_i \phi_i}{m} \qquad \text{Eq.6}$$

D is the absorbed dose in a target organ

$\tilde{A}$ is the accumulated activity

n is the number of radiations with energy E emitted per nuclear transition

E is the energy per radiation

ϕ is the fraction of radiation energy absorbed in the target

m is the mass of target region

k is the proportionality constant (unit conversion constant)

Mouse to Human Conversion:

An important part of analysis of the Lu-177-RM2 dose is extrapolation of animal data to human data. This was done by assuming that the percentage that went to each organ in the mouse is the same percentage of the dose that would travel to the organ in the human. [20]

MIRD Schema

The MIRD Schema is the most widely used method for internal dose calculations in medicine. [28] This calculation is used as generally once an organ is irradiated, it becomes a source irradiating all the organs around it. While this method is the most widely used, it is not necessary for these calculations due to the facts that the absorbed dose and the LET are not large enough for one organ to act as a source. This is due to the fact that the chosen radionuclide for this study is Lu-177. Lu-177 has a maximum energy of 500keV and a range of 2mm in tissue. Data backing this statement is shown in the appendix. [**28**] The dose to each organ can be accurately calculated in the manner outlined in this section by employing the commonly used dosimetry calculating program “OLINDA.”

The commonly used complexities in the MIRD Schema is not needed to calculate the data here. MIRD takes equation 6 and simplifies it to be as shown in equation 7.

$$D = \tilde{A} * S = A * \tau * S \qquad \text{Eq. 7}$$

τ = residence time

S is defined in equation 8

$$S = \frac{k \sum_i n_i E_i \phi_i}{m} \qquad \text{Eq. 8}$$

[28,18,20,25]

Lutetium-177

Lutetium- 177 is the isotope used in Lu-177-RM2. It is defined as a radio lanthanide. [27] Bard first researched Lu-177 for use with therapy in 1985. [16] He successfully used it to treat arthritis is rabbits. Since then it has been used for many different applications, including the one outlined in this paper. Lu-177 is known as a medium energy Beta emitter as it has a maximum energy of 0.5 MeV. However, it also emits low energy gammas with low abundance. [16]

Lu-177 has a half-life of 6.73 days and its main decay modes are shown in Table One. The half-life is still acceptable as the biological half-life is much shorter as after 2 days 90% of the injected radioactive material will be secreted from the body. While biological half-life is different in every organ, the appendix shows that this statement is true. Lu-177 emits low energy gammas at 208.4 and 112.9 KeV. [33] For Lu-177 the maximum range is 2 mm in tissue for beta particles. [10]

Table One: Major Beta Decay Modes of Lu-177

Max Energy (KeV)	Average Energy (KeV)	# per 100 Disintegrations
498	149	78.6
385	112	9.1
176	48	12.2

Biodistribution

Experimentation must be done in preclinical testing to determine the distribution of the drug in the body. The specifics of the biodistribution experiments performed to obtain the data used for this thesis have been outlined in the Methods section of this paper. The data obtained from these experiments must be analyzed by using dosimetry specifically for the radiosensitive areas the biodistribution for areas relevant for discussion is shown in Table Two. The "D" implies that this is the dose received in units of rem/mCi. The data is the mean value collected from four mice. The times given is time post injection.

Table Two: Bio-distribution of Relevant Areas (mean value of mice)

	Tumor #1		**Tumor #2**		**Kidneys**			
	PA	**NO PA**	**PA**	**NO PA**	**PA**	**NO PA**		
15 Minutes	1.61E-02	9.46E-03	1.38E-02	1.34E-02	2.76E-02	2.67E-02		
1 Hour	1.58E-02	9.52E-03	2.92E-02	6.86E-03	7.95E-03	7.75E-03		
4 Hours	1.54E-02	1.45E-02	1.09E-02	9.56E-03	4.78E-03	3.86E-03		
1 Day	1.77E-02	8.94E-03	1.70E-02	8.74E-03	2.21E-03	1.87E-03		
2 Days	9.07E-03	4.76E-03	7.59E-03	5.12E-03	9.43E-04	1.08E-03		
3 Days	6.31E-03	6.53E-03	1.13E-02	8.91E-03	7.71E-04	7.19E-04		
7 Days	7.23E-04	5.67E-04	4.98E-04	6.65E-04	1.06E-04	5.83E-05		
14 Days	1.21E-04	8.73E-05	1.22E-04	9.29E-05	2.69E-05	1.77E-05		

Phosphoramidon (PA)

In the most recent research pertaining to PRRT, Phosphoramidon (PA) is added to the Lu-177 drug in an effort to decrease the limitations in the tumor drug delivery by delivering more of the drug to the tumor as well as increase the transient retention at the tumor site. Phosphoramidon is a natural product isolated from cultures of *Steptomyces tanashiensis*. The purpose of Phosphoramidon is to be a potent competitive inhibitor of NEP. NEP is an enzyme (neutral endopeptidase) in the bloodstream that contributes to the degradation process of peptides. There are many characteristics that make PA a plausible candidate, such as: the fact that it is water-soluble, is potent, is commercial available, and has low costs. In recent papers, it has been shown that using PA with differing radio peptide chains has increased the effectiveness of treatments. [17,31] The experiments outlined within this Thesis focus on using PA to enhance drug delivery to the tumor thereby potentially improving total radiation dose delivered to the prostate tumor. [17]

Phosphoramidon is being employed in an attempt to improve drug efficiency. This is an evaluation of the radio peptide after being intravenously injected into the patient. The purpose of this NEP inhibitor is to keep the peptide chain intact as it moves through the body to the tumor. Many studies have noted an increase in tumor uptake of peptide based drugs when PA is co-injected [] In addition to its proven effectiveness in improving biodistribution it can be applied easily as it has a high level of water solubility. [31]

Currently FDA approved radiotherapy drugs

Currently the only FDA approved radiotherapy drugs for end stage prostate cancer are Quadramet and Xofigo. Quadramet is the commercial tradename name of Sm-153-EDTMP, and Xofigo is the commercial tradename for Ra-223-Chloride. Quadramet and Xofigo target a secondary process downstream of the primary tumor. This process is osteoblastic bone repair, which results from invasion of the metastatic prostate tumor cells into viable bone marrow. The difference between the targeting properties of Sm-153-EDTMP and Ra-223-Chloride compared to Lu-177 PRRT is that the Lu-177-PRRT is targeting the actual tumor cell expressed peptide receptor.

History of PRRT research at Truman VA

In 1999, research into the expression of the Bombesin receptor (BB2r) demonstrated that radiometallated peptides targeting this receptor could be synthesized and were shown to have a high specificity for targeting these receptors. Some of the earliest studies conducted involved using Technetium-99m-BB2r targeting peptides with a Single Photon Emission Tomography instrumentation to image the cancerous tumors. [8]

The Hoffman laboratory subsequently discovered that in addition to successfully demonstrating diagnostic imaging of receptor positive tumors one is able to actually treat the tumors by attaching therapeutic radioactive isotopes to the peptides in place of diagnostic radioisotopes. Originally, an in vitro model for determining the in vivo stability of lanthanide chelates was utilized to determine comparison of different radioactive

isotopes. By performing an in vivo comparison of several different radioisotopes (Sm-153 and Lu-177) that would label DO3A-amide-βAla-BBN(7-14)NH2 as well as other studies, the radioisotope Lu-177 was chosen based on many different properties. [19] [23] [21] [27] [4] [9]

The original choice of the receptor to target on prostate cancer tumors was Gastrin releasing peptide receptor because of substantial research being conducted at the time that showed its excessive expression in several tumors such as: prostate, breast, and small cell lung cancer. [23] Radiolabeled bombesin (BBN) conjugates which target the Gastrin Releasing Peptide receptor (GRPr) were developed which showed promising results. Specific bombesin, which is simply a fourteen amino acid chain, agonists were researched and patented by the University of Missouri. [23] The Hoffman laboratory and others demonstrated that specific GRPr targeting could be achieved and further studies conducted elsewhere demonstrated that the GRPr was found in approximately 80% of prostate cancer samples analyzed. [32] While the original work focused on evaluating BB2r or GRPr agonists, initial clinical trials revealed negative side effects in patients including diarrhea and nausea when Lu-177 BB2r agonists were administered in Phase 1 prostate cancer therapy trials. [Lim et al.] Future developments involved the synthesis and evaluation of BB2r antagonists, which to date appear to be devoid of the side effects seen with BB2r agonists. [5] The BB2r antagonist peptide sequence that is radiolabeled with Lu-177 in the current study is DOTA-4-amino-1-carboxymethyl-piperidine-D-Phe-Gln-Trp-Ala-Val-Gly-His-Sta-Leu-NH2 (RM2) which was developed by Maecke and co-workers. In simpler terms, this drug formulation consists of a DOTA chelator that is labeled with Lu-177 and conjugated

or linked to the bombesin antagonist peptide for targeting GRPr expressing tumors. This compound showed improved in vivo pharmacokinetics and data from the Hoffman laboratory and others has demonstrated that the Lu-177 BB2r antagonist is superior to Lu-177 BB2r agonist in preclinical therapy assessment. [7] Another advantage to Lu-177 BB2r antagonist therapy is the ability to obtain accurate SPECT imaging of therapeutic agent localization at delayed times post injection. [2]

Initial preclinical data indicates that Lu-177-BB2r therapy can be used to extend mean survival time of preclinical xenograft mouse models of prostate cancer. [1]

These last sixteen years of beneficial research have led to the experiment that is outlined in this paper. Currently the main concerns with the treatment option being researched are limitations in both the tumor drug delivery as well as the transient retention at the tumor site. De Jong and co-workers recently demonstrated that a NEP inhibitor called Phosphoramidon (PA) could be added to keep the peptide chain intact longer inside the human body, which could possibly alleviate the concerns previously outlined. [31] This research is unique as we will explore the potential of NEP inhibition to improve tumor uptake and residence time thereby improving total delivered radiation dose to the tumor.

Thesis Goals

As with every cancer research project the objective is to get one step closer to eliminating the cancer in a cost-effective manner. This current project is to establish if employment of the NEP inhibitor known as Phosphoramidon will be beneficial to improving the utility of the Lu-177-BB2r therapy drug. These beneficial effects would be to decrease the limitations in the delivery of the Lu-177 drug known as Lu-177-RM2 while increasing the transient retention at the tumor site. To determine if our hypothesis is correct, the dosimetry of the same Lu-177 BB2r targeting drug with Phosphoramidon and without Phosphoramidon must be performed. The results of the dosimetry have to be compared especially in the kidneys as this is proven by studies to be the limiting area. [5] Simultaneously with this comparison, the dosimetry in the tumors must be compared. Ideally, there will be a higher tumor to kidney ratio and a lower liver uptake will be present in the Lu-177 BB2r targeting drug containing Phosphoramidon.

Preclinical Testing

The Hoffman research group have been evaluating Lu-177 receptor targeted therapies for treatments of both prostate and breast cancers using common biological, chemical, and nuclear techniques. In an effort to provide the best treatment for the aforementioned cancers, the use of Phosphoramidon was evaluated. A biodistribition study was undertaken with the results shown in the appendices. From initial observation of these results it is shown that Phosphoramidon has improved the biodistribution when compared to the biodistribution of the drug when PA is not added.

However, dosimetry analysis is necessary to determine the true differences when PA is added to Lu-177-RM2.

Materials and Methods

Radioisotope production

Lu-177 is a particle-emitting radioisotope. It was chosen for this particular application after many experiments were performed to analyze its multiple physical properties for optimal treatment. These practical properties are listed in table one and outlined previously in this paper. It is created in the reaction ^{176}Lu (n,γ) ^{177}Lu.

Lu-177 Biodistribution Data

In an attempt to fully understand the effects of Phosphoramidon when used in conjunction with the Lu-177-BB2r targeting drug, a biodistribution study was done and the data was provided for analyses. This study as well as all others undertaken in this laboratory were conducted under the approval of the Institutional Animal Care and Use Committee. For this study, 65 severe combined immunodeficiency (SCID) mice were inoculated bilaterally in each flank with human cancer PC3 cells. These mice were left untreated for four weeks to let the tumors grow to be between 0.1mm to 8mm diameter. After this, the group of mice was randomized. These randomized mice were split into two groups. The first group was intravenously injected in the tail with the Lu-177 BB2r targeting drug containing Phosphoramidon. The second group was similarly injected with the Lu-177 BB2r targeting drug not containing Phosphoramidon. Mice were then sacrificed at time intervals: 15 minutes, 1 hour, 4 hours, 24 hours, 2 days, 3 days, 7 days and 14 days post intravenous injection of Lu-177-BB2r targeting drug. After sacrifice, the organs were harvested. During this harvest the organs were weighed, and the activity (cps) was measured using a NaI(Tl) counter. The particular parts of the

mouse that were harvested were: bladder wall, heart, lung, liver, kidneys, spleen, stomach, small intestine, large intestine, muscle, bone, brain, pancreas, left flank tumor, right flank tumor, and carcass. The data was analyzed and the percent of the original dose absorbed in each of these aforementioned areas was determined. The data was represented in the units of %D. The units of %D is known as percent of the total dose. It is convenient to measure in these units as it is easy to measure the amount of radioactivity present in each area post necropsy. This was converted to the commonly used activity unit microcurie (uCi). By plotting activity (uCi) as a function of time (hours) and by integrating under the found curve, the residence time was calculated. These residence times were then implemented into the dosimetry calculating program "OLINDA." This program uses the formulas outlined and gives results in terms of rem/mci.

Phosphoramidon Effects

The key of this study is to understand the difference between the subjects that were intravenously injected with Lu-177-RM2 containing Phosphoramidon and the subjects that intravenously injected only with Lu-177-RM2. To accomplish this, each area studied must be discussed. The main thing to observe is whether the application of Phosphoramidon in the drug increases or decreases the dosages to the tumor and other organs. Other effects that require observation are if the PA drug is decreasing the limitations in the delivery of the Lu-177 drug while increasing the transient retention at the tumor site. Ideally, there will be a higher tumor to kidney ratio and a lower liver uptake will be present in the Lu-177 drug containing Phosphoramidon

Table three is a summary of the doses in units of rem/mCi of the human dose which was calculated in the manner outlined previously.

Table Three: Radiation Absorbed (rem/mCi)

Human	**PA**	**NO PA**	**PA/NoPA**
	rem/mci	**rem/mci**	
Brain	0.017	0.018	1.0
Small Intestine	0.42	0.42	1.0
Stomach	0.41	0.41	1.0
Heart	0.40	0.40	1.0
Kidneys	0.26	0.23	1.1
Liver	0.038	0.036	1.1
Lungs	0.034	0.032	1.1
Muscle	0.032	0.031	1.0
Pancreas	0.79	0.88	0.9
Bone	0.2	0.2	1.0
Spleen	0.046	0.053	0.9
Large Intestine	0.84	0.84	1.0
Bladder	1.36	0.65	2.1
Tumors	55.6	40.6	1.4

In the discussion section, every calculated dose will be compared to the relevant limiting dose. The limiting dose is the highest dose that one can receive before possibly contracting a disease due to over irradiation. [12,23,29] Table 3 gives the dose in rem per micro curies at each time period for each discussed area. The third column (PA/NoPA) shows the relationship of the dose with and without PA. The graph for the dose for both PA and Non PA drugs can be found in the appendix

Spleen:

Table Four: Spleen Biodistribution

Spleen	**PA**	**NO PA**
Time	**D (uCi)**	**D (uCi)**
15 Minutes	5.99E-04	7.99E-04
1 Hour	1.99E-04	9.94E-05
4 Hours	4.16E-05	6.87E-05
1 Day	8.57E-05	5.15E-05
2 Days	4.58E-05	5.54E-05
3 Days	1.58E-05	7.00E-05
7 Days	1.26E-05	2.01E-05
14 Days	1.56E-05	1.46E-05
Dose (mRem/mCi)	0.046	0.053

Spleen: Phosphormidon improved the drug performance in the spleen as the dose delivered to the spleen decreases to 87% of the dose delivered when no PA is added to the drug change when PA is added to the drug based on the results expressed in Table 4.

Heart:

Table Five: Heart Biodistribution

Heart	PA	NO PA
Time	D (uCi)	D (uCi)
15 Minutes	8.99E-04	1.10E-03
1 Hour	0.00E+00	1.99E-04
4 Hours	1.31E-04	4.71E-05
1 Day	6.38E-05	4.12E-05
2 Days	2.04E-05	6.40E-05
3 Days	8.19E-06	4.35E-05
7 Days	1.13E-05	5.93E-06
14 Days	1.45E-05	8.88E-06
Dose (mRem/uCi)	0.40	0.40

Heart: With the help of Phosphormidon, the amount of radiation in the heart dissipates more quickly as shown in the biodistribution data. However, the heart will receive approximately the same amount of dose regardless of whether Phosphormidon was used.

Lungs:

Table Six: Lung Biodistribution

Lung	PA	NO PA
Time	D (uCi)	D (uCi)
15 Minutes	3.49E-03	4.09E-03
1 Hour	6.96E-04	5.96E-04
4 Hours	2.12E-04	8.61E-05
1 Day	1.08E-04	8.59E-05
2 Days	1.07E-04	4.43E-05
3 Days	6.13E-06	3.08E-05
7 Days	4.41E-05	7.46E-06
14 Days	1.13E-05	1.16E-05
Dose (mRem/uCi)	0.034	0.032

Lungs: The most common toxicities in the lungs due to irradiation is symptomatic radiation pneumonitis. The maximum dosages were published by a group that researched by reviewing over seventy different published articles and found that there is a 20 percent chance of a patient developing symptomatic radiation pneumonitis with a dose of 2000 rem.

This is an area where Phosphormidon did not help. While less radiation originally went to the lungs, more stayed over time. With the use of PA, the lungs absorbed % percent more radiation. While this is not optimal, it is not truly concerning as the lungs are not a “limiting” organ and the 7% difference is very slight.

Liver:

Table Seven: Liver Biodistribution

Liver	PA	NO PA
Time	D (uCi)	D (uCi)
15 Minutes	1.59E-02	1.79E-02
1 Hour	3.58E-03	2.78E-03
4 Hours	1.16E-03	7.10E-04
1 Day	7.98E-04	4.77E-04
2 Days	3.82E-04	4.49E-04
3 Days	3.65E-04	2.81E-04
7 Days	6.90E-05	9.27E-05
14 Days	1.37E-05	3.11E-05
Dose (mRem/uCi)	0.038	0.036

Liver: Radiation-induced liver disease is the sensibly named disease as it can occur when the liver absorbs radiation in excess of the threshold value. In order for there to be, a five percent chance of this occurring the patient's liver must receive a dose of 3000 rem of radiation. The amount of radiation to the liver is shown in the table.

Phosphoramidon did not improve the dosimetry of the liver. Again, less radiation initially irradiated the liver, but more stayed over time. An extra 6% of the dose present in the original drug was absorbed when PA was employed.

Kidneys:

Table Eight: Kidney Biodistribution

Kidneys	PA	NO PA
Time	D (uCi)	D (uCi)
15 Minutes	2.76E-02	2.67E-02
1 Hour	7.95E-03	7.75E-03
4 Hours	4.78E-03	3.86E-03
1 Day	2.21E-03	1.87E-03
2 Days	9.43E-04	1.08E-03
3 Days	7.71E-04	7.19E-04
7 Days	1.06E-04	5.83E-05
14 Days	2.69E-05	1.77E-05
Dose (mRem/uCi)	0.26	0.23

Kidneys: Renal dysfunction is the main concern when irradiation of the kidneys occurs. Again, it is estimated by Quantec that the limiting dosage should be 1500 rem to make sure there is not even a five percent chance over the next five years that renal dysfunction occurs. Again, the calculated dose is much lower than this limiting dosage as it is shown.

Phosphoramidon increased the amount absorbed by the kidneys by 13%. This is considered by many to be the limiting organ as it only requires 18 Gy of absorbed radiation to potentially cause renal dysfunction. Further comparison of extra amount absorbed here when PA was employed in the kidneys to the amount absorbed in the tumors will have to be performed to gain perspective.

Stomach:

Table Nine: Stomach Biodistribtion

Stomach	PA	NO PA
Time	D (uCi)	D (uCi)
15 Minutes	8.79E-03	9.78E-03
1 Hour	4.77E-03	3.78E-03
4 Hours	1.56E-03	8.37E-04
1 Day	2.72E-04	1.87E-04
2 Days	1.17E-04	2.77E-05
3 Days	2.25E-05	3.59E-05
7 Days	2.06E-05	2.24E-05
14 Days	1.94E-06	3.47E-06
Dose (mRem/uCi)	0.41	0.41

Stomach: The main toxicities related to irradiation of the stomach are dyspepsia and ulceration. The limiting amount of radiation for making sure that there is only a two to six percent chance of this occurring over the next five years is 5000 rem. [34]

Phosphoramidon had a negligible effect on the dose delivered to the stomach. . This dose value falls far beneath the threshold values for damage of the stomach, which means the stomach is not a limiting organ.

Small Intestines:

Table Ten: Small Intestine Biodistribution

S. Intestine	PA	NO PA
Time	D (uCi)	D (uCi)
15 Minutes	7.75E-02	8.22E-02
1 Hour	3.14E-02	2.68E-02
4 Hours	7.10E-03	3.60E-03
1 Day	9.03E-04	6.06E-04
2 Days	2.79E-04	2.74E-04
3 Days	1.26E-04	2.32E-04
7 Days	2.21E-05	2.60E-05
14 Days	0.00E+00	1.08E-05
Dose (mRem/uCi)	0.42	0.42

Small Intestines: Again the addition of PA to the drug had a negligible effect on the dose delivered the small intestines. The biodistribition data also shows that the use of PA allows for a faster clearing of the drug from the body.

Large Intestines:

Table Eleven: Large Intestine Biodistribution

L. Intestine	PA	NO PA
Time	D (uCi)	D (uCi)
15 Minutes	2.93E-02	3.30E-02
1 Hour	7.55E-03	4.87E-03
4 Hours	6.11E-03	4.87E-03
1 Day	2.19E-03	1.33E-03
2 Days	5.44E-04	8.25E-04
3 Days	1.97E-04	2.46E-04
7 Days	1.87E-05	3.06E-05
14 Days	2.26E-05	2.15E-05
Dose (mRem/uCi)	0.84	0.84

Large Intestines: This an area where Phosphoramidon did help. With the use of PA the large intestine absorbed 14.3% percent less radiation. The biodistribution data shows that the use of PA does not clear the drug any faster.

Muscle:

Table Twelve: Muscle Biodistribution

Muscle	**PA**	**NO PA**
Time	**D (uCi)**	**D (uCi)**
15 Minutes	6.99E-04	1.40E-03
1 Hour	1.99E-04	9.94E-05
4 Hours	4.09E-05	3.47E-05
1 Day	4.48E-05	5.50E-05
2 Days	4.91E-05	8.60E-05
3 Days	2.66E-05	6.44E-05
7 Days	1.98E-05	3.37E-05
14 Days	2.06E-05	2.38E-05
Dose (mRem/uCi)	0.032	0.031

Muscle: The application of Phosphoramidon had virtually no effect on the irradiation and biodistribution of the muscle.

Pancreas:

Table Thirteen: Pancreas Biodistribution

Pancreas	**PA**	**NO PA**
Time	**D (uCi)**	**D (uCi)**
15 Minutes	1.39E-01	1.40E-01
1 Hour	4.47E-02	3.00E-02
4 Hours	3.53E-03	6.54E-03
1 Day	9.29E-04	6.24E-04
2 Days	3.16E-04	2.96E-04
3 Days	2.75E-04	1.10E-04
7 Days	1.58E-05	2.80E-04
14 Days	6.48E-07	5.63E-06
Dose (mRem/uCi)	0.79	0.88

Pancreas: Phosphoramidon had a positive effect on the irradiation of the pancreas. The dose to the pancreas was 10% less when PA was employed. This is an important discovery as the pancreas could possibly be a limiting organ as it is shown that it receives a much higher dose than many other organs. The fact that the addition of PA to the original drug decreases the dose to this area implies that an even higher

amount of the PA infused drug could be administered to the patients that are shown to have the pancreas as the limiting organ.

Bone:

Table Fourteen: Bone Biodistribution

Bone	**PA**	**NO PA**
Time	**D (uCi)**	**D (uCi)**
15 Minutes	5.99E-04	5.99E-04
1 Hour	9.94E-05	1.99E-04
4 Hours	3.82E-05	0.00E+00
1 Day	1.01E-04	1.05E-04
2 Days	6.49E-05	2.99E-05
3 Days	3.28E-05	2.95E-05
7 Days	2.93E-05	1.79E-05
14 Days	1.30E-06	6.88E-06
Dose (mRem/uCi)	0.23	0.23

Bone: There are many risks associated with radiation to the bone, specifically the spinal cord. In order for a five percent chance of these risks occurring in the next five years the bone must be irradiated by 59300 rem.

Phosphoramidon had no true effect on the irradiation of the bone. Roughly, the same amount was absorbed by both treatments.

Brain:

Table Fifteen: Brain Biodistribution

Brain	PA	NO PA
Time	D (uCi)	D (uCi)
15 Minutes	5.99E-04	2.00E-04
1 Hour	0.00E+00	9.94E-05
4 Hours	4.69E-05	2.13E-05
1 Day	0.00E+00	7.33E-05
2 Days	5.47E-05	4.00E-05
3 Days	2.25E-05	1.17E-05
7 Days	0.00E+00	2.11E-05
14 Days	0.00E+00	2.42E-06
Dose (mRem/uCi)	0.017	0.018

Brain: The main danger associated with radiation dosage of the brain is necrosis. However, even for a five percent chance for this to happen in the next five years the patient's brain has to absorb 7200 rem. The absorbed dose for the brain is shown on Table 3. These numbers show that there is no risk of any negative effect on the brain resulting from the radiation present in this therapy unless many mCi of radiation are used.

With the help of Phosphoramidon the amount of radiation in the brain dissipates more quickly. Thus, the brain only receives, 96% of the radiation that would it would otherwise encounter.

Tumor One:

Table Sixteen: Tumor One Biodistribution

Tumor #1	PA	NO PA
Time	D (uCi)	D (uCi)
15 Minutes	1.61E-02	9.46E-03
1 Hour	1.58E-02	9.52E-03
4 Hours	1.54E-02	1.45E-02
1 Day	1.77E-02	8.94E-03
2 Days	9.07E-03	4.76E-03
3 Days	6.31E-03	6.53E-03
7 Days	7.23E-04	5.67E-04
14 Days	1.21E-04	8.73E-05

Tumor Two:

Table Seventeen: Tumor Two Biodistribution

Tumor #2	PA	NO PA
Time	D (uCi)	D (uCi)
15 Minutes	1.38E-02	1.34E-02
1 Hour	2.92E-02	6.86E-03
4 Hours	1.09E-02	9.56E-03
1 Day	1.70E-02	8.74E-03
2 Days	7.59E-03	5.12E-03
3 Days	1.13E-02	8.91E-03
7 Days	4.98E-04	6.65E-04
14 Days	1.22E-04	9.29E-05
Dose (mRem/uCi)	55.6	40.6

Tumors:

Phosphoramidon truly helped in the irradiation of tumors, an extra 40% was absorbed by the tumor. It is apparent when shown the biodistribution of the tumor why PRRT is being researched as a potential therapy for prostate cancer. The fact that the PA helps keep the peptide chain intact explains the higher percentages later.

Comparison with other published papers:

In this section, the hope is to clarify and explain the perceived discrepancies between reported dosages in this paper and results of published papers. It will be shown that the calculated dose, based on an average human male (70kg) and delivered to the tumor, as well as relevant organs, are similar to the previously published work for Lu-177-RM2 and within an acceptable range of Lu-177 somatostatin agents currently being used in humans.

In addition to this discussion, the urinary bladder dose calculations in Table 1 was included as well as describe the software applications used for dose calculation.

Table Eighteen: Calculated Dosages for Human (Male 70 kg)

Human	PA	NO PA	
	mGy/MBq	mGy/MBq	PA/NoPA
Brain	4.5E-03	4.7E-03	9.6E-01
Small Intestine	1.1E-01	1.1E-01	1.0E+00
Stomach	1.1E-01	1.1E-01	1.0E+00
Heart	1.1E-01	1.1E-01	1.0E+00
Kidneys	7.0E-02	6.3E-02	1.1E+00
Liver	1.0E-02	9.8E-03	1.1E+00
Lungs	9.2E-03	8.6E-03	1.1E+00
Muscle	8.6E-03	8.4E-03	1.0E+00
Pancreas	2.1E-01	2.4E-01	9.0E-01
Bone	1.5E-02	1.5E-02	1.0E+00
Spleen	1.3E-02	1.4E-02	8.7E-01
Large Intestine	2.3E-01	2.3E-01	1.0E+00
Urinary Bladder	3.8E-01	1.9E-01	2.1E+00
Tumors	3.0E+01	2.2E+01	1.4E+00

Ms. Wexler's Master's Thesis

In an effort to show that the results shown in Table 18 are correctly calculated, these values must first be compared with the values expressed in Ms. Amelia Wexler's Master's Thesis. In this published work, Ms. Wexler stresses doses to the tumor, kidneys, bladder, and pancreas. These doses were given in units [mGy/mCi]. Conversion to Table 18 units of [mGy/MBq] was performed for ease of comparison. This was performed by multiplying [1mCi/37MBq]. These values are expressed in Table Nineteen.

Table Nineteen: Ms. Wexler's Results [1]

Wexler	**mGy/MBq**
Av.Tumor	340
Kidneys	120
Bladder	150
Pancreas	140

At first glance it may appear that the calculated dose in Table 18 is not close to the values shown in Table Two. However, upon closer reading of Ms. Wexler's Thesis it becomes apparent that her doses were calculated for the mouse as she states "calculated assuming a 20 g mouse with a 200mg tumor." This differs greatly from the calculation method employed in the thesis defended last week, as the method used for Table One assumes a 70kg human with a 10g tumor. (If my assumption for size of tumor in a human is incorrect please let me know as it is very easy to change, I based it on the fact that the human prostate is 20-25 g and that the tumor would take up roughly half of the prostate) As shown by equation 1, the mass of the target is significant in establishing dose. Since the assumed weight of the target, in this example case the tumor, varies greatly in each thesis, it stands to reason that the reported dose would vary greatly as well.

$$D = \frac{dE}{dm} \qquad \text{Eq.1}$$

dE is average energy delivered to matter by ionizing radiation

dM is the mass of matter imparted with energy

Since it has now been established that Table 18 is the dose of Lu-177-RM2 to a human and Table Two is the dose of a very similar drug to a mouse, a simple conversion can be applied to Table One to show that the difference of mass is the driving factor behind the

differences in reported dose. By multiplying the “NO PA” result of Table One by the conversion factor [10/ (0.2*2)] based on the aforementioned assumed differing masses of the tumor, 10g and 0.2g, as well as the fact that Ms. Wexler took the average of both tumors, the Table One dose became 550 mGy/Mbq. By comparing 550 mGy/Mbq to 340 mGy/MBq it is apparent that these doses are similar in order of magnitude. The slight difference can be explained as Ms. Wexler’s data was done using manual synthesis, which is the previous method of compound formulation. The new method used in procuring the data entrusted to me was an Eckert & Ziegler automated radiochemistry synthesis system.

Dumont et al., J. Nucl. Med 54:762-769, 2013

The paper *Targeted Radiotherapy of Prostate Cancer with a Gastrin-Releasing Peptide Receptor Antagonist Is Effective as Monotherapy and in Combination with Rapamycin* published an estimated dose to the tumor. This dose is essential to compare to Table 18’s estimated dose as it also employs Lu-177-RM2. The published dose to the prostate tumor is 840 mGy/MBq. [2] Again, this dose is specified as pertaining to a mouse. It has been established that a conversion from the human dose reported in Table One to the mouse dose mentioned in the paper by Dumont is essential to correctly judge the results shown in Table One. This time the dose pertaining to the drug containing Phosphoramidon will be converted from human dose to mouse dose. Understanding the method employed by Dumont and co-workers is important in conversion. Since this was not reported in terms of average dose there is no need to account for that as there was in Ms. Wexler’s Thesis. However, since there is no reported weight in grams, an assumption must be made. Since Ms. Wexler assumed 200mg, this will serve as a practical assumption for this calculation. This time the conversion factor will be [10/0.2]. The converted dose from Table One is 1500 mGy/Mbq. This is similar enough to the 840 mGy/MBq reported in the paper by Dumont as the weight of the tumor is not specified. Again, the results from Table One are proven correct by comparison with published literature.

Lantry et al, J Nucl Med 47:1144-1152, 2006

The paper *^{177}Lu-AMBA: Synthesis and Characterization of a Selective ^{177}Lu-Labeled GRP-R Agonist for Systemic Radiotherapy of Prostate Cancer* also published an estimated dose to tumor. Since this paper is 10 years old, it is expected that the result from Table One will be much improved. The published estimated dose to a mouse is 500mGy/MBq. [3] Similarly to the paper by Dumont, there is no specified mass so the same assumptions will have to be made. This means that the estimated mouse dose found by conversion of the human dose found in Table One will apply here as well. The 1500 mGy/Mbq estimated dose is obviously much larger than the 500mGy/MBq dose published in the paper by Lantry. However, this can be explained by the fact that a decade of research has taken place since it was published, as well as the fact that no mass for the tumor was reported in this published work.

Dalm et al; J Nucl Med 57:260-265, 2016

Dalm wrote the paper *Comparison of the therapeutic response to treatment with a 177-lutetium labeled somatostatin receptor agonist and antagonist in preclinical models*. In this paper a published mouse tumor dose of 1800 mGy/MBq was reported. Again there is no data about the size of this tumor, but the converted Table 18 value of 1500 mGy/MBq again favorably compares with published values.

Wild et al; J Nucl Med 55:1248-1252, 2014

In an effort to compare the calculated human doses expressed in Table One with other published human doses the paper *Comparison of Somatostatin Receptor Agonist and Antagonist*

for Peptide Receptor Radionuclide Therapy: A Pilot Study was utilized. In Table Three of this paper on page 1251, there are published doses. The doses calculated for the antagonist are relevant to the study being performed in this thesis. These doses match Table One of this document within the error specified in these 5 areas: brain, small intestine, heart, large intestine, and urinary bladder. The drug outlined in the paper by Wild pertains to research in treatment of neuroendocrine tumors. Since the drug isn't the same as the one outlined in this thesis and has a different target, it is logical that it will not accumulate in every area similarly to the drug Lu-177-RM2. However, the fact that these doses match up so well in five areas shows that Table One is accurate.

Limiting Dose:

In many publications, the limiting organ is the kidney since the limiting dose to the kidneys is 15 Gy based on ICRP Publication 118. However, since there is a higher accumulation in the pancreas as well as urinary bladder in this particular study as shown on Table One, they also deserve consideration as the limiting dose is 40 Gy and 65 Gy respectively based on ICRP Publication 118. Determining the true limiting organ will have to be performed on a case by case basis.

Software Applications used in this study:

KaleidaGraph *4.1*

KaleidaGraph 4.1 was created by Synergy Software and the copy write is June 19, 2009. KaleidaGraph is a thoughtfully designed graphing and data analysis application for research scientists, as well as for those in business and engineering fields. It produces publication-quality graphs, and easily converts the most complex data into a functional display. KaleidaGraph allows the user to import, manipulate, and analyze data, as well as create customized plots. Statistics, linear and nonlinear curve fitting, and the ability to produce precise graphic visualization of data all make KaleidaGraph powerful and flexible (www.synergy.com)

OLINDA/EXM 1.0

OLINDA/EXM stands for Organ Level Internal Dose Assessment code / Exponential Modeling. It was developed in 2004 by Dr. Mike Stabin Ph.D, CHP. This software program was utilized by many papers cited in the bibliography, including the paper by Wild et al. The FDA recognizes this program, and they typically do not review the dose calculations if one can show their study employed this program. This can speed along the review process.

Summary:

This has clarified and explained the differences between the calculated dosages and results of published papers. The calculated dosages were converted appropriately and based on an average human male (70kg) while other papers only considered the dosage model for the laboratory animal in this case a mouse. The rationale for converting for a human model was to be able to better understand if dosages were considered safe by current safety regulations that are stated in ICRP. These calculated dosages delivered to the tumor, as well as relevant organs, are similar to the previously published work for Lu-177-RM2 and within an acceptable range of Lu-177 somatostatin agents currently being used in humans.

Conclusion

The key point that needs to be addressed for a complete dosimetry analysis is the Tumor to Kidney Dose ratio. The pancreas is mentioned as a possible limiting organ, but since the addition of Phosphoramidon to the drug decreases the dose to the organ and increases the dose to the tumors it is not relevant to study the pancreas in this particular study as it is a comparison of two drugs. Obviously since the addition of the PA benefits both aspects a ratio need not be reported. A very important tool in analysis of the dosimetry of the biodstribution is this ratio. This ratio shows how much more radiation the tumor will absorb than the main relevant limiting organ which is the kidney. The Tumor to Kidney Dose Ratio is 214.1 with PA and 177.9 without PA. That means that there is a safe dose to the tumor for a limiting dose to the kidney with the use of PA. This shows that for both possible limiting organs, kidneys and pancreas, that the administration of Phosphoramidon helps in the delivery of the drug.

One possible way to learn about the in vivo stability of the drug is to look at the dosimetry of the liver. The liver having a higher uptake of radiation when using PA could possibly be concerning regarding the in vivo stability; however, if one was to look at the total amount of radiation in both the PA and non-PA study they would realize that they were both very low values. The percentage increase in uptake in the liver must be on the order of hundreds higher than found to truly thebe suggestive of in vivo stability. [5]

The data shows that the use of Phosphoramidon as a NEP inhibitor in Lu-177-RM2 is beneficial. PA successfully decreased the limitations in the delivery of the Lu-177 BB2r targeted drug as shown by the Tumor to Kidney Dose Ratio. The addition of PA also increased the transient retention in the tumors at times up to one week as shown in the Biodistribution data. The negative findings related to the increased absorption in certain areas are not as important as the aforementioned beneficial outcomes. The increased dosage to the areas that were stated in the results section still fall under the published safety maximum treatment doses. It would be prudent to include Phosphormidon in all Lu-177 BB2r Antagonist peptides as research continues.

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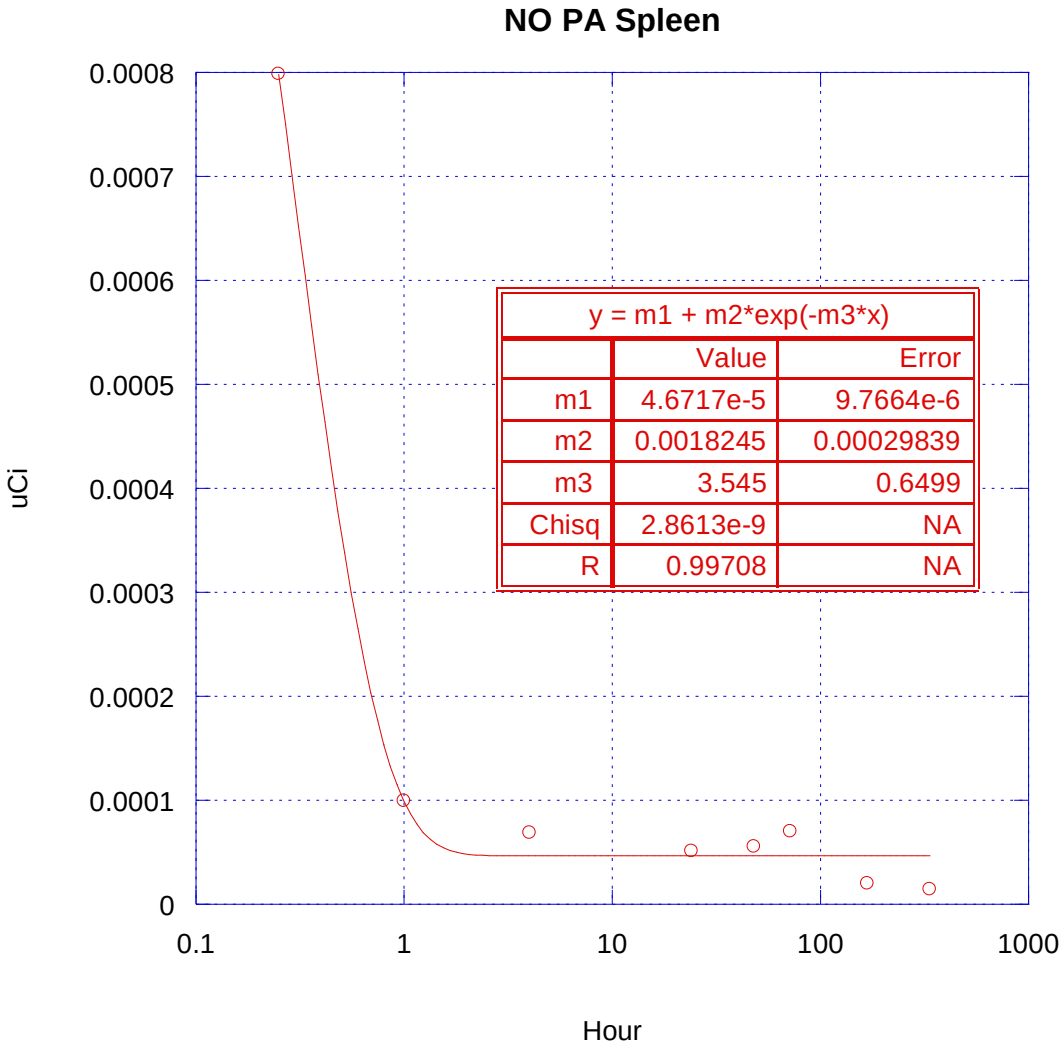
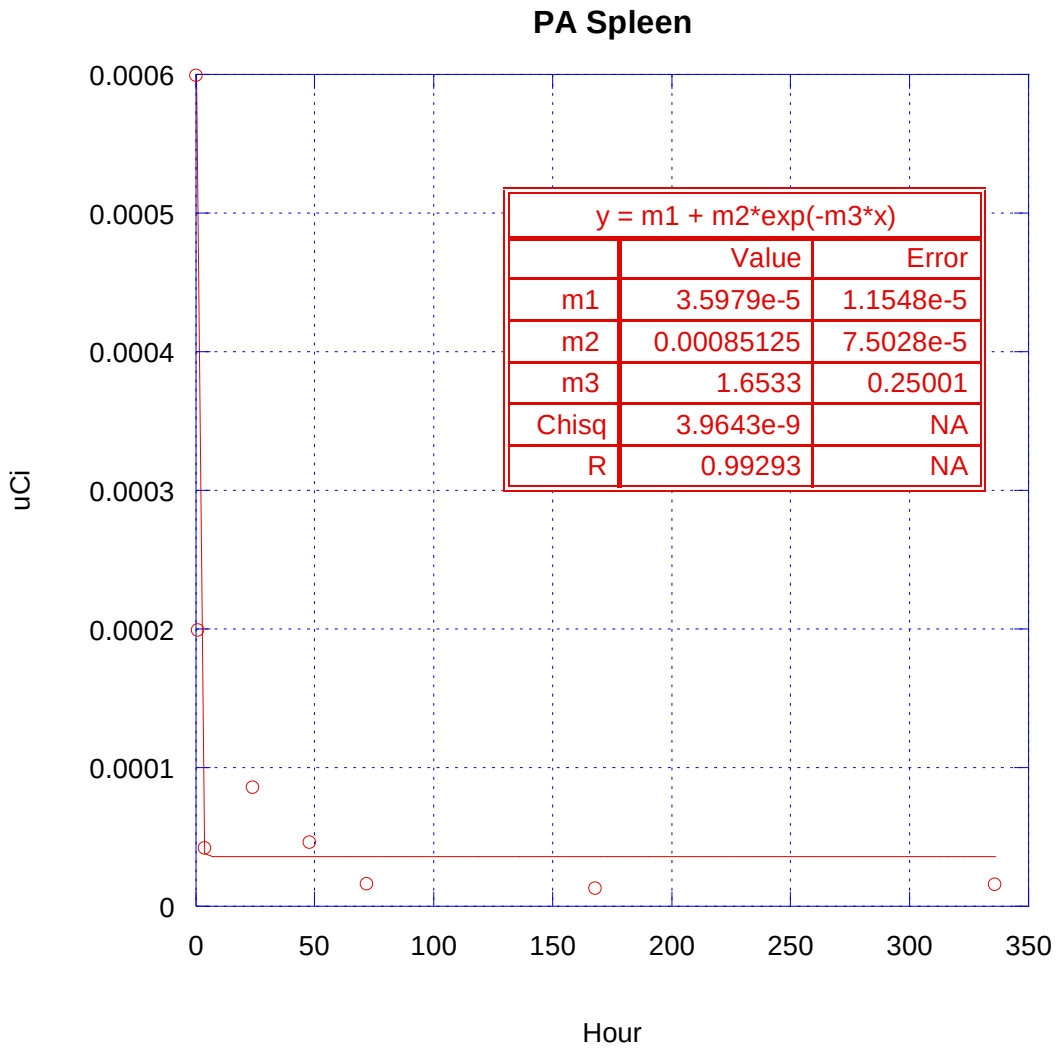
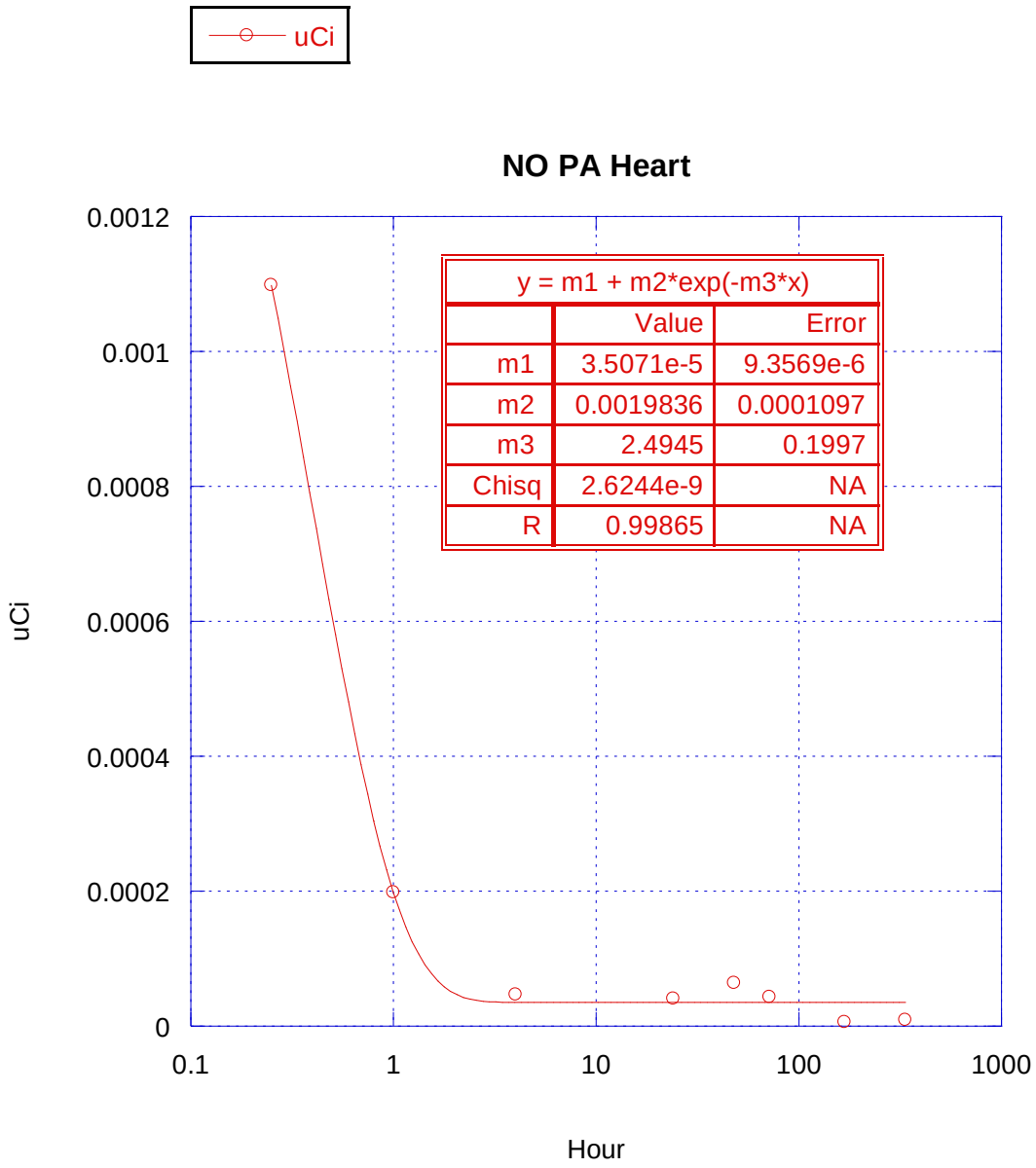
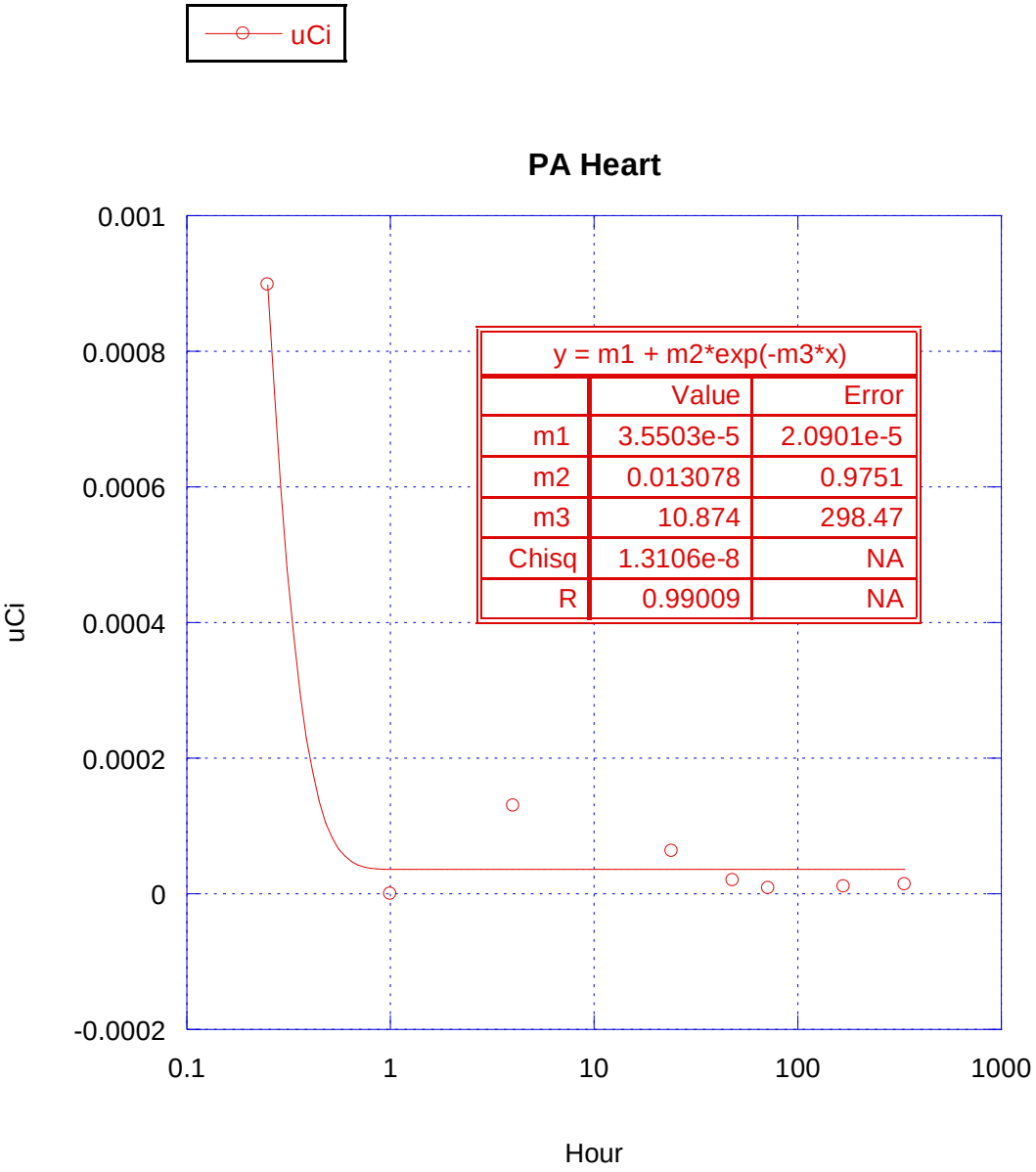
Appendix


NO PA Spleen
0.0008
0.0007
0.0006
0.0005
0.0004
0.0003
0.0002
0.0001
0
uCi
0.1
1
10
100
1000
Hour
y = m1 + m2*exp(-m3*x)
Value
Error
m1
4.6717e-5
9.7664e-6
m2
0.0018245
0.00029839
m3
3.545
0.6499
Chisq
2.8613e-9
NA
R
0.99708
NA


PA Spleen
y = m1 + m2*exp(-m3*x)
Value Error
m1 3.5979e-5 1.1548e-5
m2 0.00085125 7.5028e-5
m3 1.6533 0.25001
Chisq 3.9643e-9 NA
R 0.99293 NA
uCi
Hour
0.0006
0.0005
0.0004
0.0003
0.0002
0.0001
0
0 50 100 150 200 250 300 350


uCi
NO PA Heart
0.0012
0.001
0.0008
0.0006
0.0004
0.0002
0
uCi
0.1
1
10
100
1000
Hour
y = m1 + m2*exp(-m3*x)
Value
Error
m1
3.5071e-5
9.3569e-6
m2
0.0019836
0.0001097
m3
2.4945
0.1997
Chisq
2.6244e-9
NA
R
0.99865
NA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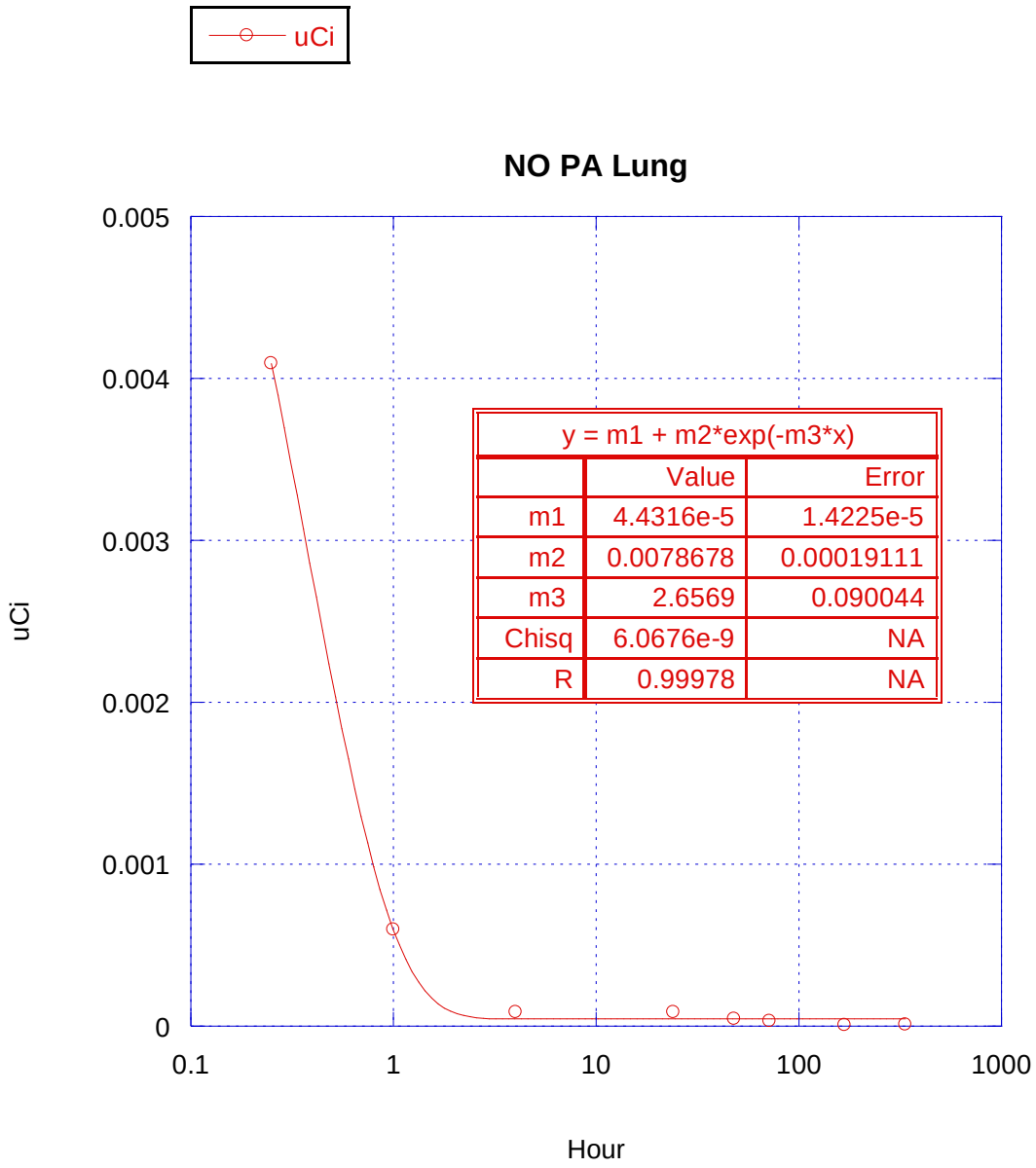
PA Heart
0.001
0.0008
0.0006
0.0004
0.0002
0
-0.0002
uCi
0.1
1
10
100
1000
Hour
y = m1 + m2*exp(-m3*x)
Value
Error
m1
3.5503e-5
2.0901e-5
m2
0.013078
0.9751
m3
10.874
298.47
Chisq
1.3106e-8
NA
R
0.99009
NA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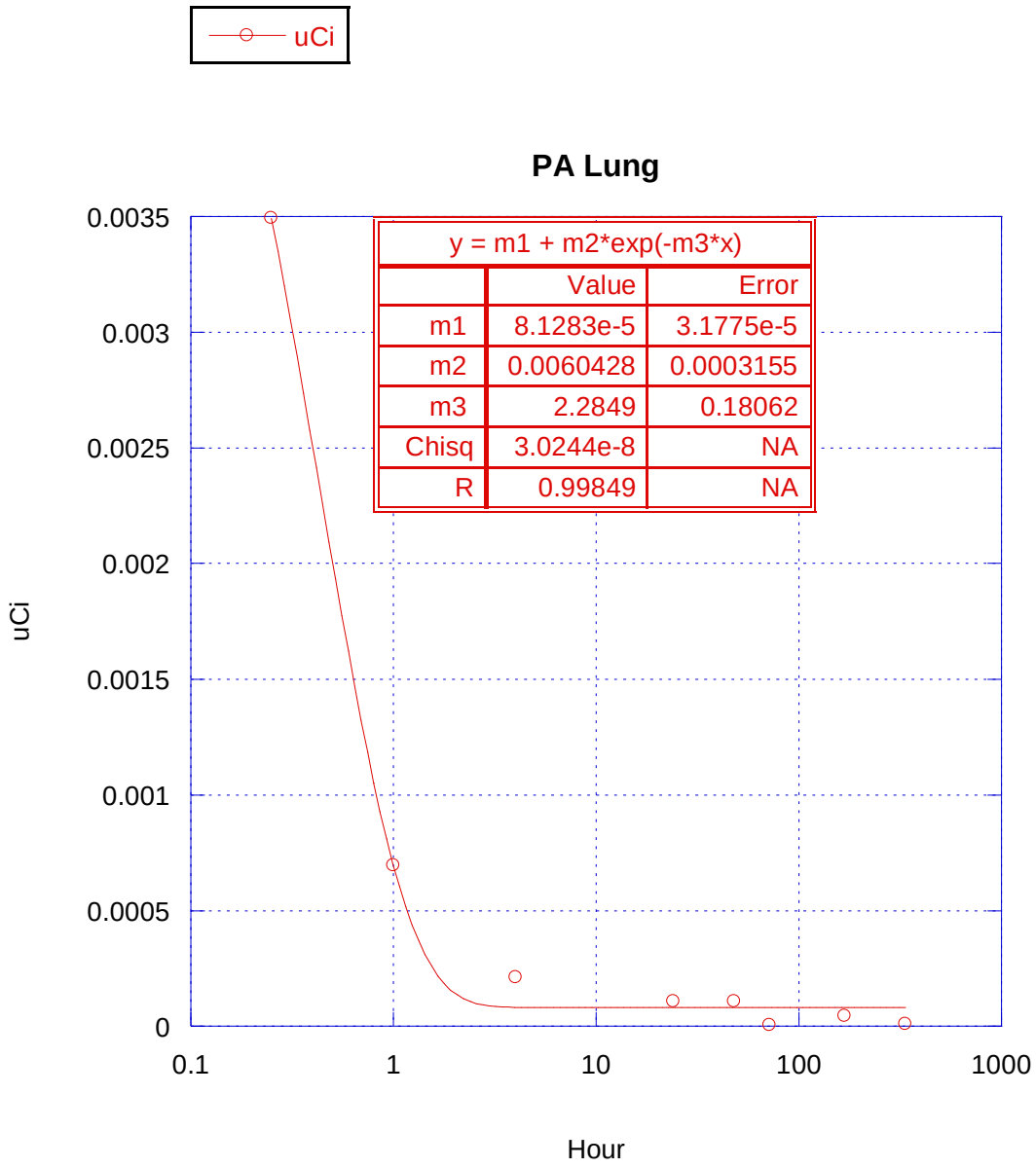
0.005
0.004
0.003
0.002
0.001
0
uCi
0.1
1
10
100
1000
Hour
y = m1 + m2*exp(-m3*x)
Value
Error
m1
4.4316e-5
1.4225e-5
m2
0.0078678
0.00019111
m3
2.6569
0.090044
Chisq
6.0676e-9
NA
R
0.99978
NA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PA Lung
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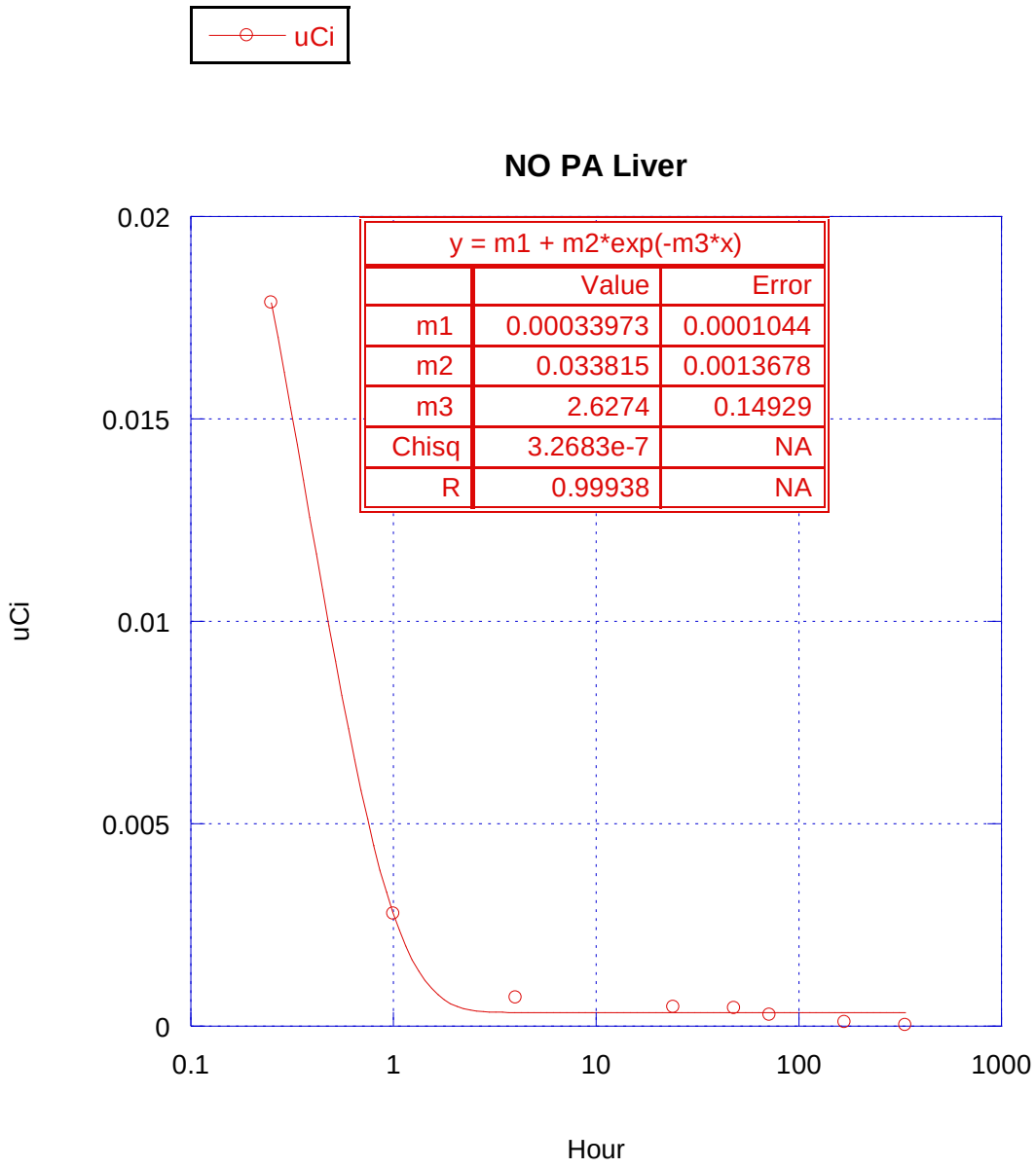
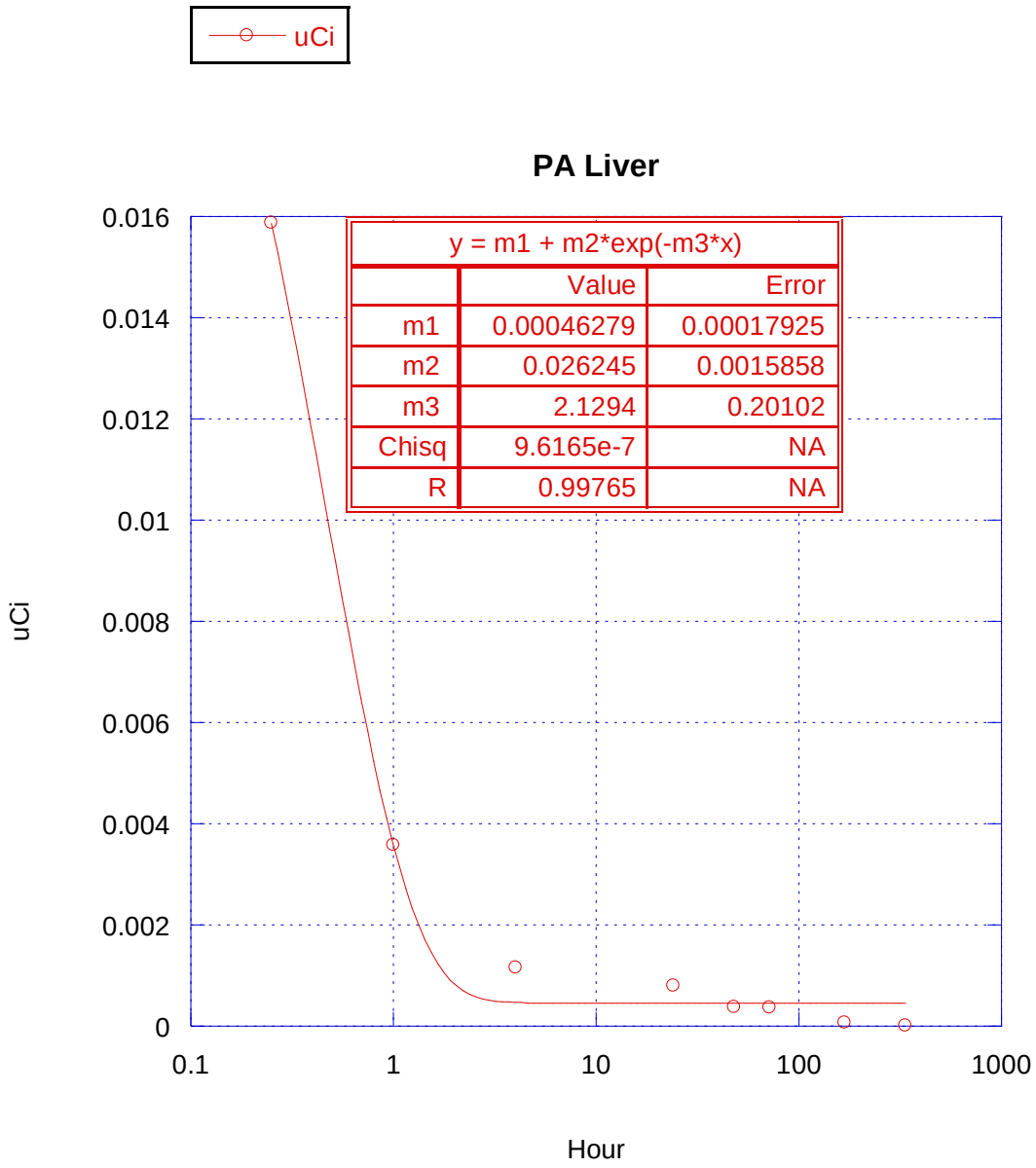
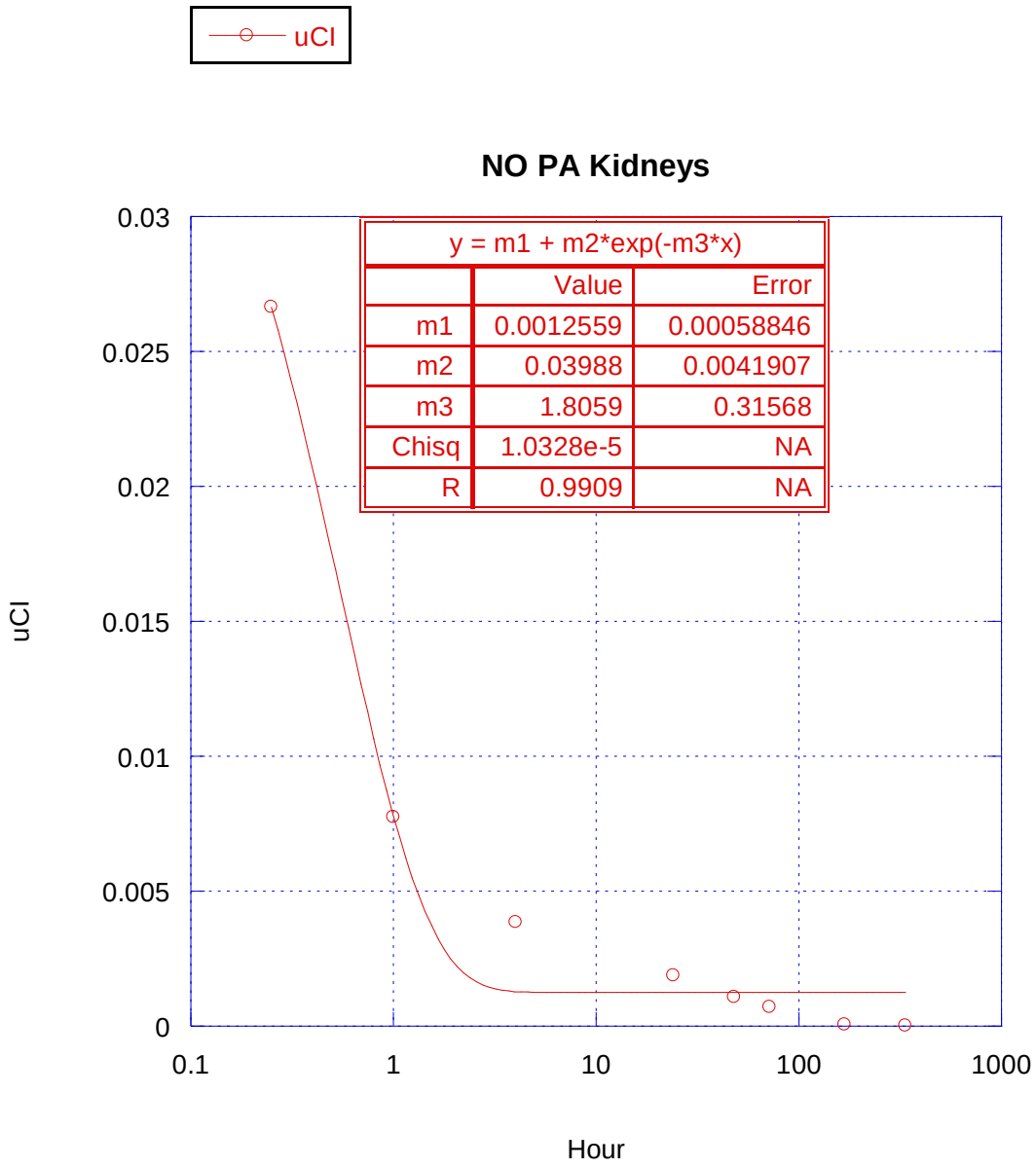
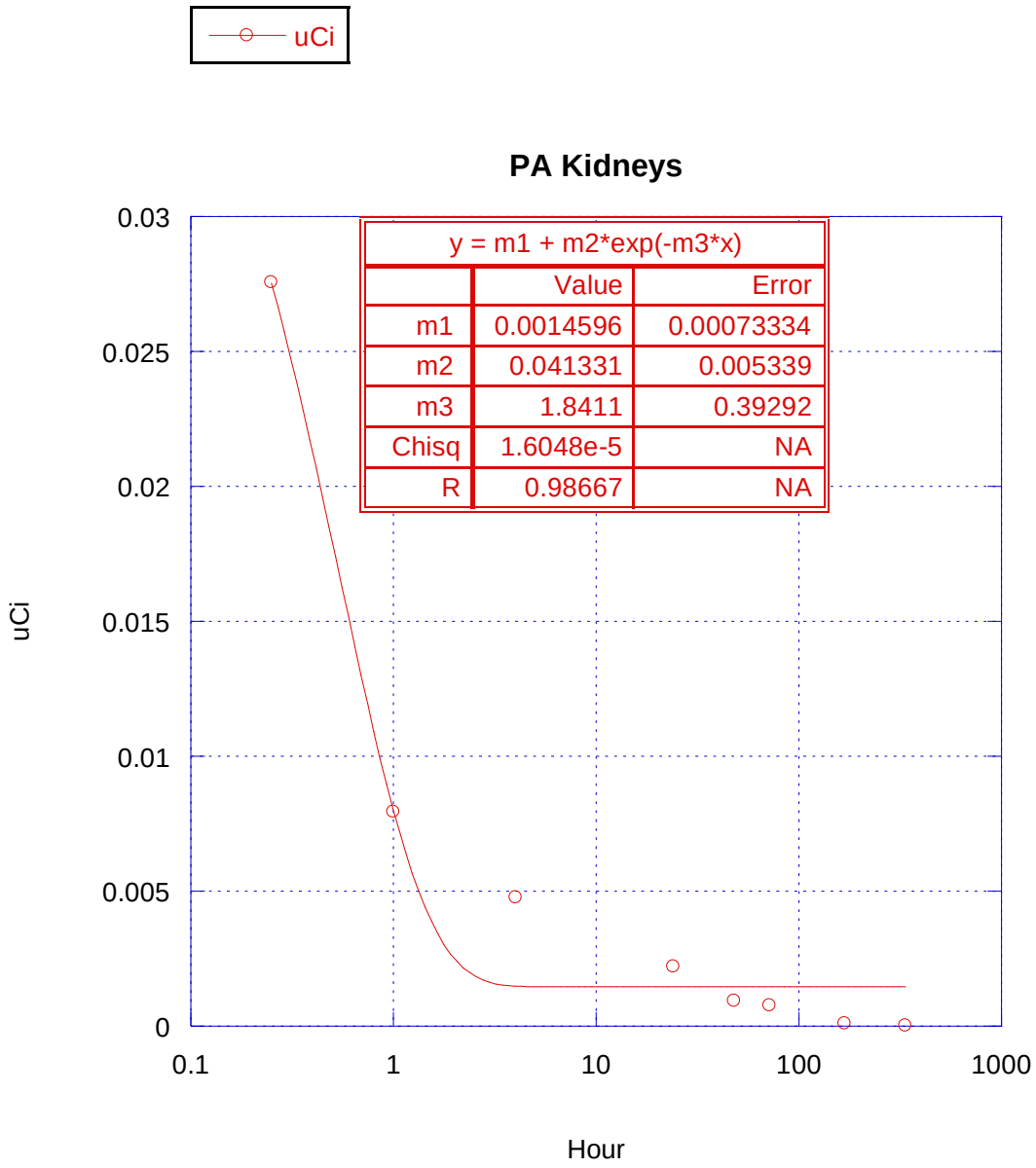
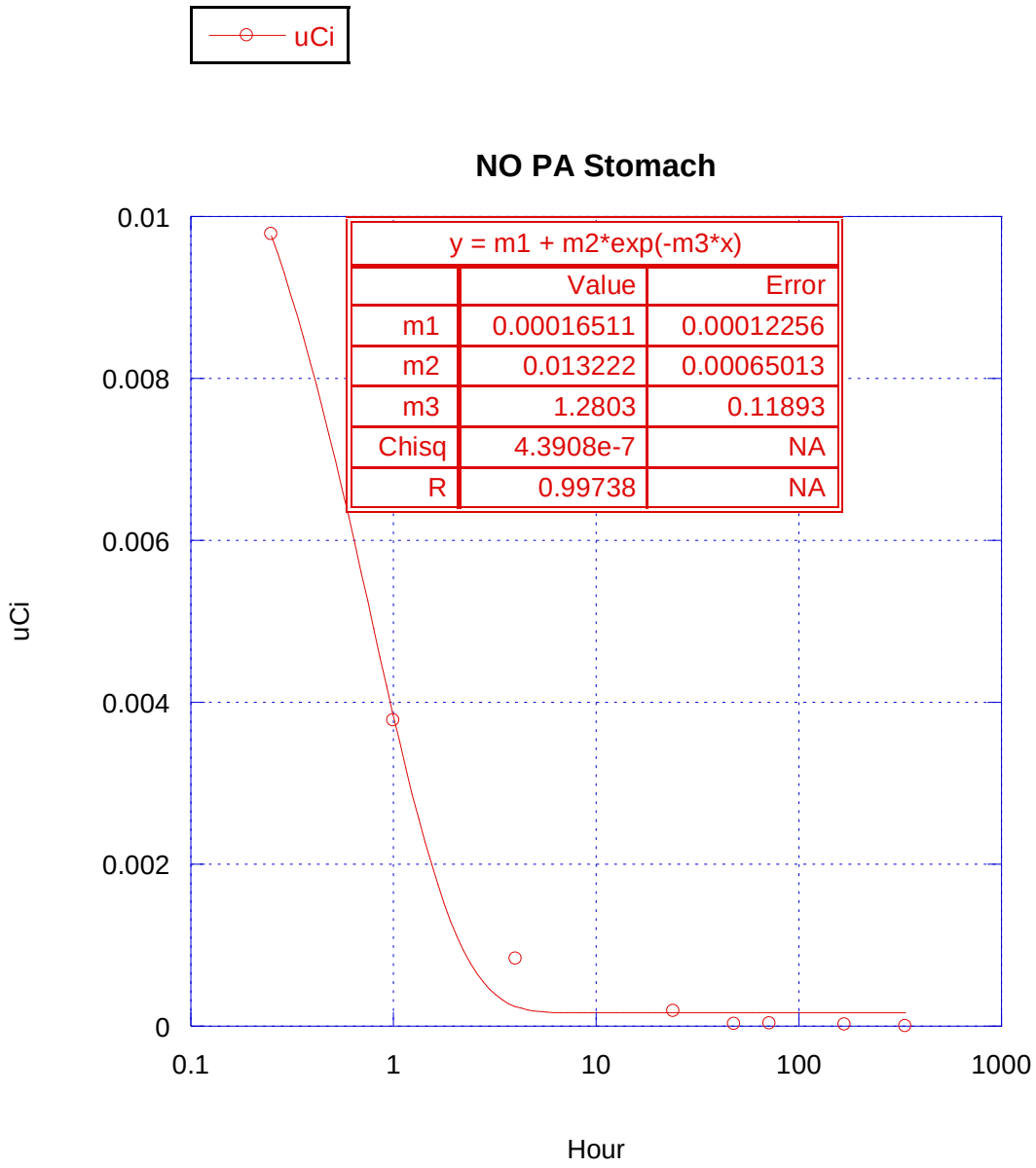
Value Error
m1 8.1283e-5 3.1775e-5
m2 0.0060428 0.0003155
m3 2.2849 0.18062
Chisq 3.0244e-8 NA
R 0.99849 NA
0.0035
0.003
0.0025
0.002
0.0015
0.001
0.0005
0
uCi
0.1
1
10
100
1000
Hour

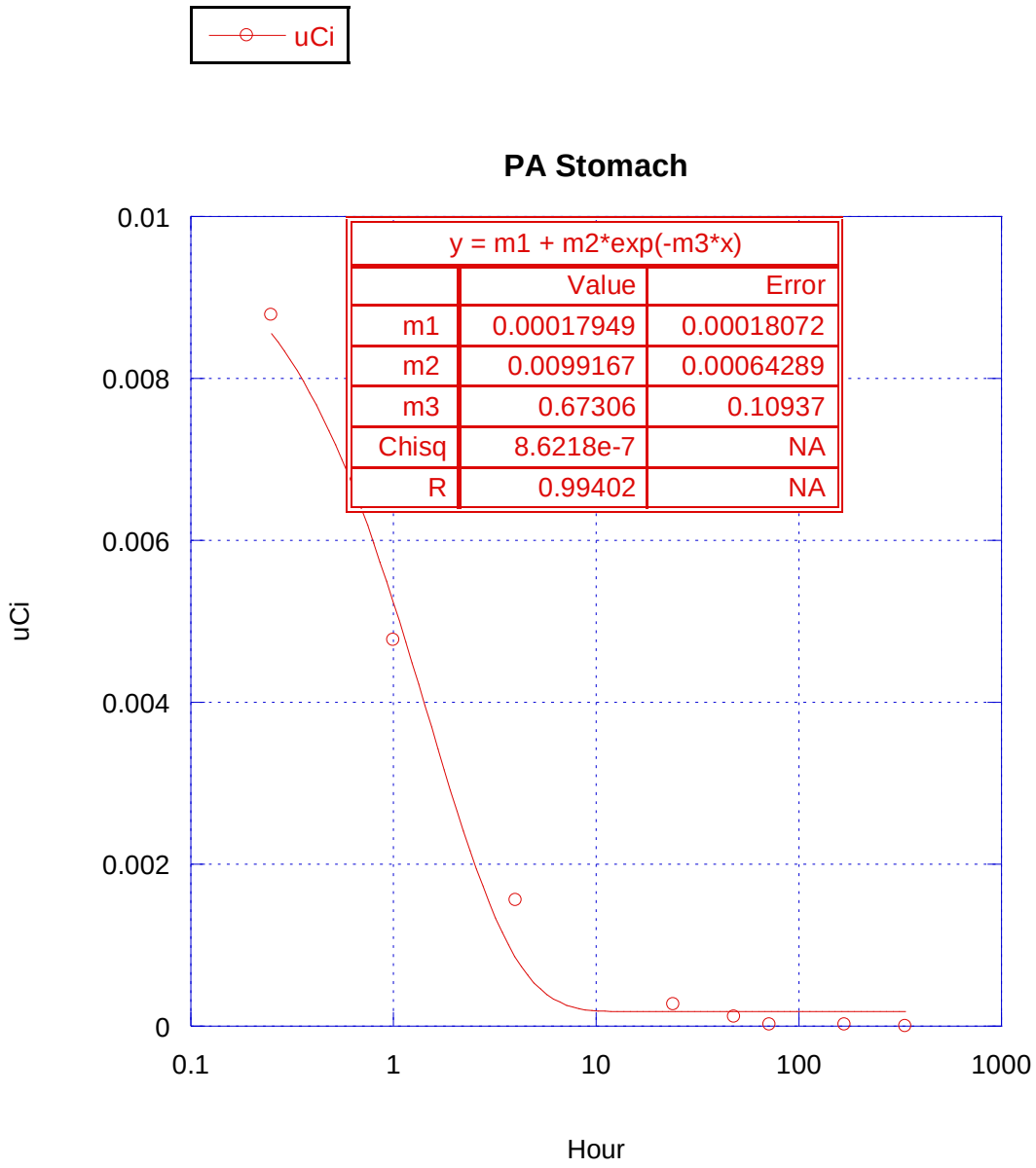

uCi
NO PA Liver
y = m1 + m2*exp(-m3*x)
Value
Error
m1
0.00033973
0.0001044
m2
0.033815
0.0013678
m3
2.6274
0.14929
Chisq
3.2683e-7
NA
R
0.99938
NA
0.02
0.015
0.01
0.005
0
uCi
0.1
1
10
100
1000
Hour

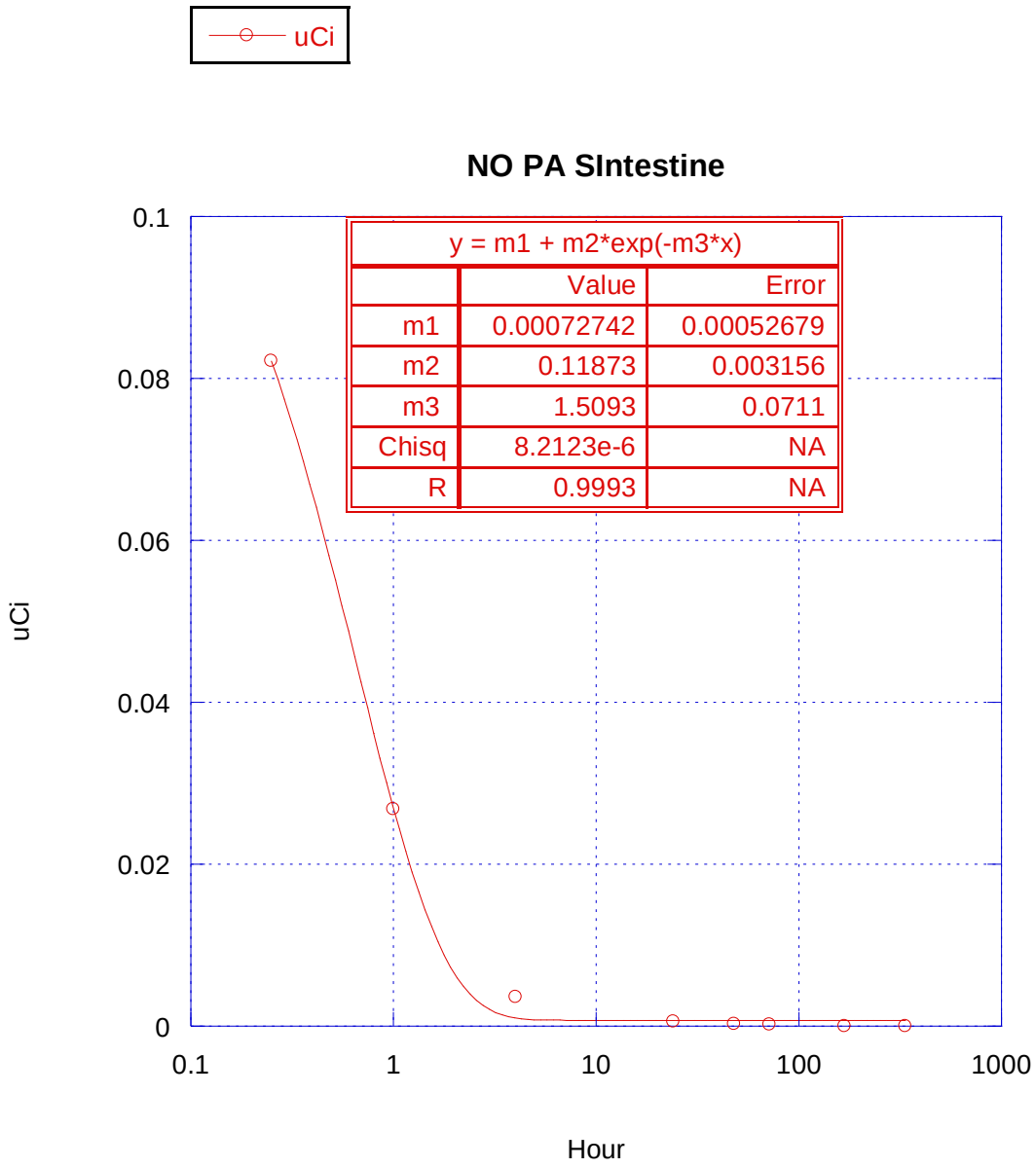

uCi
PA Liver
y = m1 + m2*exp(-m3*x)
Value
Error
m1
0.00046279
0.00017925
m2
0.026245
0.0015858
m3
2.1294
0.20102
Chisq
9.6165e-7
NA
R
0.99765
NA
0.016
0.014
0.012
0.01
0.008
0.006
0.004
0.002
0
uCi
0.1
1
10
100
1000
Hour


uCl
NO PA Kidneys
y = m1 + m2*exp(-m3*x)
Value
Error
m1
0.0012559
0.00058846
m2
0.03988
0.0041907
m3
1.8059
0.31568
Chisq
1.0328e-5
NA
R
0.9909
NA
0.03
0.025
0.02
0.015
0.01
0.005
0
uCl
0.1
1
10
100
1000
Hour


uCi
PA Kidneys
y = m1 + m2*exp(-m3*x)
Value Error
m1 0.0014596 0.00073334
m2 0.041331 0.005339
m3 1.8411 0.39292
Chisq 1.6048e-5 NA
R 0.98667 NA
0.03
0.025
0.02
0.015
0.01
0.005
0
uCi
0.1
1
10
100
1000
Hour


uCi
NO PA Stomach
y = m1 + m2*exp(-m3*x)
Value Error
m1 0.00016511 0.00012256
m2 0.013222 0.00065013
m3 1.2803 0.11893
Chisq 4.3908e-7 NA
R 0.99738 NA
0.01
0.008
0.006
0.004
0.002
0
uCi
0.1
1
10
100
1000
Hour


uCi
PA Stomach
y = m1 + m2*exp(-m3*x)
Value
Error
m1
0.00017949
0.00018072
m2
0.0099167
0.00064289
m3
0.67306
0.10937
Chisq
8.6218e-7
NA
R
0.99402
NA
0.01
0.008
0.006
0.004
0.002
0
uCi
0.1
1
10
100
1000
Hour


uCi
NO PA SIntestine
y = m1 + m2*exp(-m3*x)
Value Error
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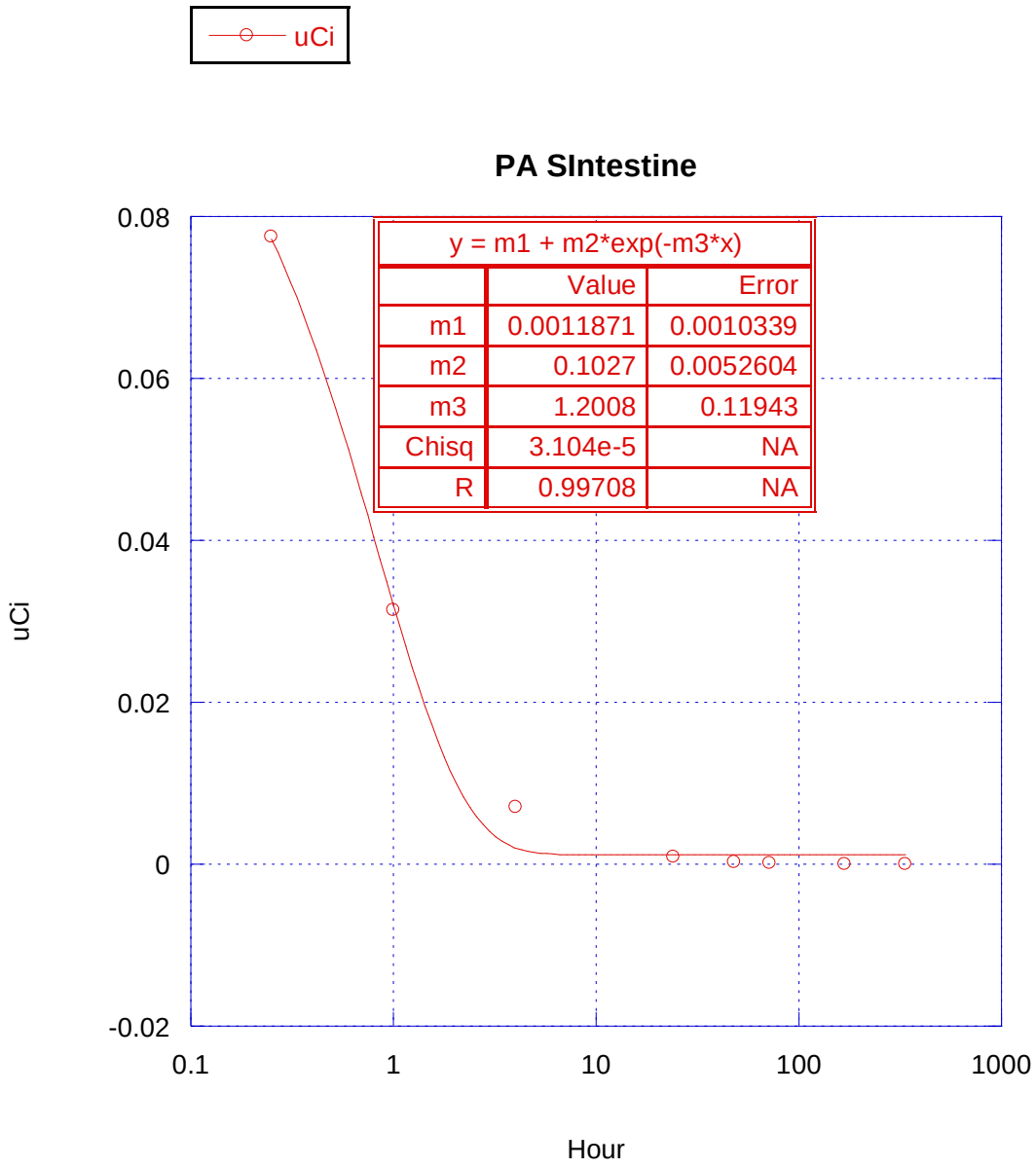
m2 0.11873 0.003156
m3 1.5093 0.0711
Chisq 8.2123e-6 NA
R 0.9993 NA
0.1
0.08
0.06
0.04
0.02
0
uCi
0.1
1
10
100
1000
Hour


uCi
PA SIntestine
y = m1 + m2*exp(-m3*x)
Value
Error
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0.0011871
0.0010339
m2
0.1027
0.0052604
m3
1.2008
0.11943
Chisq
3.104e-5
NA
R
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NA
0.08
0.06
0.04
0.02
0
-0.02
uCi
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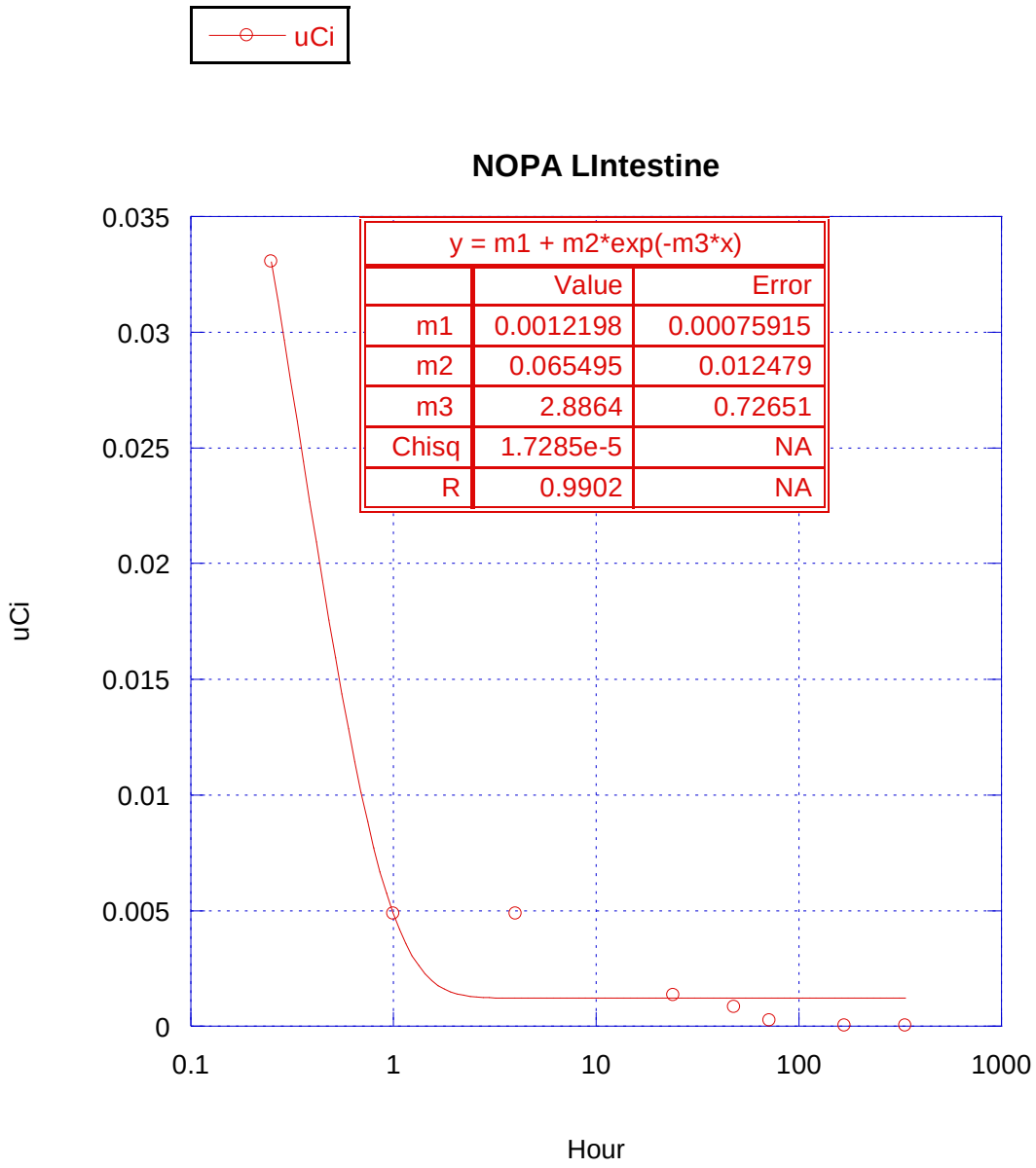
1
10
100
1000
Hour


uCi
NOPA LIntestine
y = m1 + m2*exp(-m3*x)
Value Error
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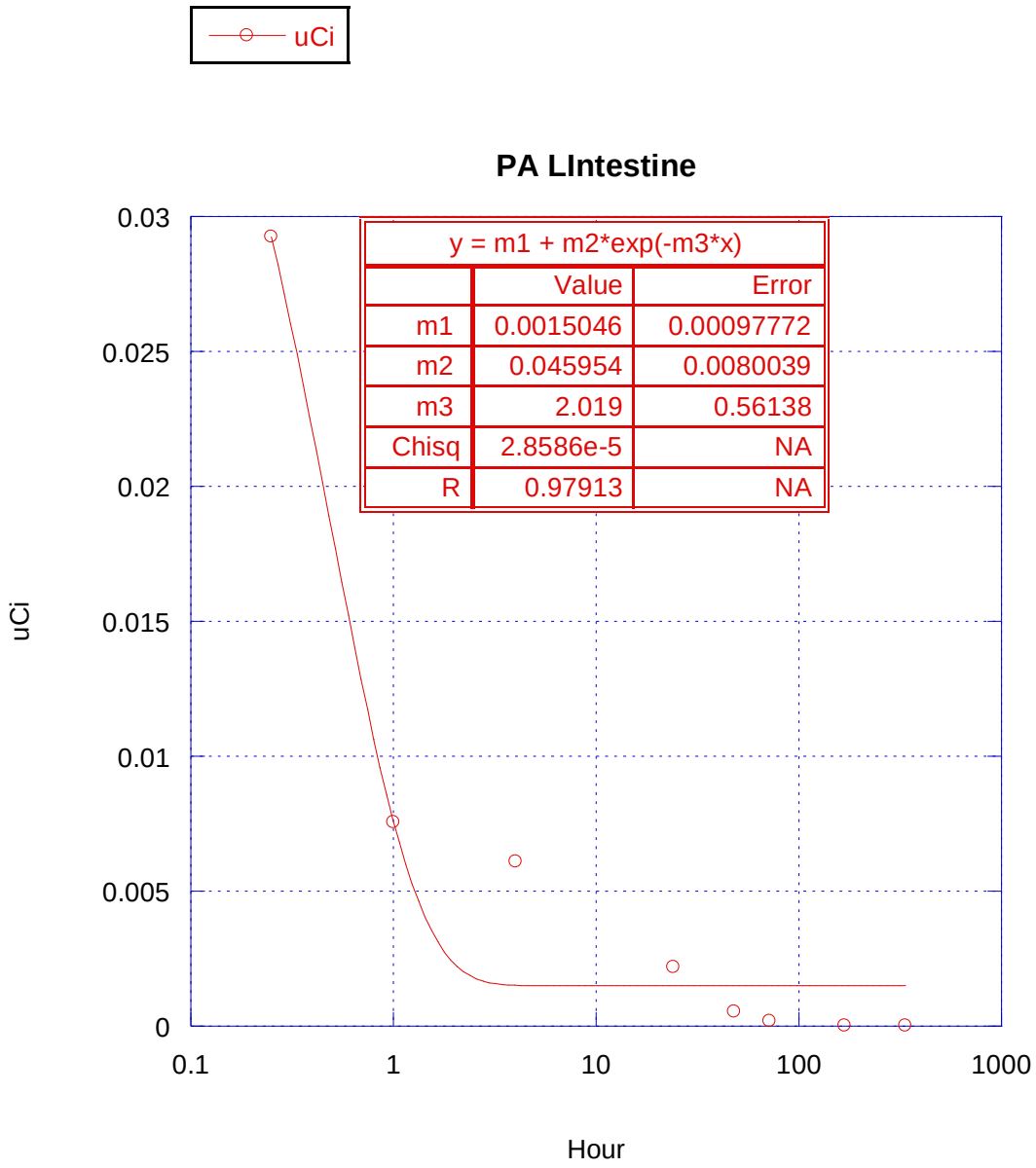
m2 0.065495 0.012479
m3 2.8864 0.72651
Chisq 1.7285e-5 NA
R 0.9902 NA
0.035
0.03
0.025
0.02
0.015
0.01
0.005
0
uCi
0.1
1
10
100
1000
Hour


uCi
PA LIntestine
y = m1 + m2*exp(-m3*x)
Value Error
m1 0.0015046 0.00097772
m2 0.045954 0.0080039
m3 2.019 0.56138
Chisq 2.8586e-5 NA
R 0.97913 NA
0.03
0.025
0.02
0.015
0.01
0.005
0
uCi
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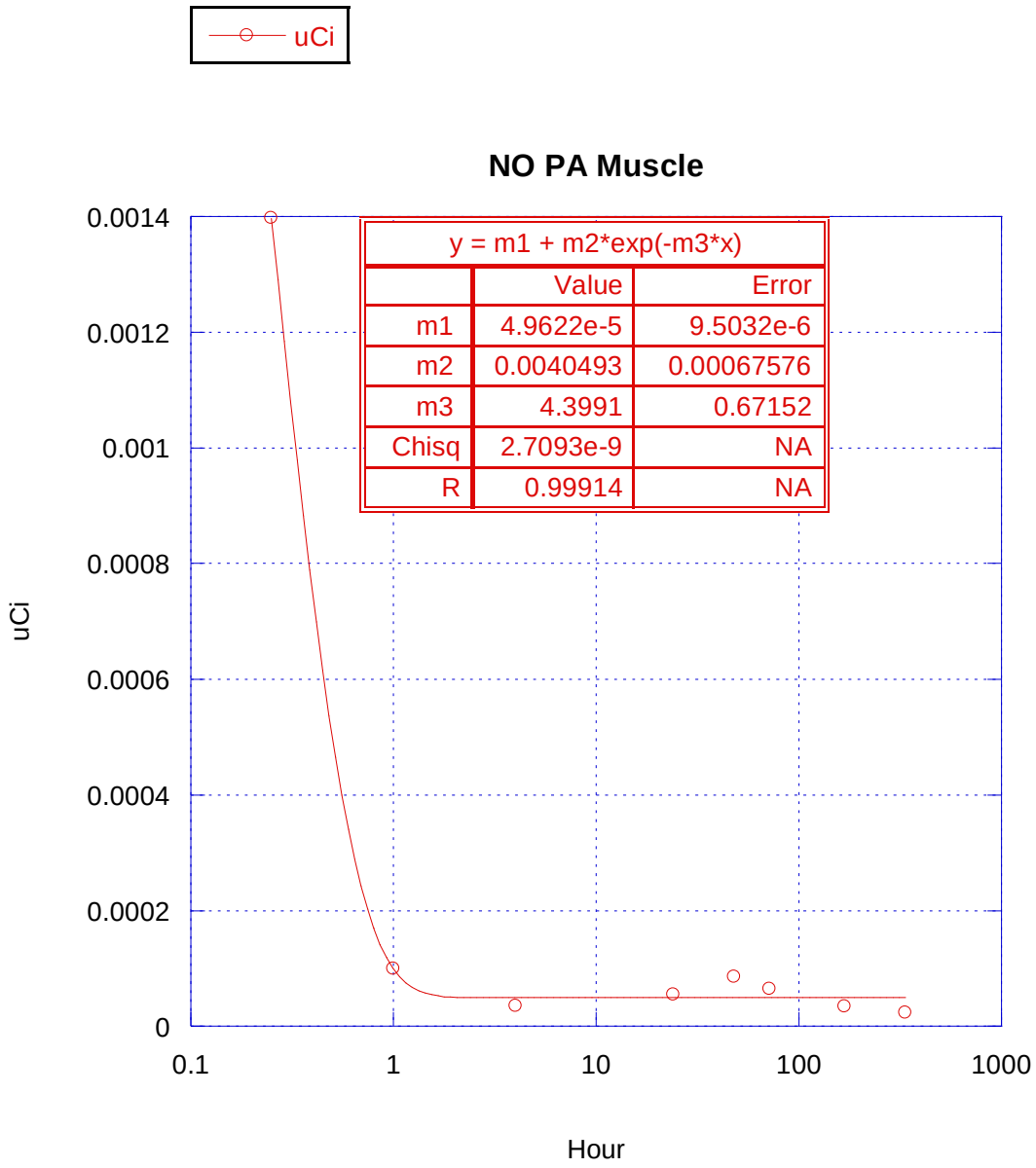
1
10
100
1000
Hour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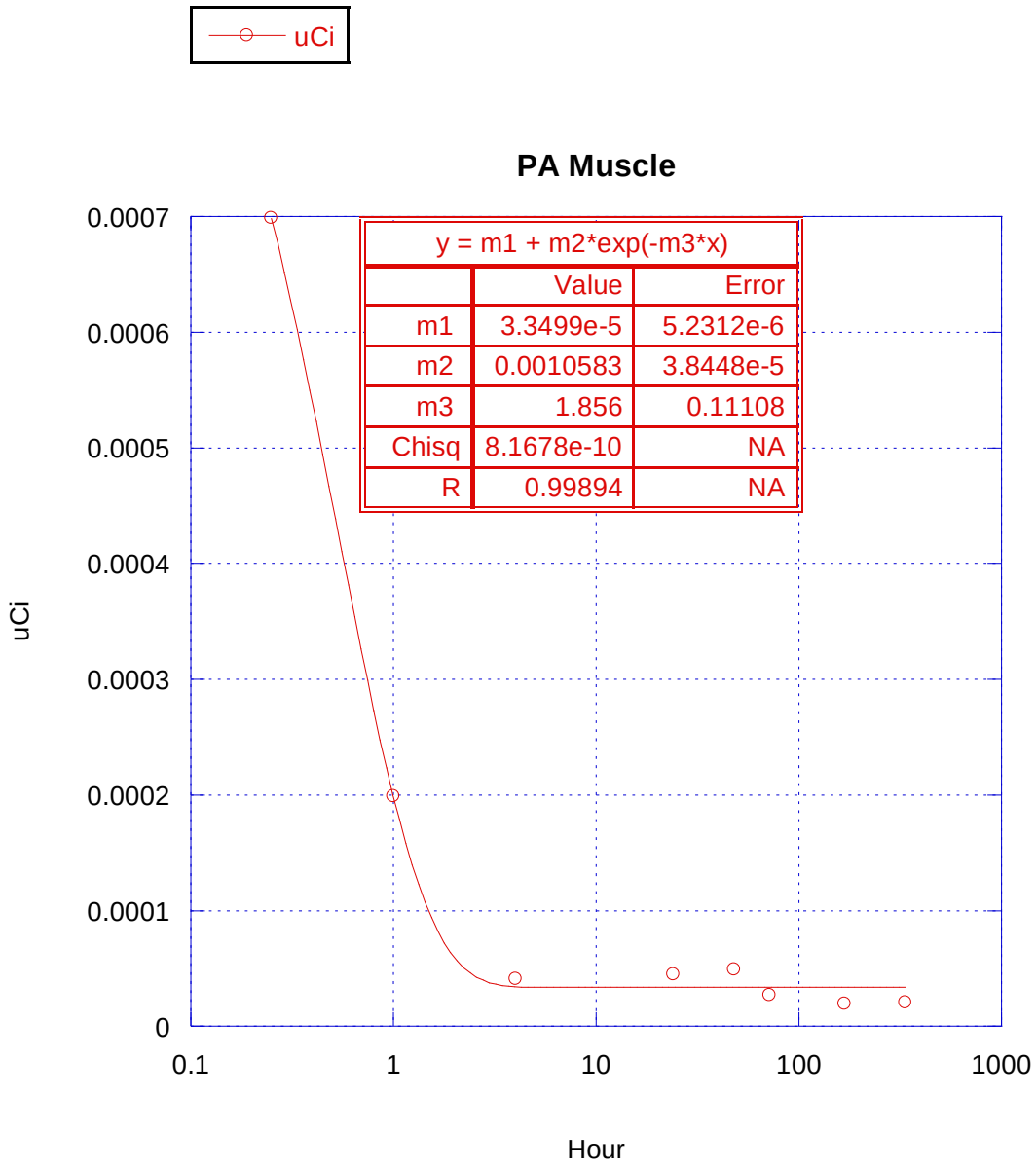
m2 0.0040493 0.00067576
m3 4.3991 0.67152
Chisq 2.7093e-9 NA
R 0.99914 NA
0.0014
0.0012
0.001
0.0008
0.0006
0.0004
0.0002
0
uCi
0.1
1
10
100
1000
Hour


uCi
PA Muscle
y = m1 + m2*exp(-m3*x)
Value
Error
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5.2312e-6
m2
0.0010583
3.8448e-5
m3
1.856
0.11108
Chisq
8.1678e-10
NA
R
0.99894
NA
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0.0006
0.0005
0.0004
0.0003
0.0002
0.0001
0
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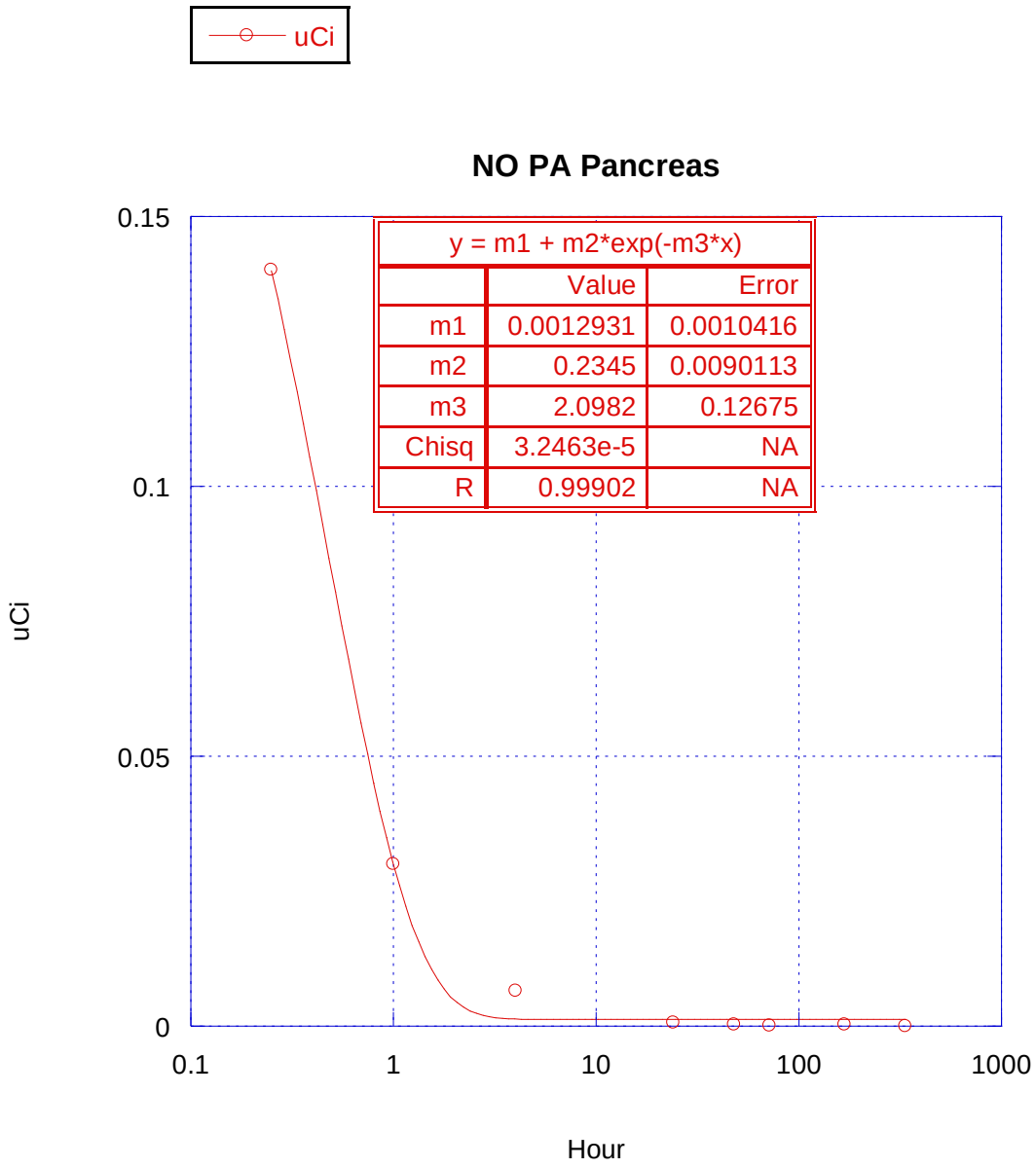
1
10
100
1000
Hour


uCi
NO PA Pancreas
y = m1 + m2*exp(-m3*x)
Value
Error
m1
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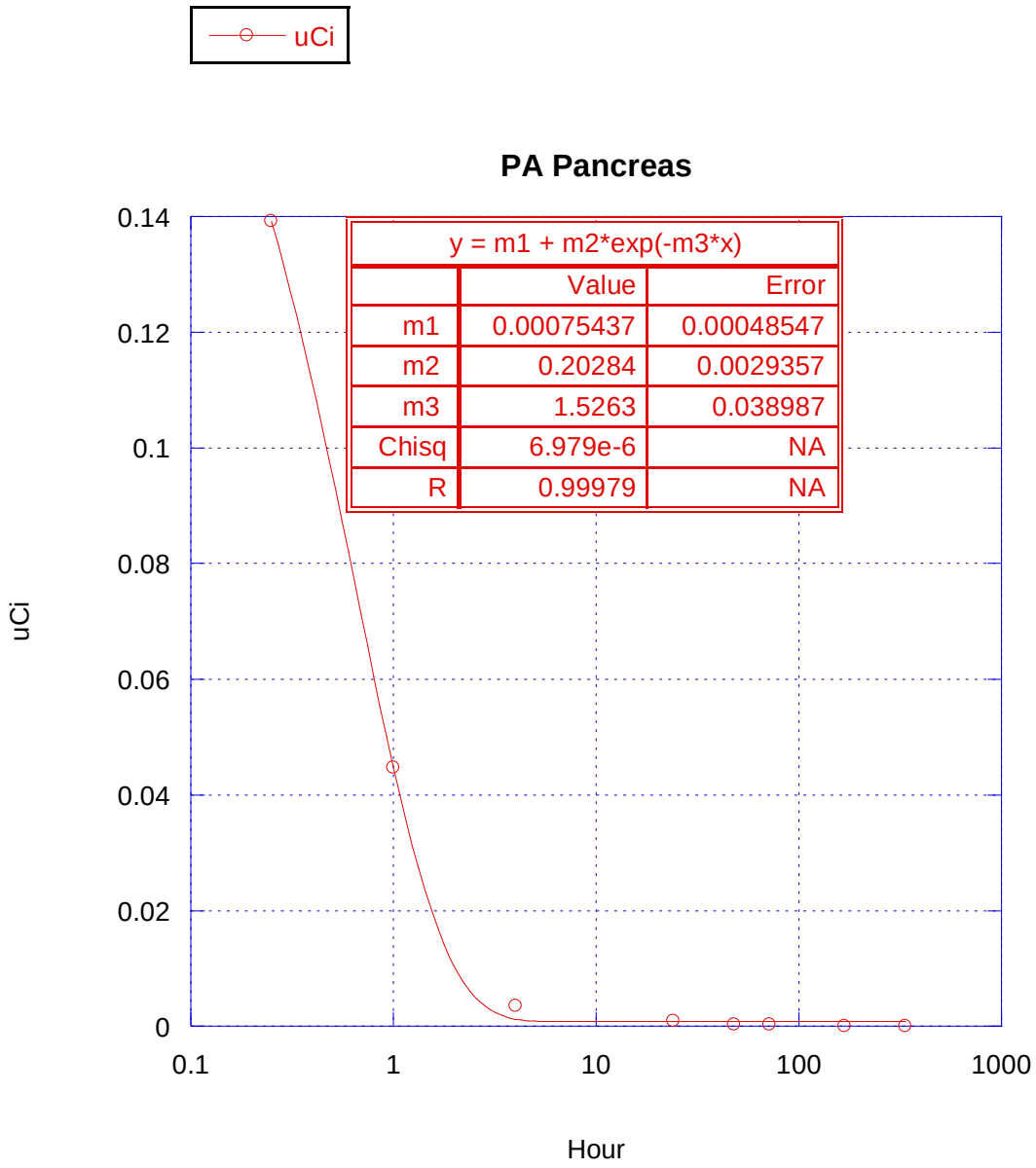
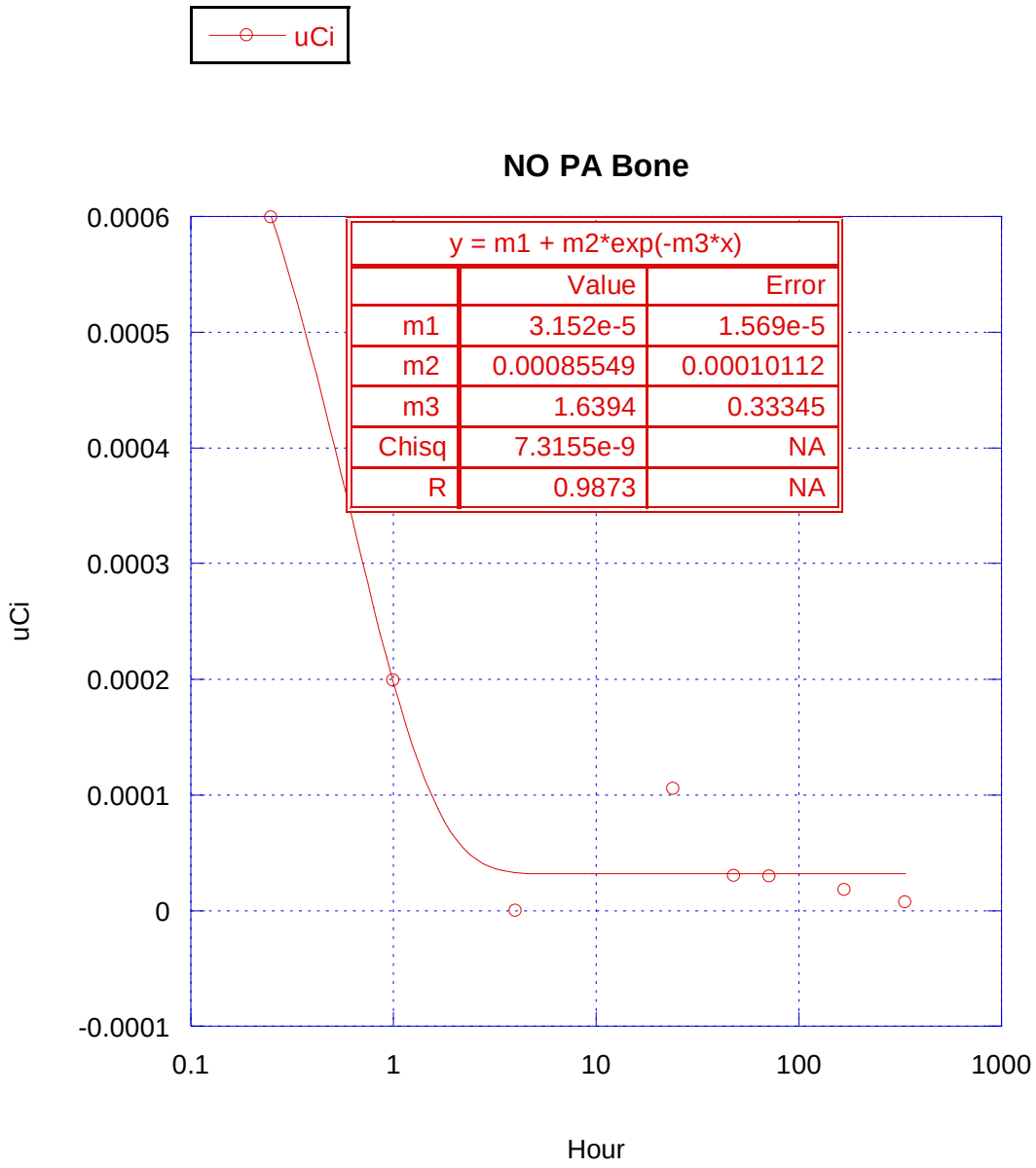
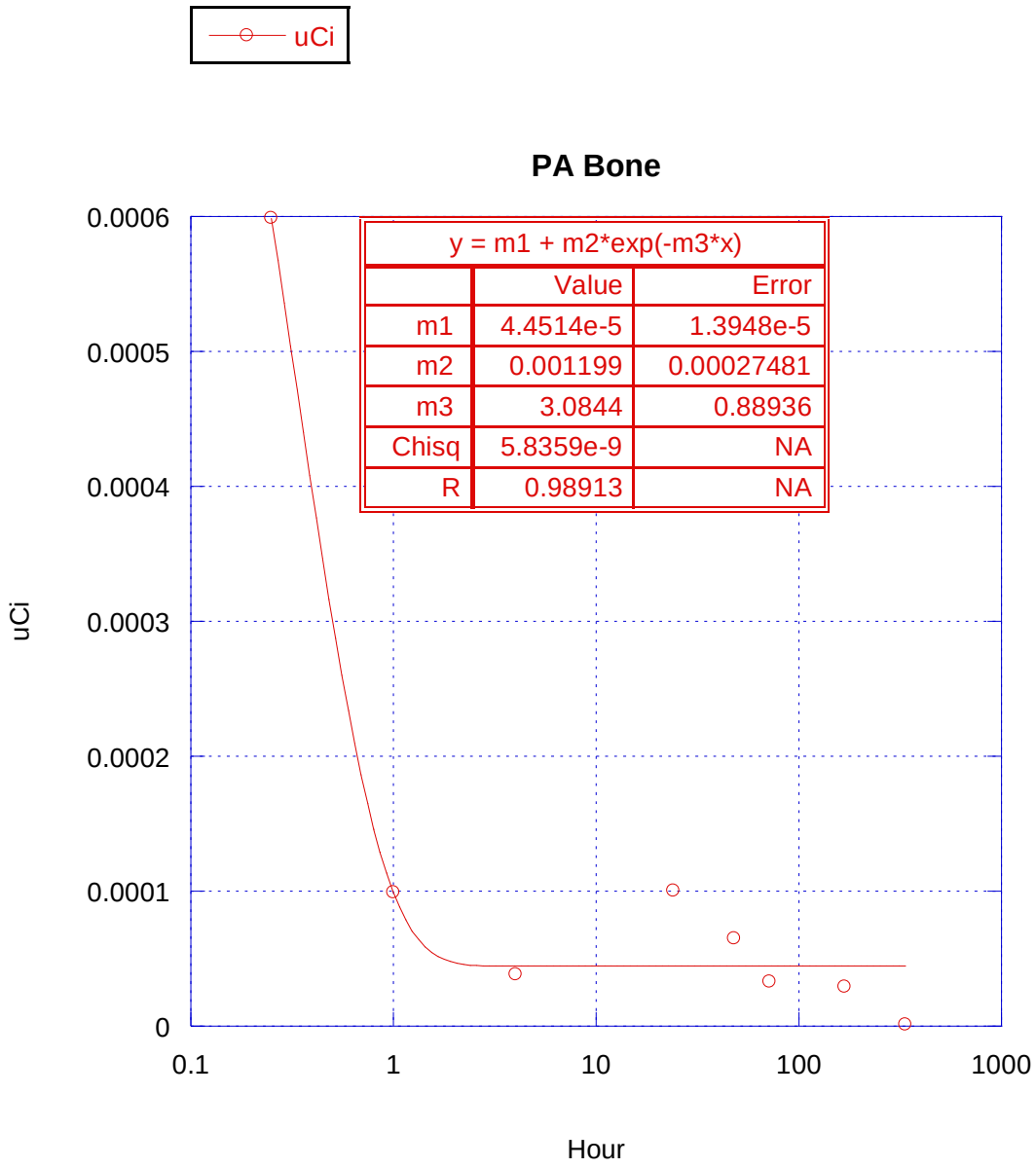
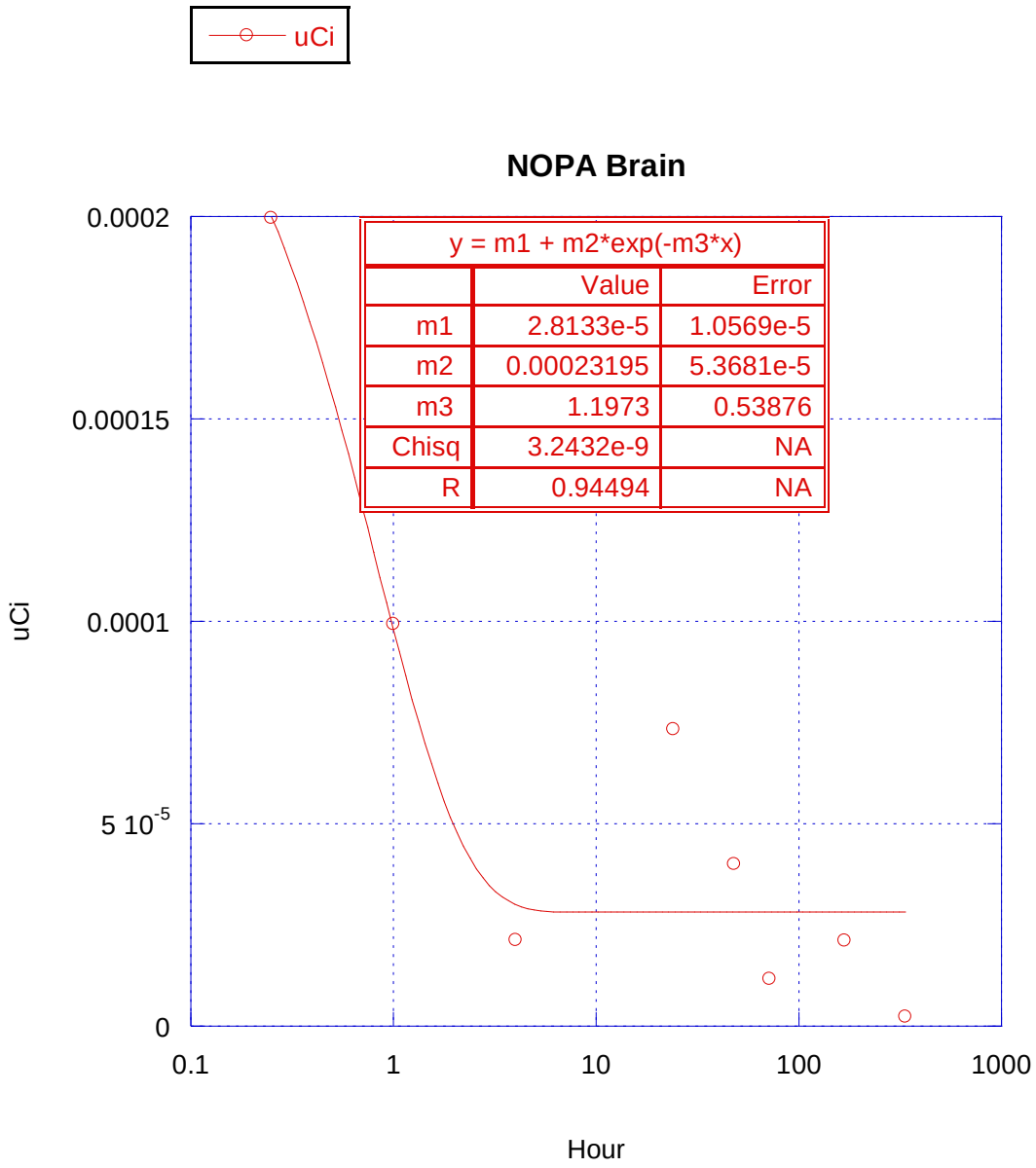
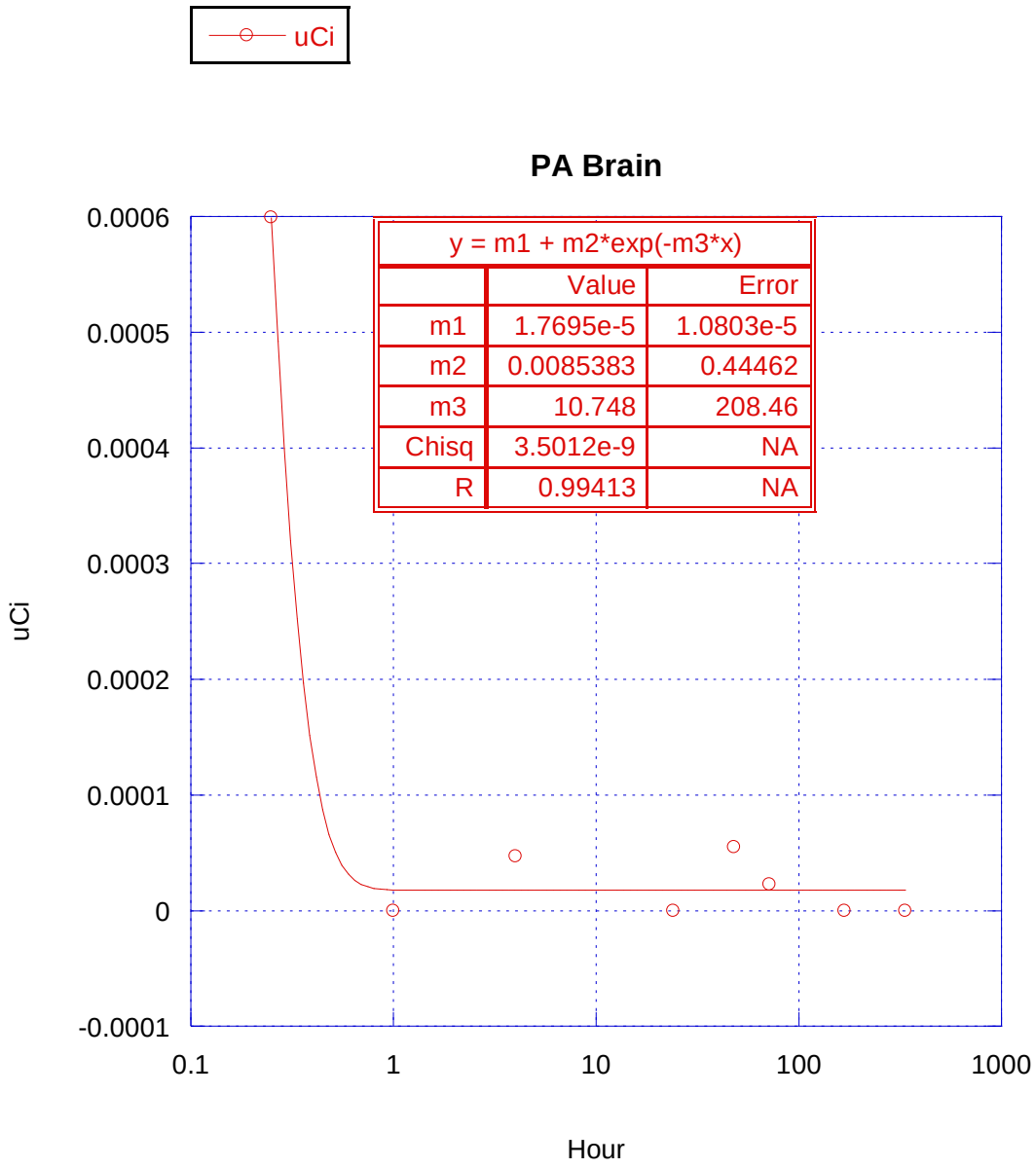
0.0010416
m2
0.2345
0.0090113
m3
2.0982
0.12675
Chisq
3.2463e-5
NA
R
0.99902
NA
0.15
0.1
0.05
0
uCi
0.1
1
10
100
1000
Hour

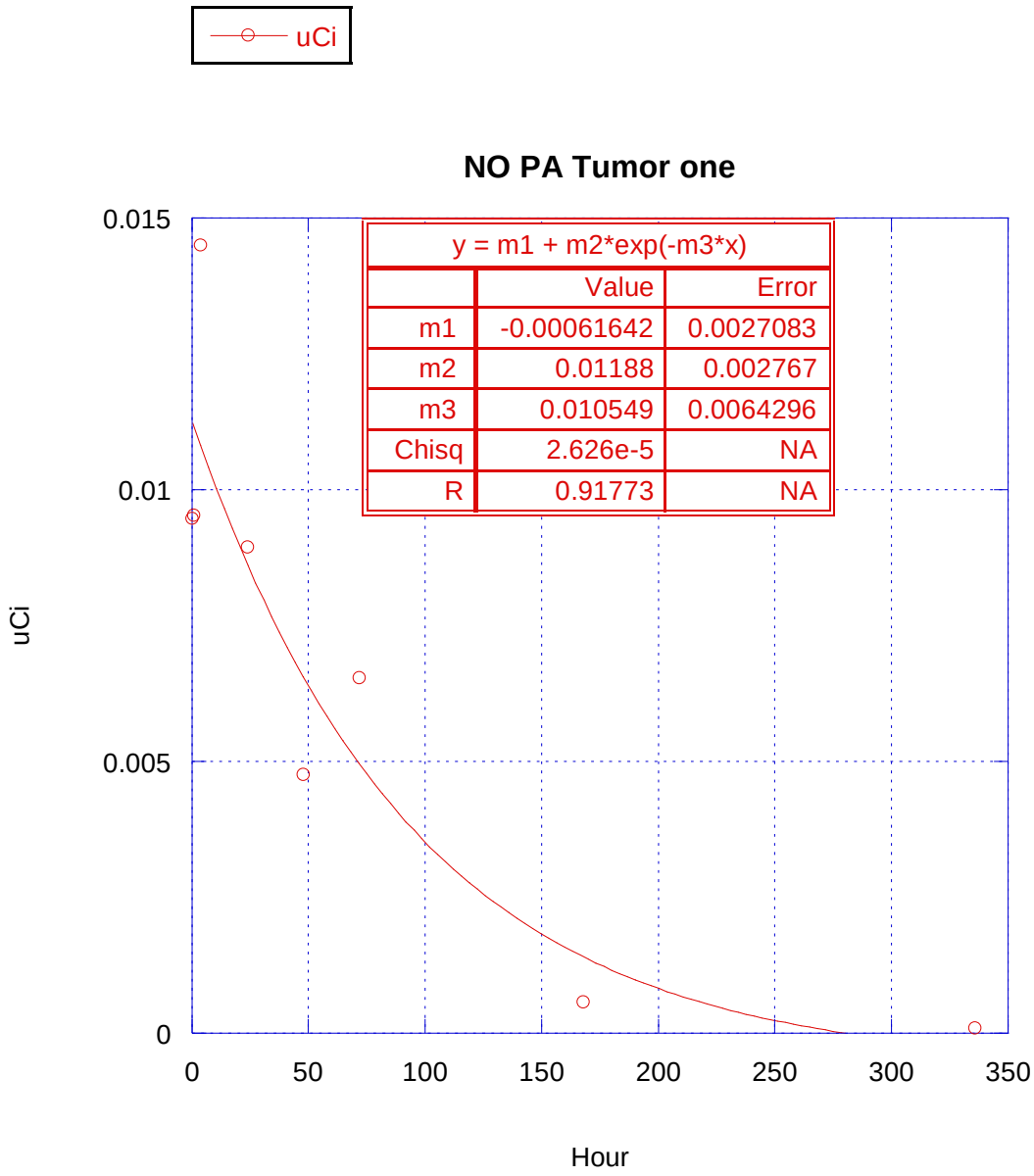

uCi
PA Pancreas
y = m1 + m2*exp(-m3*x)
Value
Error
m1
0.00075437
0.00048547
m2
0.20284
0.0029357
m3
1.5263
0.038987
Chisq
6.979e-6
NA
R
0.99979
NA
0.14
0.12
0.1
0.08
0.06
0.04
0.02
0
uCi
0.1
1
10
100
1000
Hour

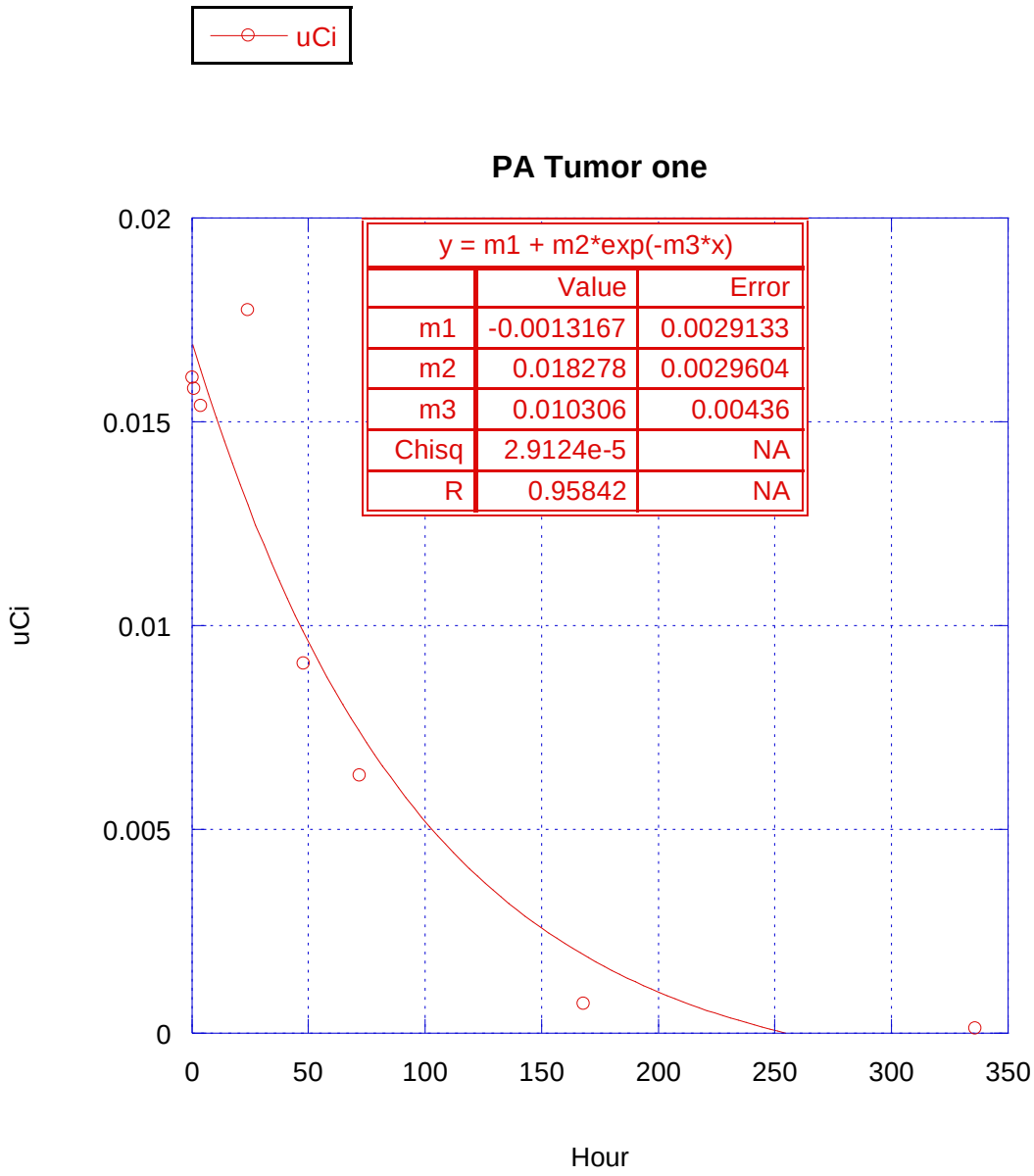

uCi
NO PA Bone
y = m1 + m2*exp(-m3*x)
Value
Error
m1
3.152e-5
1.569e-5
m2
0.00085549
0.00010112
m3
1.6394
0.33345
Chisq
7.3155e-9
NA
R
0.9873
NA
0.0006
0.0005
0.0004
0.0003
0.0002
0.0001
0
-0.0001
uCi
0.1
1
10
100
1000
Hour

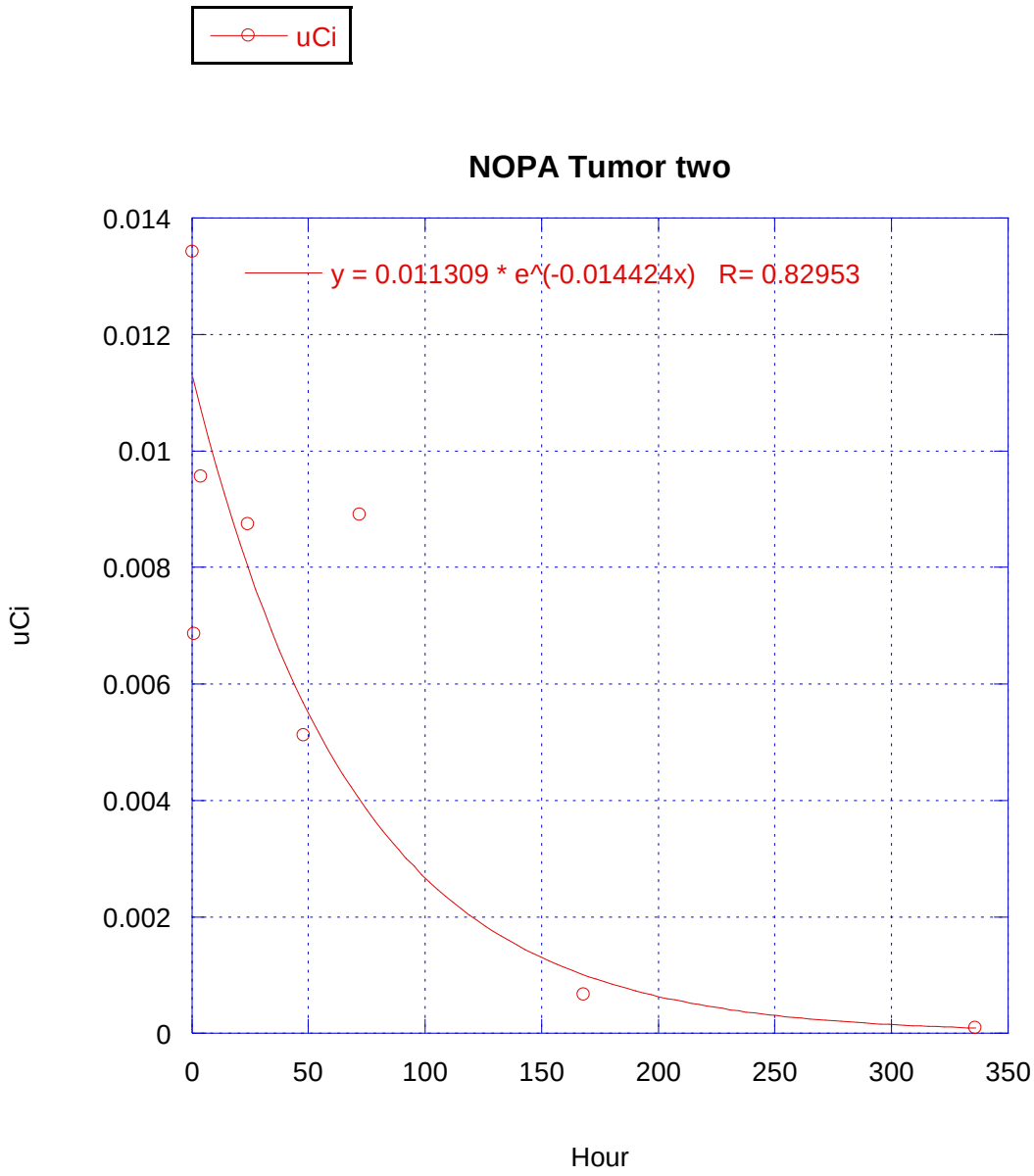

uCi
PA Bone
y = m1 + m2*exp(-m3*x)
Value
Error
m1
4.4514e-5
1.3948e-5
m2
0.001199
0.00027481
m3
3.0844
0.88936
Chisq
5.8359e-9
NA
R
0.98913
NA
0.0006
0.0005
0.0004
0.0003
0.0002
0.0001
0
uCi
0.1
1
10
100
1000
Hour


uCi
NOPA Brain
y = m1 + m2*exp(-m3*x)
Value Error
m1 2.8133e-5 1.0569e-5
m2 0.00023195 5.3681e-5
m3 1.1973 0.53876
Chisq 3.2432e-9 NA
R 0.94494 NA
0.0002
0.00015
0.0001
5 10-5
0
uCi
0.1
1
10
100
1000
Hour


uCi
PA Brain
y = m1 + m2*exp(-m3*x)
Value
Error
m1
1.7695e-5
1.0803e-5
m2
0.0085383
0.44462
m3
10.748
208.46
Chisq
3.5012e-9
NA
R
0.99413
NA
0.0006
0.0005
0.0004
0.0003
0.0002
0.0001
0
-0.0001
uCi
0.1
1
10
100
1000
Hour


uCi
NO PA Tumor one
y = m1 + m2*exp(-m3*x)
Value
Error
m1
-0.00061642
0.0027083
m2
0.01188
0.002767
m3
0.010549
0.0064296
Chisq
2.626e-5
NA
R
0.91773
NA
0.015
0.01
0.005
0
uCi
0
50
100
150
200
250
300
350
Hour


uCi
PA Tumor one
y = m1 + m2*exp(-m3*x)
Value Error
m1 -0.0013167 0.0029133
m2 0.018278 0.0029604
m3 0.010306 0.00436
Chisq 2.9124e-5 NA
R 0.95842 NA
0.02
0.015
0.01
0.005
0
uCi
0 50 100 150 200 250 300 350
Hour


uCi
NOPA Tumor two
y = 0.011309 * e^(-0.014424x) R= 0.82953
0.014
0.012
0.01
0.008
0.006
0.004
0.002
0
uCi
0
50
100
150
200
250
300
350
Hour

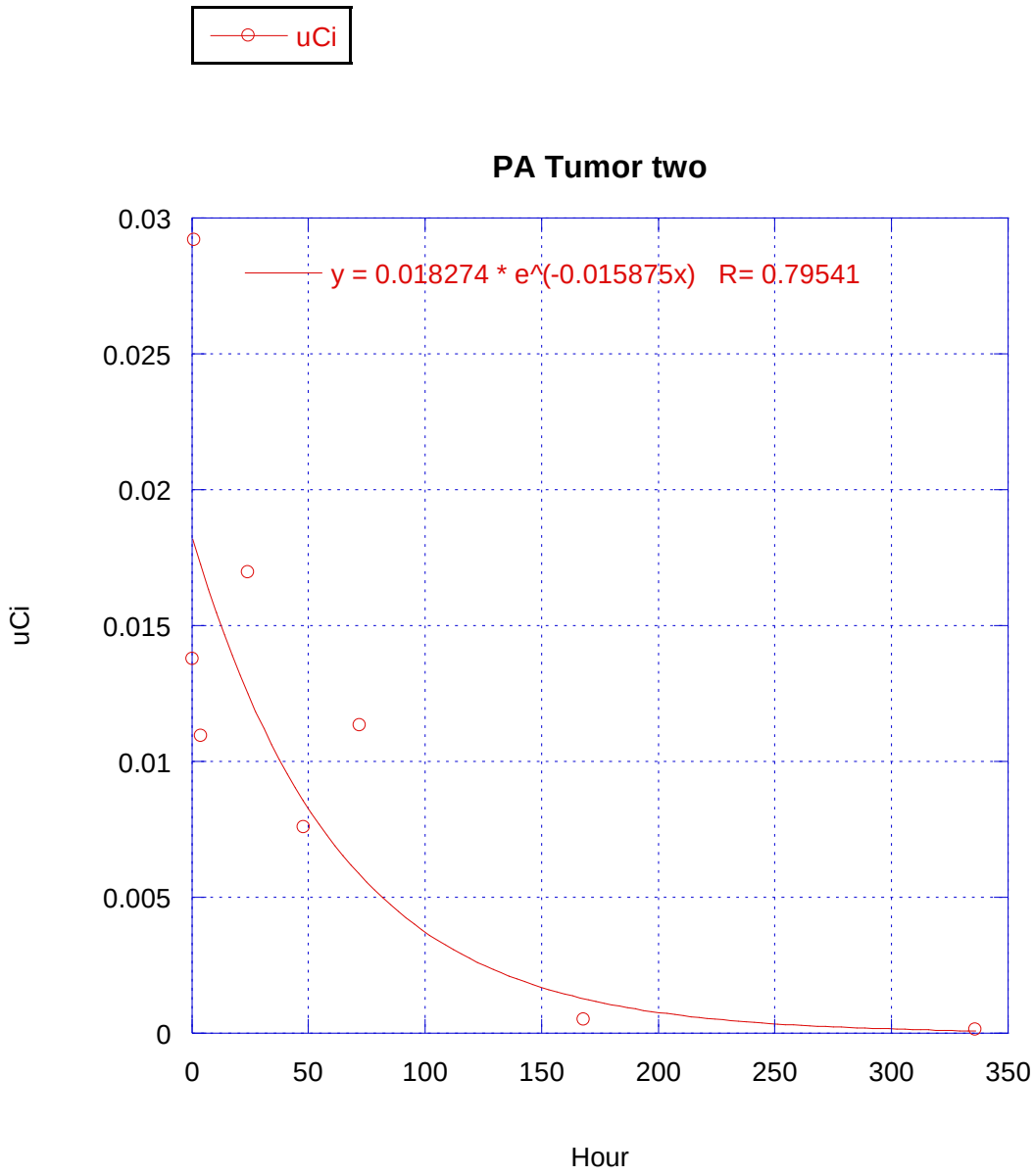

uCi
PA Tumor two
y = 0.018274 * e^(-0.015875x) R= 0.79541
0.03
0.025
0.02
0.015
0.01
0.005
0
uCi
0
50
100
150
200
250
300
350
Hour

Table A4 **Lu-177 Dose (mGy per mCi Injected)**

	Source									
Target	Bladder	Urine	Heart	Lung	Liver	Kidneys	Spleen	Stomach	S. Bowel	L. Bowel
Bladder	606	4759	0	0	0	0	0	0	0	0
Urine	0	0	0	0	0	0	0	0	0	0
Heart	0	0	157	0	5	0	0	0	0	0
Lung	0	0	5	11	31	0	0	3	12	0
Liver	0	0	0	1	642	17	0	3	1	1
Kidneys	0	0	0	0	5	4369	3	6	0	3
Spleen	0	0	0	0	0	73	299	22	0	0
Stomach	0	0	0	1	7	50	10	1228	7	0
S. Bowel	0	0	0	0	5	30	0	2	1281	69
L. Bowel	0	0	0	0	2	20	0	0	20	3846
Bone	0	0	0	0	0	0	0	0	0	0
Marrow	0	0	0	0	0	0	0	0	0	0
Brain	0	0	0	0	0	0	0	0	0	0
Pancreas	0	0	0	0	0	62	8	5	0	0
Tumor #1	0	0	0	0	0	0	0	0	0	0
Tumor #2	0	0	0	0	0	0	0	0	0	0
Feces	0	0	0	0	0	0	0	0	0	0
Tail	0	0	0	0	0	0	0	0	0	0
Blood	1	11	0	2	3	4	0	0	8	1
Muscle	0	2	0	0	1	1	0	0	1	0
Carcass	1	3	0	0	1	1	0	0	2	0

Table A4 continued Lu-177 Dose (mGy per mCi Injected)

					Source						
Target	Bone	Marrow	Brain	Pancreas	Tumor #1	Tumor #2	Feces	Tail	Blood	Muscle	Carcass
Bladder	0	0	0	0	0	0	0	0	0	0	21
Urine	0	0	0	0	0	0	0	0	0	0	0
Heart	0	0	0	0	0	0	0	0	0	0	2
Lung	0	0	0	0	0	0	0	0	0	0	12
Liver	0	0	0	0	0	0	0	0	0	0	1
Kidneys	0	0	0	89	0	0	0	0	0	0	0
Spleen	0	0	0	421	0	0	0	0	0	0	1
Stomach	0	0	0	82	0	0	0	0	0	0	1
S. Bowel	0	0	0	0	0	0	77	0	0	0	2
L. Bowel	0	0	0	0	0	0	203	0	0	0	1
Bone	101	0	0	0	0	0	0	0	0	0	7
Marrow	273	0	0	0	0	0	0	0	0	0	0
Brain	0	0	128	0	0	0	0	0	0	0	0
Pancreas	0	0	0	4924	0	0	0	0	0	0	0
Tumor #1	0	0	0	0	15271	0	0	0	0	0	1
Tumor #2	0	0	0	0	0	10149	0	0	0	0	1
Feces	0	0	0	0	0	0	67482	0	0	0	0
Tail	0	0	0	0	0	0	0	0	0	0	0
Blood	2	0	0	3	99	66	0	0	4	1	538
Muscle	0	0	0	0	16	10	0	0	1	0	85
Carcass	1	0	0	1	27	18	0	0	1	0	147