UNIVERSITY OF GOTHENBURG

Biodistribution of free ^{125}I, ^{131}I and ^{211}At in rats

M.Sc. THESIS

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GOTHENBURG, SWEDEN

June 16, 2010

Abstract

^{125}I, ^{131}I and ^{211}At are all members of the group of elements known as halogens, therefore they share chemical properties. ^{131}I is widely used in clinical applications and ^{125}I and ^{211}At are often used in *in vitro* studies and research. It is important to know the dose response in normal tissue for these radionuclides in order to determine potential risk organs when treating tumors in humans. To determine the dose response requires a known biodistribution of accumulated activities for these radionuclides and tissues. The aim of this project was to study and compare the biodistribution of ^{125}I, ^{131}I and ^{211}At in an animal model and to determine absorbed doses from all three radionuclides to various organs and tissues. Male Sprague Dawley rats were injected with ^{125}I and ^{131}I simultaneously and ^{211}At and sacrificed after 1, 6, 18, 24, 72 hours or 7 days for the iodine study and after 1, 5, 18 or 24 hours for the study on astatine. The animals received between 140 and 340 kBq of radioiodine and between 50 and 180 kBq of astatine per rat. Radioactivity measurements were performed on thyroid gland, salivary glands, blood, lung, heart, liver, kidney, stomach, muscle (from neck), brain, large intestine, small intestine and spleen and uptake as %IA and %IA/g was calculated. A study of absorbed doses to the organs and tissues was also performed. Results show a maximum accumulation of radioiodine of 13 %IA for ^{125}I and 14 %IA for ^{131}I. These activity concentrations were found in the thyroid gland 18 hours after injection. Only the thyroid was found to selectively accumulate iodine. Results for ^{211}At show a maximum thyroid activity concentration of 2.4 %IA after 18 hours. Measured activity concentrations for other organs and tissues were higher in general for ^{211}At compared to ^{125}I and ^{131}I. The absorbed dose per unit injected activity to the thyroid was calculated to 2700 mGy/MBq for ^{125}I and $1.3 \cdot 10^5$ mGy/MBq for ^{131}I after 7 days and $1.8 \cdot 10^4$ mGy/MBq for ^{211}At after 24 hours. Results show that the biodistribution of ^{211}At are different to that of ^{125}I and ^{131}I. Further studies are needed to properly investigate the biodistribution of ^{125}I, ^{131}I and free ^{211}At in thyroid and other normal tissue in rats. This is important for the research on thyroid disorder treatments as well as studies on thyroid stunning, due to the fact that, to our knowledge, only one paper [12] (from 1953) has presented biodistribution data from radioiodine and ^{211}At in rats. These further studies should be based on the results in this work, with a few changes.

Sammanfattning

^{125}I, ^{131}I och ^{211}At är alla medlemmar av den grupp av grundämnen som kallas halogener. På grund av detta har de liknande kemiska egenskaper. ^{131}I används ofta för kliniska tillämpningar, och ^{125}I och ^{211}At används ofta i *in vitro* studier och forskning. Det är viktigt att veta dos-responsen för normalvävnad för dessa radionuklider för att kunna bestämma potentiella riskorgan vid behandling av tumörer i människa. För att bestämma dos-responsen behövs en känd biodistribution av ackumulerade aktiviteter för dessa radionuklider och vävnader. Målet med detta arbete var att studera och jämföra biodistributionen av ^{125}I, ^{131}I och ^{211}At i en djurmodell samt att bestämma absorberade doser från samtliga tre radionuklider till diverse organ och vävnader. Sprague Dawley hanråttor injicerades med ^{125}I och ^{131}I samtidigt och även ^{211}At och offrades efter 1, 6, 18, 24, 72 timmar eller 7 dagar i jodstudien och efter 1, 5, 18 eller 24 timmar i studien för ^{211}At. Djuren gavs mellan 140 och 340 kBq radioaktivt jod och mellan 50 och 180 kBq ^{211}At per råtta. Radioaktivitetsmätningar genomfördes på thyroidea, spottkörtlar, blod, lunga, hjärta, lever, njure, ventrikel, muskel (från nacke), hjärna, tjocktarm, tunntarm och mjälte och upptag i form av %IA och %IA/g beräknades. En studie av absorberade doser till organ och vävnader genomfördes också. Resultaten visar en maximal ackumulering av radioaktivt jod på 13 %IA för ^{125}I och 14 %IA för ^{131}I. Dessa aktivitetskoncentrationer hittades I thyroidea 18 timmar efter injicering. Endast thyroidea visade selektivt upptag av jod. Resultaten för ^{211}At visar en maximal thyroideaaktivitetskoncentration på 2.4 %IA efter 18 timmar. Uppmätta aktivitetskoncentrationer för andra organ och vävnader var generellt högre för ^{211}At jämfört med ^{125}I och ^{131}I. Den absorberade dosen per enhet injicerad aktivitet till thyroidea beräknades till 2700 mGy/MBq för ^{125}I och $1.3 \cdot 10^5$ mGy/MBq för ^{131}I efter 7 dagar och $1.8 \cdot 10^4$ mGy/MBq för ^{211}At efter 24 timmar. Resultaten visar att biodistributionen av ^{211}At skiljer sig från den för ^{125}I och ^{131}I. Fortsatta studier är nödvändiga för att ordentligt utreda biodistributionen av ^{125}I, ^{131}I och fritt ^{211}At i thyroidea och annan normalvävnad i råtta. Detta är viktigt för forskningen på behandlingsmetoder för thyroideasjukdomar tillika studier på thyroideastunning, eftersom det, så vitt vi vet, endast en artikel [12] (från 1953) har presenterat biodistributionsdata från radioaktivt jod och ^{211}At i råttor. Dessa fortsatta studier bör vara baserade på resultaten I detta arbete, med några ändringar.

Contents

1 Introduction

Radioiodine has long been a radionuclide of use for medical purposes. There are several isotopes of radioiodine and only ^{127}I is stable. ^{131}I is the radionuclide most widely used for treatment of various thyroid disorders such as hyperthyroidism and thyroid cancer. This is due to the fact that iodide mainly accumulates in the thyroid gland, but also since ^{131}I has decay properties favorable for treatment. ^{131}I disintegrates by β^- decay to ^{131}Xe and the energy is mostly absorbed locally (the maximum β range in tissue is about 2 mm [1]), which minimizes doses to nearby organs and tissues. The half life of ^{131}I (8.0 days) also insures a realistic treatment time. In addition, ^{131}I also emits γ-radiation [2], which makes it possible to measure the uptake using a γ-counter.

^{125}I is mostly used in research and *in vitro* studies, this on account of the longer half life of 59 days [3] which makes it a simpler isotope to work with over longer periods of time. This however, along with less favorable decay properties, makes it less suitable for clinical applications.

Astatine is the heaviest of the halogens, the chemical group also containing iodine; therefore these both elements share chemical properties. There are no stable isotopes of astatine, however both ^{210}At and ^{211}At decay with a half time of 8.1 and 7.2 hours, respectively [4, 5]. Due to the physical properties, ^{211}At is more suitable for radiation therapy. ^{211}At has a complex disintegration and emits α-particles which have a very short range in tissue compared to electrons.

The thyroid is an endocrine gland which consists of two lobes which are located on each side of the trachea, below the thyroid cartilage in the neck. The lobes are connected through the isthmus. One of the purposes of the thyroid is to produce two hormones: triiodothyronine (T3) and thyroxine (T4) which both contain iodine. These hormones are used in the body to *e.g.* regulate the metabolism and help the central nervous system so develop properly. Iodine is accumulated in the thyroid and stored there until released with the T3 and T4 hormones.

The thyroid gland can suffer from a number of different disorders, *e.g.* hyperthyroidism and thyroid cancer. Hyperthyroidism is a disorder where the thyroid overproduces T3 and T4 which disturbs the metabolism of the patient. This has effects on appetite, weight and body temperature.

Radioiodine is often used when treating these disorders to destroy thyroid tissue or tumor tissue. The thyroid uptake of iodine is highly individual and affects the amount of dose absorbed, and thus the result of the therapy. On account of this a small diagnostic quantity is often given prior to the therapeutic quantity, in order to determine the individual thyroid uptake. However, there are studies that demonstrate a phenomenon called thyroid stunning, which is an effect that reduces the ability of the thyroid to accumulate iodine, as a result of a previous irradiation. Due to this effect the therapeutic dose could be lowered owing to the administration of the diagnostic quantity.

Animal models are often used to test methods for treatment of diseases, *e.g.* hyperthyroidism and thyroid cancer, using radioactive substances marked with radioiodine or astatine. This is an important area of research in order to improve existing treatment methods. It is therefore important to know the dose response for normal tissue for these radionuclides in order to determine potential risk organs when treating tumors in humans. To determine the dose response requires a known biodistribution of accumulated activities for these radionuclides and tissues.

A known biodistribution is also necessary to study other phenomenon such as thyroid stunning. *In vivo* studies in animal models could here be used to potentially determine the effects of thyroid stunning on the efficiency of the treatment.

The biodistribution of radioiodine and ^{211}At has been studied in mice [8-11]. The results demonstrate clear differences between the radionuclides and show a higher accumulation of ^{211}At compared to radioiodine, in all organs and tissues except the thyroid. To our knowledge the biodistribution of ^{211}At in rats has been presented in only one paper, published in 1953 [12]. There is therefore a need to repeat such a study.

The purpose of this project was to study and compare the kinetics of ^{125}I, ^{131}I and ^{211}At in rats and to determine absorbed doses from all three radionuclides to various organs and tissues.

2 Materials and methods

Several experiments were performed on rats with the intention of studying the uptake of radioactive isotopes of iodine as well as astatine in various organs. All conditions were kept as constant as possible throughout the experiments, and the only variable modified was the time between injection and measurement, this in order to study the distribution of the activity at different times.

2.1 Animal model

The animals used in all studies were male Sprague Dawley rats weighing 180-210 g. These were delivered from Scanbur AB, Sollentuna, Sweden. The rats were kept in groups of 5 individuals per cage. Drinking water and autoclaved food were given *ad libitum*. For five days prior to injection the animals were given autoclaved food with reduced iodine content (0.05 ppm), at all other times it was regular autoclaved laboratory food. The studies were approved by the Ethics committee for Animal Research at University of Gothenburg.

2.2 Detectors

Radioactivity measurements made *ex vivo* on the rat organs were performed using a Wizard 1480 NaI (Tl) γ-counter, produced by Wallac, Finland, consisting of a 3" NaI (Tl) crystal, which has pre-installed protocols for various radionuclides.

Injected activities were established by performing measurements on the syringes prior to injection using a CRC-15 dose calibrator ion chamber, produced by Capintec, IA, USA, and also by measuring syringe remnants and batch solutions in the γ-counter.

2.3 Calibration

Calibrations were made to find the relationship between count rates and activity for the γ-counter using Eppendorf tubes filled with 30 µl radioactive solution, with varying activities. The same geometric conditions as in the *ex vivo* measurements was employed. This resulted in linear relationships between measured count rates and activity which were used to interpret the measured data. This was performed for ^{125}I and ^{131}I simultaneously and also for ^{211}At.

The calibration for the ion chamber was known and this detector was used as reference detector in the calibration of the γ-counter.

2.4 Measurement corrections

When performing measurements on ^{125}I and ^{131}I simultaneously the Compton spectra originating from the ^{131}I isotope is situated partially in the energy window for ^{125}I. This results in an overestimation of the pulses originating from ^{125}I; this spill-over factor was calculated to 12.4 %.

Efforts were also made to determine the dead-time properties of the γ-counter. This was accomplished by measuring activities ranging from 2 to 200 kBq using Eppendorf tubes filled with 30 µl radioactive solution for activities up to 50 kBq, 34 µl for the 100 kBq solutions and 67 µl for the 200 kBq solutions. The same geometric conditions as in the *ex vivo* measurements were used. This was performed for ^{125}I and ^{131}I simultaneously. No dead-time curve was produced for ^{211}At, since activities higher than those considered in the calibration were not expected owing to the, in this context, short half life of astatine.

A correction to counteract the effects of self attenuation in larger volumes was also determined for all three radionuclides used in the experiments.

The uptake in the organs or tissues was defined as the activity found in the measurement divided with the injected activity. On account of this, all measured activities were decay corrected back to the time of injection, in order to properly compare the two activities.

2.5 Administration and organ sampling

Radioactive solutions were prepared using sodium radioiodide dissolved in phosphate buffered saline (PBS, pH 7.2). ^{125}I was delivered from PerkinElmer, Boston, USA and ^{131}I was delivered from GE Healthcare, Braunschweig, Germany. ^{211}At was produced through the ^{209}Bi(α,2n)^{211}At reaction and delivered from the Cyclotron and PET Unit at Rigshospitalet in Copenhagen, Denmark. The extraction procedure of the 211At has previously been presented [13]. The syringes were weighed individually before and after adding the solution, and also after injection, to determine the amount of radioactive solution administered. The syringes were also measured before and after injection in the ion chamber, and after injection in the γ-counter.

2.5.1 Absorbed dose calculations

The absorbed dose to the various organs and tissues from the different radionuclides was calculated using equation 1.

$$D = \tilde{A} \cdot E \cdot \frac{\emptyset}{m}, \qquad (1)$$

where $\tilde{A}$ is the cumulated activity in the organ, E is the mean emitted energy per disintegration, $\emptyset$ is the absorbed fraction and m is the mass of the organ.

$\tilde{A}$ was calculated from the data using equation 2.

$$\tilde{A} = C_i \cdot A_{inj}, \quad (2)$$

where A_{inj} is the injected activity and C_i is the time integral of the activity concentration in the organ or tissue, in terms of percent of A_{inj}, from injection time to the dose determination time.

On account of the short range of α- and β-particles compared to the size of most of the rat organs, the self-absorbed fraction was set to 1.0, and the cross-absorbed fraction was set to 0 for all organs for all three radionuclides.

2.5.2 Biodistribution of ^{125}I and ^{131}I

The rats were divided into two study groups. The first study comprised of 30 animals which were divided into six groups with five animals in each group. These were injected intravenously with iodine isotopes ^{125}I and ^{131}I in iodide form. Injected activities (A_{inj}) can be seen in table 1.

Table 1: Injected activities for animals in study 1.

Group	A_{inj} (^{125}I) [kBq]	A_{inj} (^{131}I) [kBq]
1 hour	240-325	215-320
6 hours	303-335	288-326
18 hours	139-174	113-172
24 hours	218-270	207-282
3 days	171-184	263-282
7 days	171-191	263-301

The rats were sacrificed 1, 6, 18, 24, 72 hours or 7 days after injection. Radioactivity measurements were made *ex vivo* on throat (including thyroid), salivary glands, blood, lung, heart, liver, kidney, stomach, muscle from neck, brain, large intestine, small intestine and spleen. Uptake in terms of percent of injected activity per organ (%IA) and percent of injected activity per gram (%IA/g) were calculated. For the blood 0.5-1 ml per animal was taken. The measurements were then corrected to concern the total blood volume of the animal, which was determined using an approximation (see equation 3) [14].

$$V_{Blood} = 0.06 \cdot M_{Body} + 0.77 \quad (3)$$

Where M_{Body} is the body weight in grams. When calculating the %IA/g for the throat (including thyroid) it was assumed that the throat had no uptake of iodine and the weight used in this calculation was therefore the mean weight of the thyroids collected in the biodistribution of ^{211}At.

2.5.3 Absorbed doses from ^{125}I and ^{131}I

^{131}I disintegrates by β^- decay to ^{131}Xe with a mean energy of 190 keV per disintegration, it also emits γ-radiation with a mean energy of 381 keV per disintegration which makes it possible to measure the uptake using a γ-counter.

^{125}I decays to ^{125}Te by electron capture and emits electron and photon radiations with the mean energy of 16.6 and 42.3 keV per disintegration, respectively [3].

Absorbed doses per unit injected activity were calculated using equation 1. E was assumed to include only the electrons emitted by the radio-iodine isotopes and was therefore set to 190 keV/Bq·s for ^{131}I [2] and 16.6 keV/Bq·s for ^{125}I [3]. For dose calculations on thyroids containing radioiodine the mean weight of the thyroids collected in the biodistribution of ^{211}At was used as m.

2.5.4 Biodistribution of ^{211}At

The second study group involved 20 animals. These were divided into four groups with five animals in each group and injected with free ^{211}At. Injected activities (A_{inj}) can be seen in table 2.

Table 2: Injected activities for animals in study 2.

Group	A_{inj} (^{211}At) [kBq]
1 hour	114-169
5 hours	135-179
18 hours	52-65
24 hours	110-165

The rats were sacrificed 1, 6, 18, or 24 hours after injection. Measurements were made *ex vivo* on thyroid, salivary glands, blood, lung, heart, liver, kidney, stomach, muscle from neck, large intestine, small intestine and spleen. Uptake in terms of percent per organ and percent per gram were then calculated. For the blood 1 ml per animal was taken. The measurements were then corrected to concern the total blood volume of the animal, using equation 3.

2.5.5 Absorbed doses from ^{211}At

^{211}At has a complex disintegration and decays by α-disintegration to ^{207}Bi with a mean energy of 2.5 MeV per disintegration, and by electron capture to ^{211}Po [5]. ^{207}Bi and ^{211}Po are also radioactive and must be considered when calculating doses from ^{211}At. ^{207}Bi disintegrates by electron capture and β^+-decay to ^{207}Pb and emits electron and photon radiations with the mean energy of 0.11 and 1.54 MeV per disintegration, respectively [6]. ^{211}Po has a half life of 0.516 seconds and disintegrates by α-decay to ^{207}Pb with a mean energy of 7.58 MeV per disintegration [7].

Absorbed doses per unit injected activity were calculated using equation 1. For ^{211}At E was assumed to concern only the α-disintegrations and was calculated from the complex disintegration of ^{211}At and ^{211}Po to 6910 keV/Bq·s [5, 7].

2.5.6 Statistical analysis

The statistical uncertainties in the measurements are represented by SEM (standard error of the mean). SEM is calculated using equation 4.

$$SEM_{\bar{x}} = \frac{s}{\sqrt{n}} = \frac{\sqrt{\frac{1}{n-1}\sum_{i=1}^{n}(x_i - \bar{x})^2}}{\sqrt{n}}, \quad (4)$$

where s is the sample standard deviation, n is the number of samples in the group, $\{x_1, x_2, \ldots, x_n\}$ are the observed values of the sample items, and $\bar{x}$ is the mean value of these observations.

3 Results

3.1 Measurement corrections

The results from the calibration and dead-time measurements are shown in figure 1 for ^{125}I. The black line shows the linear relationship between count rates and activity. The response can be considered to be linear up to about 20 000 counts/s. Count rates obtained above this value (up to 25 000 counts/s) were corrected using the linear approximation shown by the red line, generated from the measurements on 20 and 50 kBq.

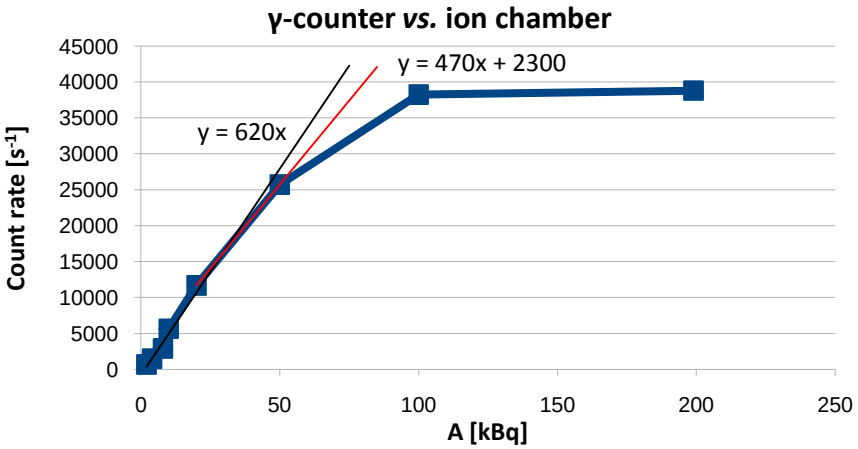

Figure 1: The relationship between count rate measured by the γ-counter and activity determined by the ion chamber for ^{125}I. Black line shows activity calibration, red line shows linear approximation between 20 and 50 kBq.

Figure 2 shows the results from the calibration and dead-time measurements on ^{131}I. The black line shows the linear relationship between count rates and activity. The response can be considered to be linear up to about 7000 counts/s. Count rates obtained above this value (up to 15 000 counts/s) were corrected using the linear approximation shown by the red line, generated from the measurements on 8, 20 and 50 kBq.

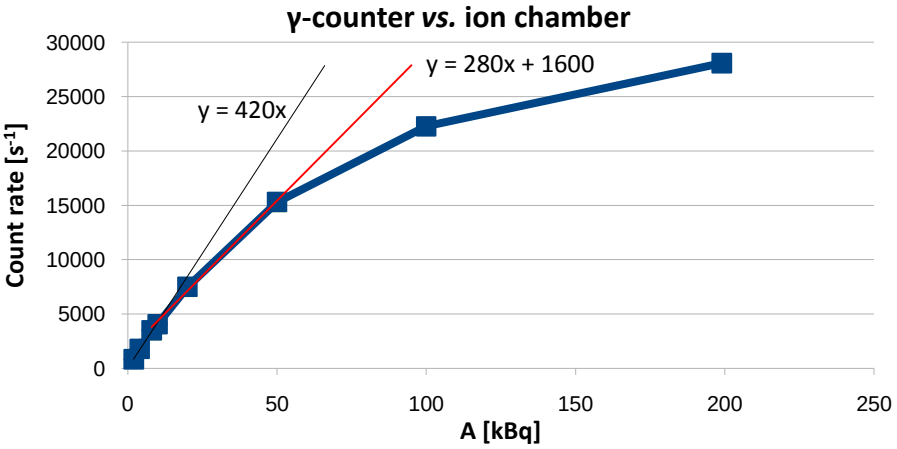

Figure 2: The relationship between count rate measured by the γ-counter and activity determined by the ion chamber for ^{131}I. Black line shows calibration, red line shows linear approximation between 8 and 50 kBq.

The calibration for ^{211}At is shown in figure 3. The black line shows the linear relationship between count rates and activity.

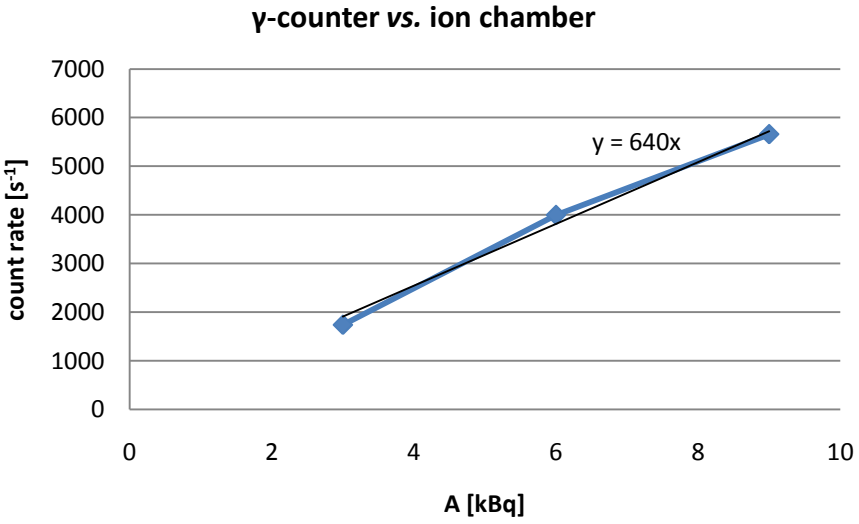

Figure 3: The relationship between count rate measured by the γ-counter and activity determined by the ion chamber for ^{211}At.

Figure 4 shows the volume correction curve obtained for ^{125}I, ^{131}I and ^{211}At as a function of the sample volume. Values are given in relation to the measurement obtained for 30 µl.

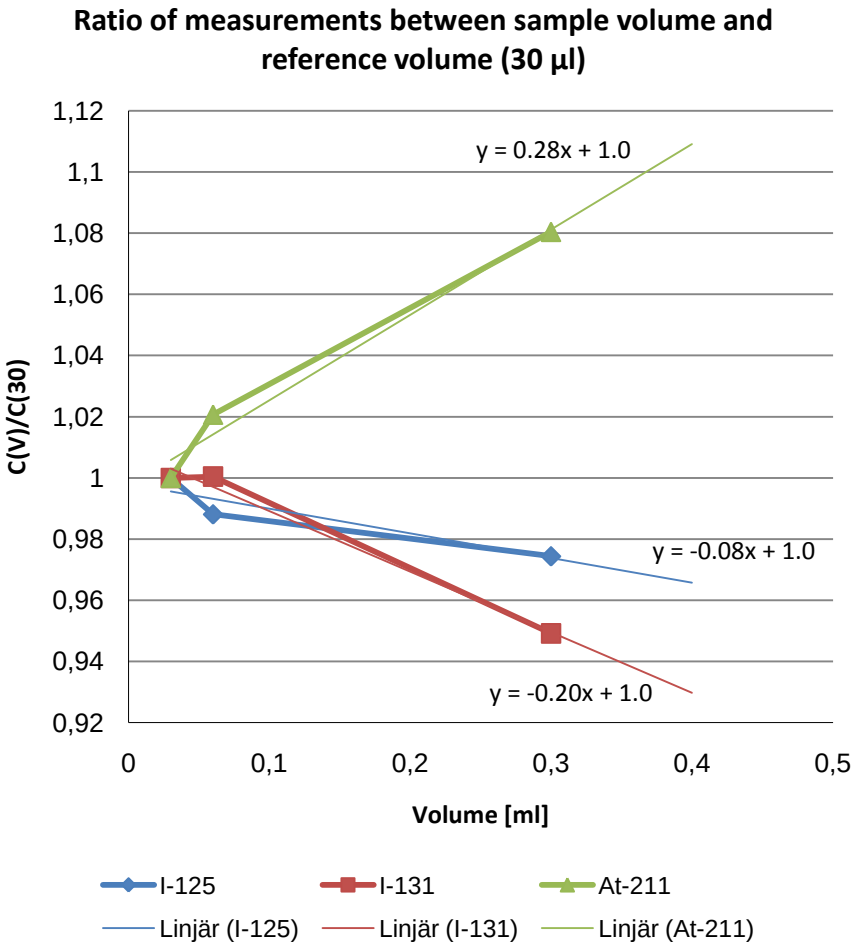

Figure 4: The ratio between count rate obtained for different sample volumes and count rate obtained for 30 µl samples for ^{125}I, ^{131}I and ^{211}At.

3.2 Biodistribution of ^{125}I and ^{131}I

Figure 5 shows the uptake of ^{125}I and ^{131}I per organ for throat (including thyroid), blood and stomach. Each bar represents the mean uptake of five animals. Error-bars show ±SEM of the mean uptake value (n=5). The throat (including thyroid) had a maximum uptake of 13 %IA for ^{125}I and 14 %IA for ^{131}I, both registered for the 18 hour group. The blood had a maximum uptake of 7.2 %IA for ^{125}I and 7.5 %IA for ^{131}I, both registered for the 1 hour group. The stomach had a maximum uptake of 2.2 %IA for ^{125}I at 6 hours and 2.2 %IA for ^{131}I at 1 hour.

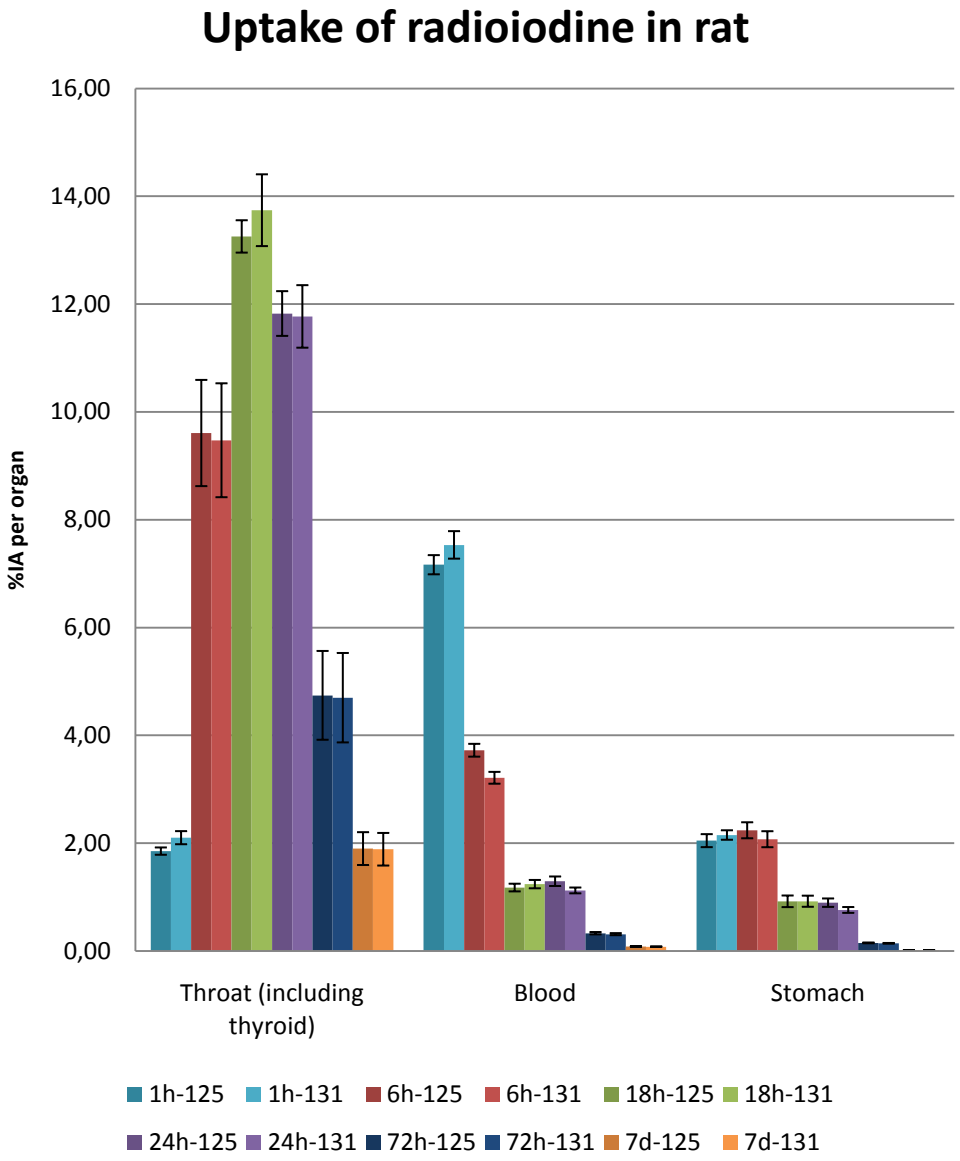

Figure 5: The percentage uptake of radioiodine per organ for throat (including thyroid), blood and stomach. Bars show mean values ±SEM, n=5.

Figure 6 shows the uptake of ^{125}I and ^{131}I per organ for salivary glands, lung, heart, liver, kidney, muscle, brain, large intestine, small intestine and spleen. Each bar represents the mean uptake of five animals. Error-bars show ±SEM of the mean uptake value (n=5). For ^{125}I the maximum uptake was 0.09 %IA for salivary glands, 0.26 %IA for lung, 0.12 %IA for heart, 0.37 %IA for liver, 0.29 %IA for kidney, 0.04 %IA for muscle, 0.03 %IA for brain, 0.08 %IA for large intestine, 0.09 %IA for small intestine and 0.18 %IA for spleen. These were registered at 6 hours for muscle and small intestine, and at 1 hour for salivary glands, lung, heart, liver, kidney, brain, large intestine and spleen. For ^{131} the maximum uptake was 0.09 %IA for salivary glands, 0.28 %IA for lung, 0.12 %IA for heart, 0.38 %IA for liver, 0.25 %IA for kidney, 0.04 %IA for muscle, 0.03 %IA for brain, 0.09 %IA for large intestine, 0.25 %IA for small intestine and 0.19 %IA for spleen. These were registered at 6 hours for muscle and small intestine, and at 1 hour for salivary glands, lung, heart, liver, kidney, brain, large intestine and spleen.

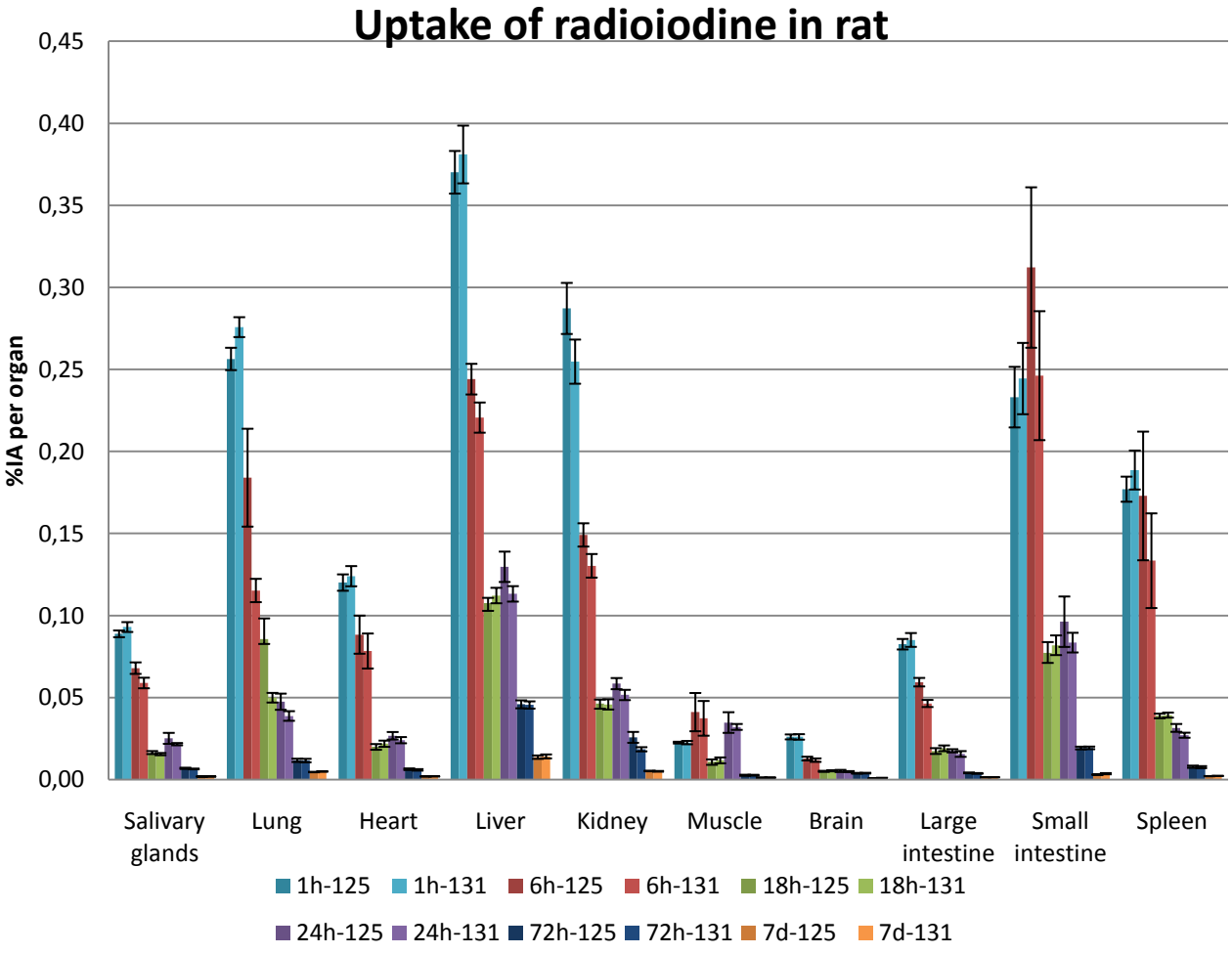

Figure 6: The percentage uptake of radioiodine per organ for salivary glands, blood, lung, heart, liver, kidney, muscle, brain, large intestine, small intestine and spleen. Bars show mean values ±SEM, n=5.

Figure 7 shows the uptake of ^{125}I and ^{131}I per gram of tissue for thyroid and stomach. Each bar represents the mean uptake of five animals. Error-bars show ±SEM of the mean uptake value (n=5). The thyroid had a maximum uptake of 350 %IA/g for ^{125}I and 370 %IA/g for ^{131}I, both registered for the 18 hour group. The stomach had a maximum uptake of 1.5 %IA/g for ^{125}I and 1.4 %IA/g for ^{131}I, both registered at 1 hour.

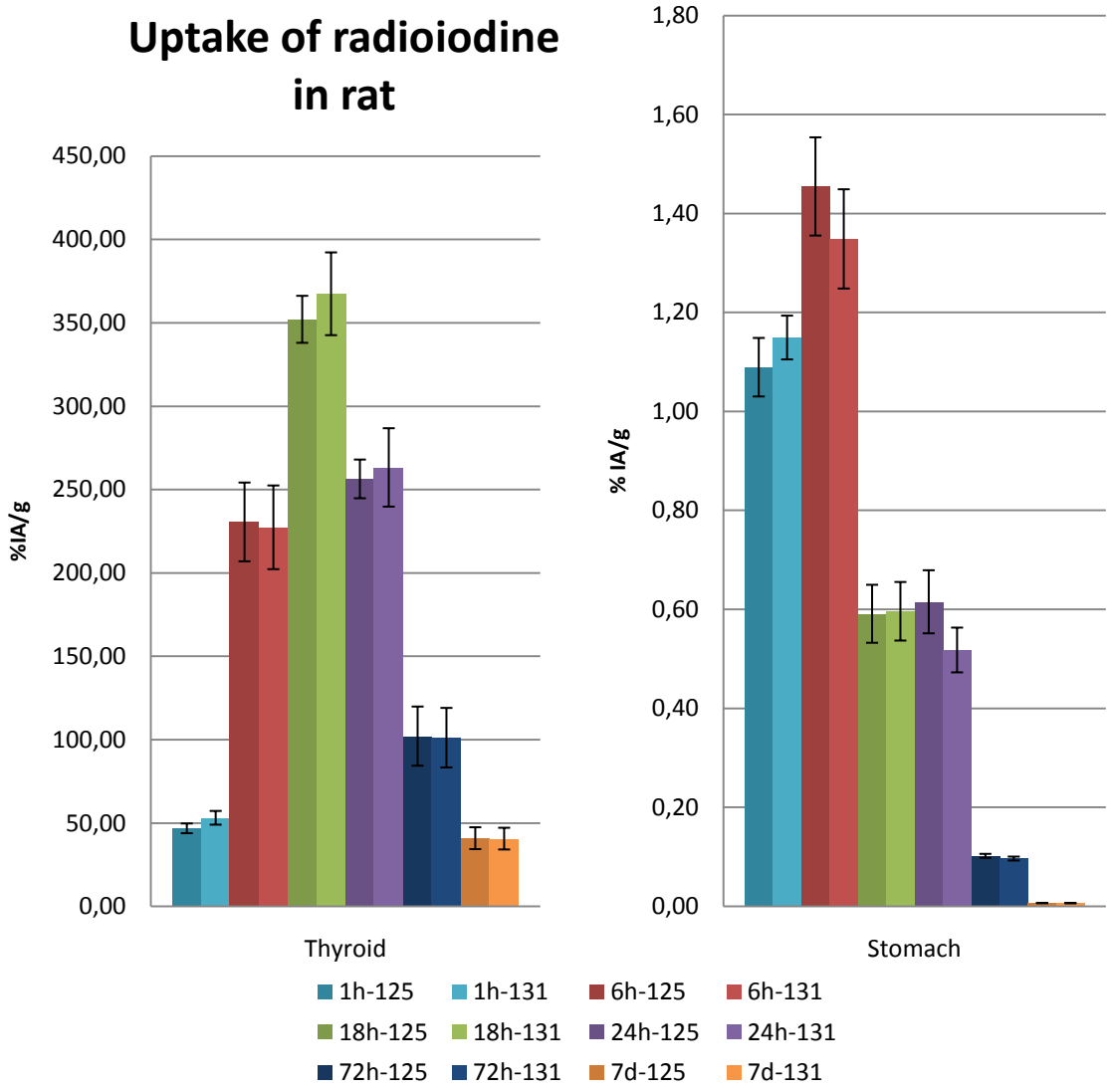

Figure 7: The percentage uptake of radioiodine per gram for throat and stomach. Bars show mean values ±SEM, n=5.

Figure 8 shows the uptake of ^{125}I and ^{131}I per gram of tissue for salivary glands, blood, lung, heart, liver, kidney, muscle, brain, large intestine, small intestine and spleen. Each bar represents the mean uptake of five animals. Error-bars show ±SEM of the mean uptake value (n=5). For ^{125}I the maximum uptake was 0.19 %IA/g for salivary glands, 0.42 %IA/g for blood,

0.28 %IA/g for lung, 0.15 %IA/g for heart, 0.17 %IA/g for liver, 0.30 %IA/g for kidney, 0.15 %IA/g for muscle, 0.02 %IA/g for brain, 0.22 %IA/g for large intestine, 0.36 %IA/g for small intestine and 0.24 %IA/g for spleen. These were registered at 6 hours for muscle, small intestine and spleen, and at 1 hour for salivary glands, lung, heart, liver, kidney, brain and large intestine. For ^{131}I the maximum uptake was 0.20 %IA/g for salivary glands, 0.45 %IA/g for blood, 0.31 %IA/g for lung, 0.15 %IA/g for heart, 0.18 %IA/g for liver, 0.26 %IA/g for kidney, 0.14 %IA/g for muscle, 0.02 %IA/g for brain, 0.22 %IA/g for large intestine, 0.29 %IA/g for small intestine and 0.21 %IA/g for spleen. These were registered at 6 hours for muscle and small intestine, and at 1 hour for salivary glands, lung, heart, liver, kidney, brain, large intestine and spleen.

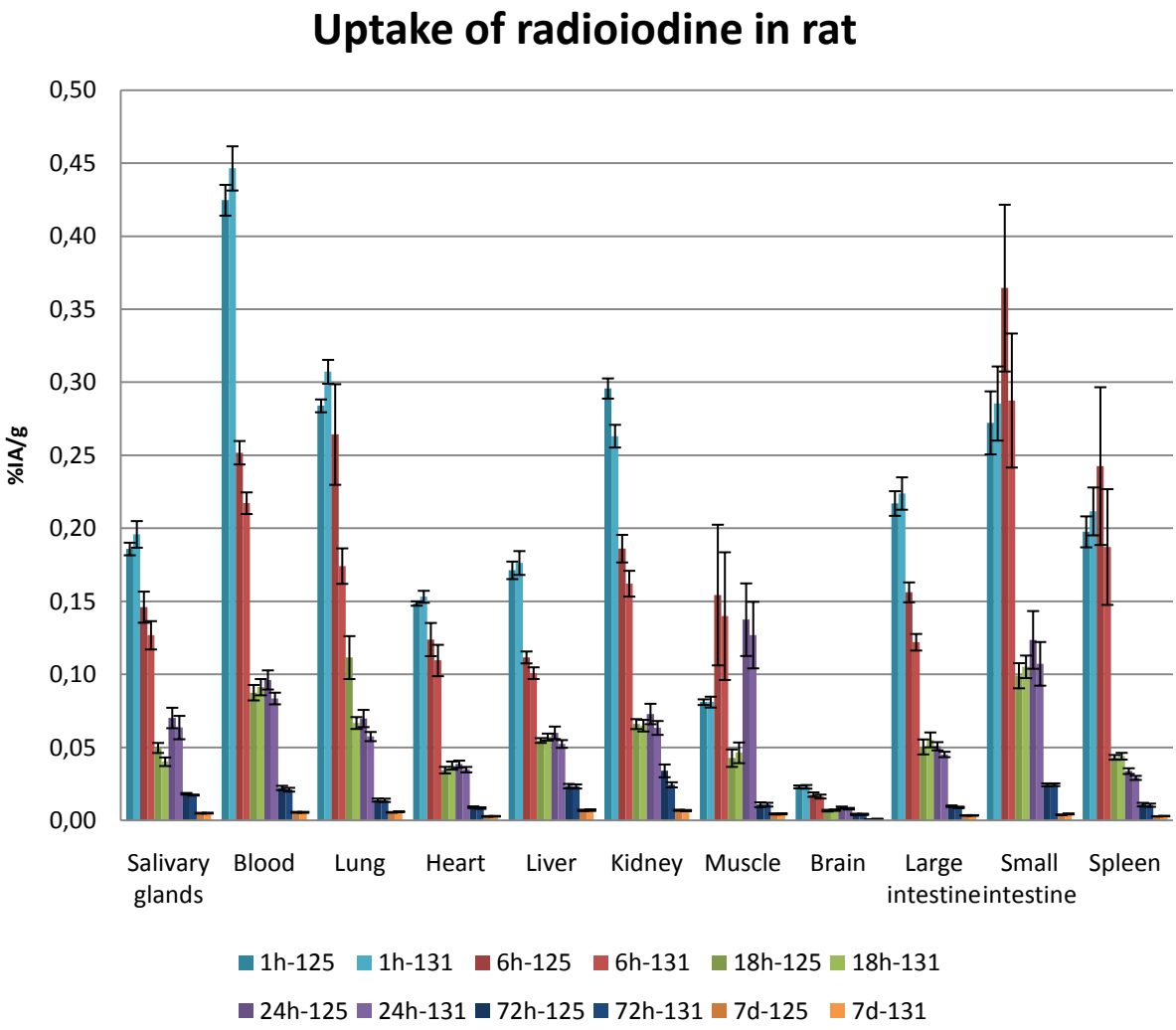

Figure 8: The percentage uptake of radioiodine per gram for salivary glands, blood, lung, heart, liver, kidney, muscle, brain, large intestine, small intestine and spleen. Bars show mean values ±SEM, n=5.

3.3 Absorbed doses from ^{125}I and ^{131}I

Table 3 shows the absorbed doses per unit injected activity as mGy/MBq for ^{125}I after different irradiation times for thyroid, salivary glands, blood, lung, heart, liver, kidney, stomach, muscle, brain, large intestine, small intestine and spleen. The maximum absorbed dose for a specific organ or tissue was found for the thyroid gland (2700 mGy/MBq) after 7 days.

Table 3: The absorbed doses per unit injected activity as Gy/MBq for ^{125}I per organ at different times after injection for thyroid, salivary glands, blood, lung, heart, liver, kidney, stomach, muscle, brain, large intestine, small intestine and spleen.

^{125}I [mGy/MBq]	1 hour	6 hours	18 hours	24 hours	72 hours	7 days
Thyroid	2.7	86	480	700	1800	2700
Salivary glands	0.01	1.4	18	18	18	18
Blood	0.47	1.6	2.6	3.5	7.7	26
Lung	0.02	3.0	6.2	6.3	6.5	6.6
Heart	0.01	0.20	0.47	0.50	0.66	0.74
Liver	0.01	0.07	0.15	0.20	0.48	0.67
Kidney	0.02	0.24	0.53	0.58	0.89	1.1
Stomach	0.08	0.85	1.3	1.7	3.5	4.1
Muscle	0.00	0.07	5.6	5.7	6.1	6.1
Brain	0.00	0.01	0.04	0.04	0.06	0.08
Large intestine	0.01	0.06	0.11	0.14	0.27	0.33
Small intestine	0.02	0.21	0.32	0.39	0.77	0.92
Spleen	0.01	0.15	0.44	0.47	0.60	0.67

Table 4 shows the absorbed doses per unit injected activity as mGy/MBq for ^{131}I after different irradiation times for thyroid, salivary glands, blood, lung, heart, liver, kidney, stomach, muscle, brain, large intestine, small intestine and spleen. The maximum absorbed dose for a specific organ or tissue was found for the thyroid ($1.3 \cdot 10^5$ mGy/MBq) after 7 days.

Table 4: The absorbed doses per unit injected activity as Gy/MBq for ^{131}I per organ at different times after injection for thyroid, salivary glands, blood, lung, heart, liver, kidney, stomach, muscle, brain, large intestine, small intestine and spleen.

^{131}I [Gy/MBq]	1 hour	6 hours	18 hours	24 hours	72 hours	7 days
Thyroid	170	4900	$2.7 \cdot 10^4$	$3.9 \cdot 10^4$	$9.6 \cdot 10^4$	$1.3 \cdot 10^5$
Salivary glands	0.75	88	990	990	1000	1000
Blood	28	82	140	190	380	1300
Lung	1.3	180	330	330	340	350
Heart	0.75	11	21	23	31	34
Liver	0.74	4.0	8.2	11	24	32
Kidney	1.2	13	28	31	45	53
Stomach	4.6	40	66	85	160	180
Muscle	0.28	4.0	190	200	210	220
Brain	0.07	0.56	2.0	2.1	3.2	4.2
Large intestine	0.62	3.2	5.8	7.2	13	16
Small intestine	0.99	11	17	21	38	45
Spleen	0.75	8.2	21	23	29	31

3.4 Biodistribution of ^{211}At

Figure 9 shows the uptake of ^{211}At per organ for thyroid and stomach. Each bar represents the mean uptake of five animals. Error-bars show ±SEM of the mean uptake value (n=5). The thyroid had a maximum uptake of 2.4 %IA at 18 hours. The stomach had a maximum uptake of 5.5 %IA at 18 hours.

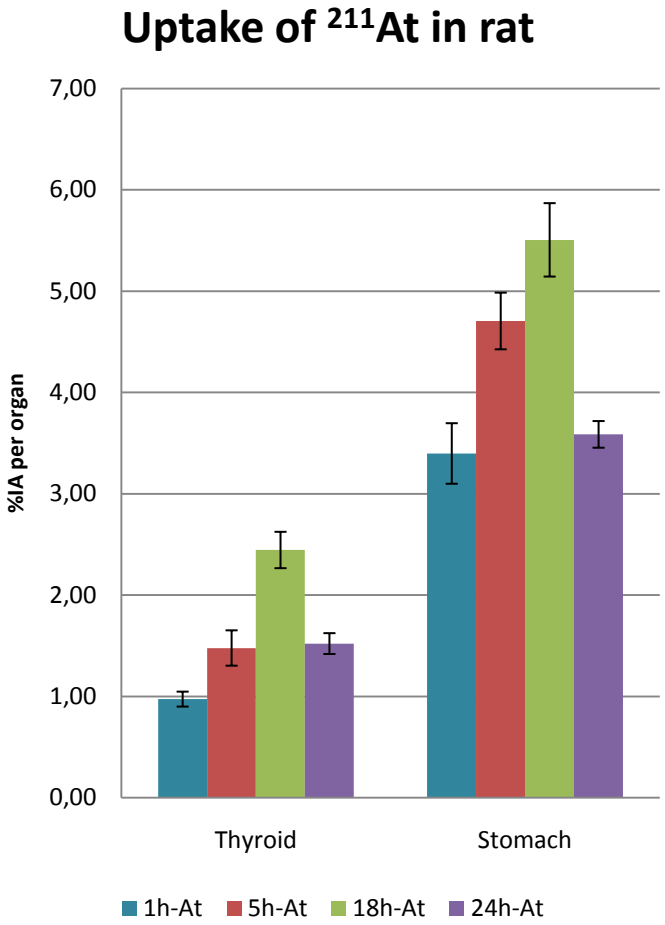

Figure 9: The percentage uptake of astatine per organ for throat and stomach. Bars show mean values ±SEM, n=5.

Figure 10 shows the uptake of ^{211}At per organ for blood and liver. Each bar represents the mean uptake of five animals. Error-bars show ±SEM of the mean uptake value (n=5). The blood had a maximum uptake of 24 %IA. The liver had a maximum uptake of 11 %IA. Both registered for the 1 hour group.

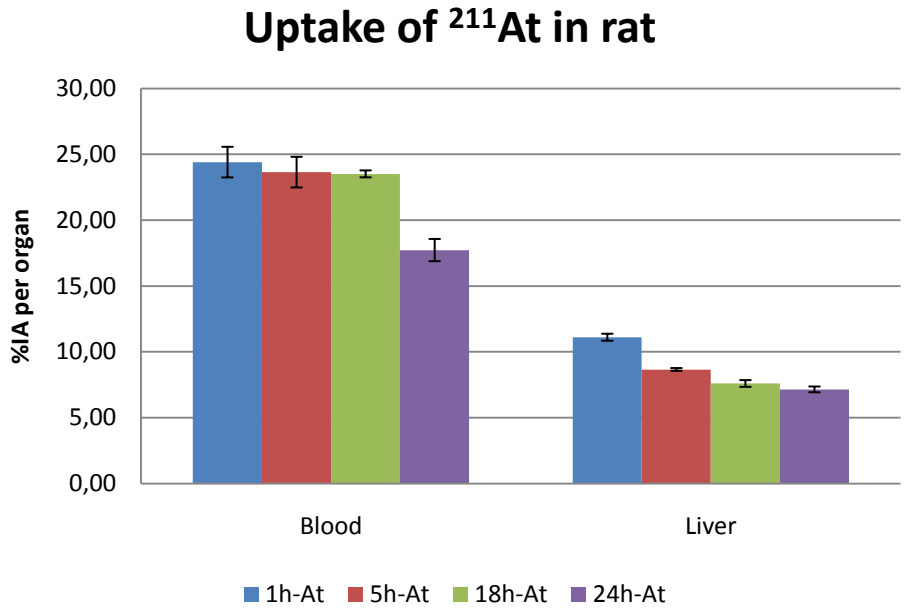

Figure 10: The percentage uptake of astatine per organ for blood and liver. Bars show mean values ±SEM, n=5.

Figure 11 shows the uptake of ^{211}At per organ for salivary glands, lung, heart, kidney, muscle, large intestine, small intestine and spleen. Each bar represents the mean uptake of five animals. Error-bars show ±SEM of the mean uptake value (n=5). The maximum uptake of ^{211}At was 0.36 %IA for salivary glands, 2.1 %IA for lung, 0.30 %IA for heart, 0.82 %IA for kidney, 0.16 %IA for muscle, 0.53 %IA for large intestine, 4.3 %IA for small intestine and 2.4 %IA for spleen. These were registered at 1 hour for salivary glands, lung, kidney and spleen and at 6 hours for heart, muscle, large intestine and small intestine.

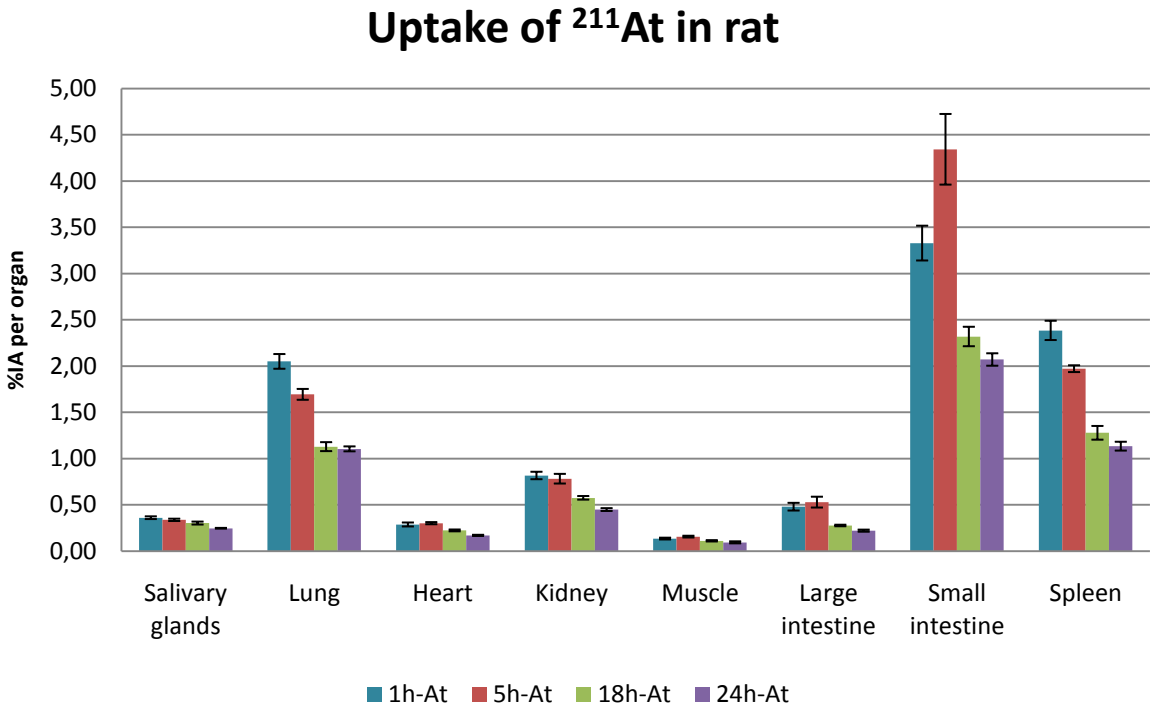

Figure 11: The percentage uptake of astatine per organ for salivary glands, blood, lung, heart, liver, kidney, muscle, large intestine, small intestine and spleen. Bars show mean values ±SEM, n=5.

Figure 12 shows the uptake of ^{211}At per gram for thyroid and stomach. Each bar represents the mean uptake of five animals. Error-bars show ±SEM of the mean uptake value (n=5). The thyroid had a maximum uptake of 77 %IA/g. The stomach had a maximum uptake of 2.9 %IA/g. Both registered for the 18 hour group.

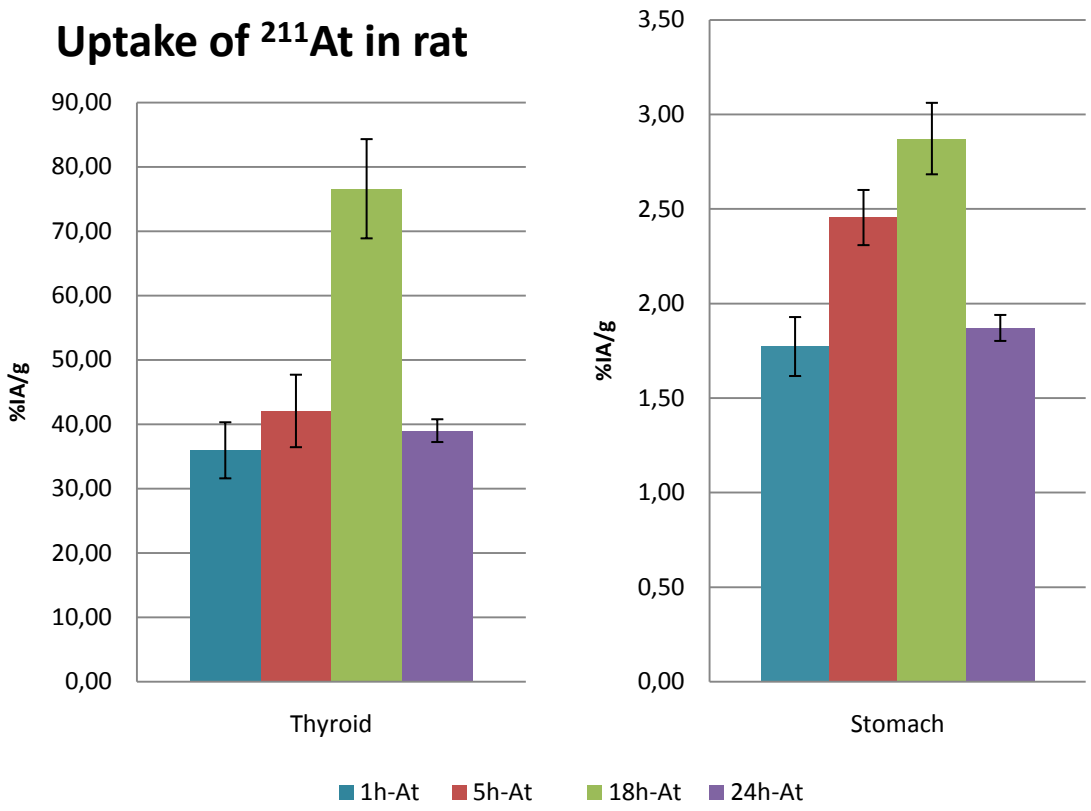

Figure 12: The percentage uptake of astatine per gram for throat and stomach. Bars show mean values ±SEM, n=5.

Figure 13 shows the uptake of ^{211}At per gram for salivary glands, blood, lung, heart, liver, kidney, muscle, large intestine, small intestine and spleen. Each bar represents the mean uptake of five animals. Error-bars show ±SEM of the mean uptake value (n=5). The maximum uptake of ^{211}At was 0.78 %IA/g for salivary glands, 0.31 %IA/g for blood, 2.1 %IA/g for lung, 0,42 %IA/g for heart, 0.39 %IA/g for liver, 0.73 %IA/g for kidney, 0.35 %IA/g for muscle, 0.62 %IA/g for large intestine, 1.3 %IA/g for small intestine and 2.7 %IA/g for spleen. These were registered at 1 hour for salivary glands, blood, lung, liver, kidney and spleen and at 6 hours for heart, muscle, large intestine and small intestine.

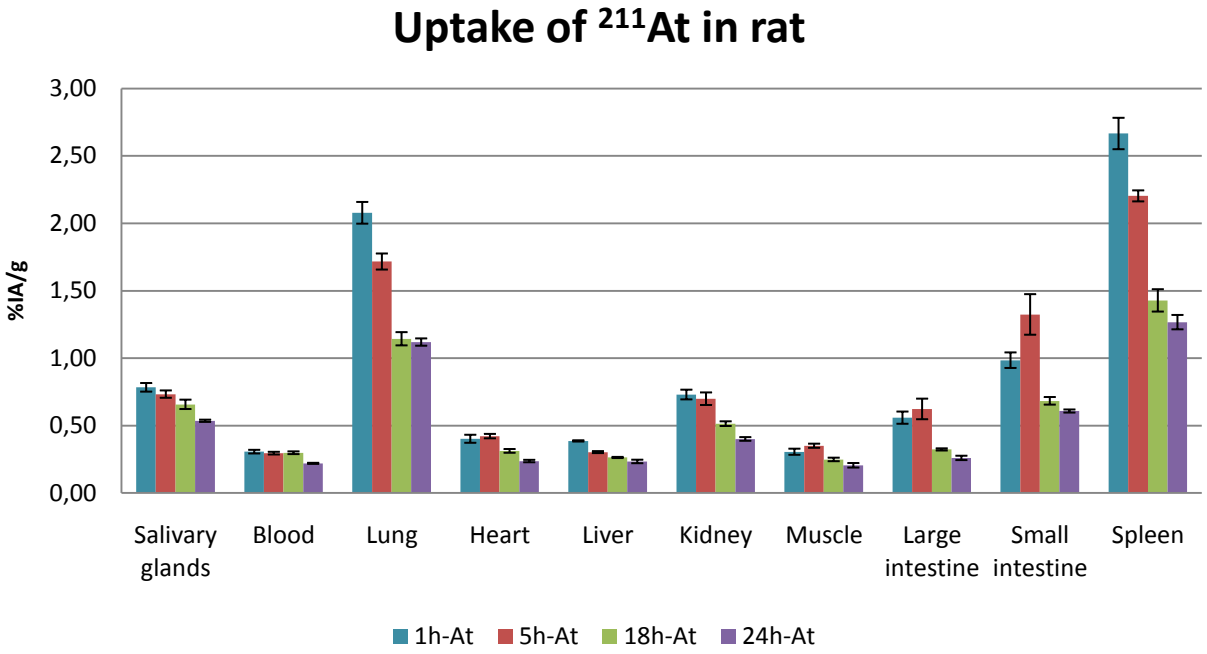

Figure 13: The percentage uptake of astatine per gram for salivary glands, blood, lung, heart, liver, kidney, muscle, large intestine, small intestine and spleen. Bars show mean values ±SEM, n=5.

3.5 Absorbed doses from ^{211}At

Table 5 shows the absorbed doses per unit injected activity as mGy/MBq for ^{211}At after different irradiation times for thyroid, salivary glands, blood, lung, heart, liver, kidney, stomach, muscle, brain, large intestine, small intestine and spleen. The maximum absorbed dose for a specific organ or tissue was found for the thyroid ($1.8 \cdot 10^4$ mGy/MBq) after 24 hours.

Table 5: The absorbed doses per unit injected activity as Gy/MBq for ^{211}At per organ at different times after injection for thyroid, salivary glands, blood, lung, heart, liver, kidney, stomach, muscle, large intestine, small intestine and spleen.

^{211}At [Gy/MBq]	1 hour	5 hours	18 hours	24 hours
Thyroid	530	4900	$1.5 \cdot 10^4$	$1.8 \cdot 10^4$
Salivary glands	19	140	340	370
Blood	97	740	1800	2000
Lung	63	450	1000	1000
Heart	12	91	220	240
Liver	140	1000	2200	2400
Kidney	26	200	460	490
Stomach	48	420	1200	1300
Muscle	11	91	230	250
Large intestine	23	190	450	470
Small intestine	89	770	2600	3000
Spleen	63	450	1300	1500

4 Discussion

Results from the biodistribution of ^{125}I and ^{131}I showed that salivary glands, blood, lung, heart, liver, kidney, brain, large intestine and spleen have a maximum activity concentration 1 hour after injection. The throat (including thyroid) had a maximum uptake 18 hours after injection (14 %IA, see figure 5). For stomach, muscle and small intestine the maximum uptake was found after 6 hours for both isotopes. This suggests that the throat (including thyroid), stomach, muscle and small intestine selectively accumulate iodide. The measurements for muscle however decreased from 0.04 %IA at 6 hours to 0.01 %IA at 18 hours and then increased to 0.03 %IA at 24 hours (see figure 6). These fluctuations are, however, not statistically significant. For the stomach the SEM values between 1 and 6 hours overlap for both isotopes (see figure 5). This was also true for the small intestine for ^{131}I and for the spleen for ^{125}I (see figure 6). The measured %IA in blood for radioiodide may have been overestimated due to the synthesis and release of thyroxine (T_4) and triiodothyronine (T_3) by the thyroid gland into the blood, since these hormones contain iodine.

There was a difference in measured activity concentrations between ^{125}I and ^{131}I. This is most visible for the 6 hour group which appears to have a higher uptake of ^{125}I, and is evident for all organs and tissues (see figures 5 and 6). This most likely emanates from uncertainties in the determination of injected activities, which was limited to two significant figures. Another potential source is uncertainties in the volume correction, which was only measured up to 300 µl and extrapolated above this (see figure 4).

Two animals showed unexpectedly low activity concentrations of both ^{125}I and ^{131}I in the thyroid. These were found at 6 and 72 hours and resulted in high SEM values for these time points (see figures 5 and 6). No abnormalities could be found in the rat anatomy for these individuals, and the measured activity concentrations for other organs and tissues did not differ as unexpectedly. A possible reason for this is that the animals in question had a slow metabolic rate. The food intake of the animals was not monitored and might have had an effect on the amount of stable iodine accumulated in the thyroid prior to injection with radioiodide. Pre-studies not presented here, were performed without the reduced iodine diet. Results from these pre-studies showed similar unexpectedly low activity concentrations of radioiodide, but in a larger number of animals. The pre-studies also had a larger spread around the mean activity concentration found. On account of this it was decided to use the food with reduced iodine content, which seems to have reduced the effect but not made it disappear completely.

The results from the biodistribution of free ^{211}At showed that salivary glands, blood, lung, liver, kidney and spleen had a maximum activity concentration 1 hour after injection (see figures 10 and 11). The heart, muscle, large intestine and small intestine had a maximum uptake 6 hours after injection (see figures 10 and 11). For thyroid and stomach the maximum activity concentration was found after 18 hours (see figure 9). This suggests that the thyroid, heart, stomach, muscle, large intestine and small intestine selectively accumulate ^{211}At. For heart, muscle and large intestine however, the SEM values between the 1 hour and 6 hour groups overlap (see figure 11), making it difficult to determine whether the uptake is selective or not.

Compared to the biodistribution of radioiodide the maximum activity concentration of free ^{211}At in the thyroid was low (about one-fifth). For the other organs and tissues there was a higher accumulation of free ^{211}At than radioiodide in general. This suggests that free ^{211}At differs from radioiodine in terms of biodistribution.

The measurements on ^{211}At in different volumes showed that the count rate increases with the volume (see figure 4). This was not expected, on account of the self attenuation in larger volumes which according to theory should lead to a lesser amount of pulses reaching the detector. No explanation has been found for this.

Hamilton *et al.* [12] showed a maximum uptake in thyroid for ^{131}I and ^{211}At 24 hours after injection. The study was conducted on female Sprague-Dawley rats kept on standard laboratory chow. The maximum activity concentration of ^{131}I found in the thyroid was about two times lower in our study compared to that by Hamilton *et al.* [12] (14 %IA compared to 28 %IA). Similar relations were found for most of the other organs and tissues (excluding spleen which has a comparable maximum activity concentration). The animals studied here were given a much lower activity of ^{131}I compared those those studied by Hamilton *et al.* [12] (0.11-0.33 MBq compared to 1.37 MBq) which may affect the accumulation. No organs or tissues studied by Hamilton *et al.* [12] in excess of the thyroid gland showed a selective accumulation of radioiodide.

The maximum activity concentration of ^{211}At found by Hamilton *et al.* [12] was about one-tenth of the maximum concentration of radioiodide. The maximum activity concentration of ^{211}At in the thyroid in our study (at 18 hours) is similar to that found by Hamilton *et al.* [12] (at 24 hours), (2.4 %IA compared to 2.7 %IA). For the other organs and tissues Hamilton *et al.* [12] observed somewhat higher maximum activity concentrations in general. Only the thyroid gland and the stomach showed selective accumulation of ^{211}At.

Results from the absorbed dose calculations show that the thyroid receives the maximum absorbed dose per unit injected activity, for all three radionuclides. This was to be expected due to the high relative accumulation (350 %IA/g for ^{125}I, 370 %IA/g for ^{131}I and 77%IA/g for ^{211}At). The highest dose per unit injected activity to the thyroid was found for ^{131}I followed by ^{211}At ($3.9 \cdot 10^4$ mGy/MBq compared to $1.8 \cdot 10^4$ mGy/MBq, values compared at 24 hours after injection). This is due to the higher activity concentration of radioiodide accumulated compared to ^{211}At and also on account of the shorter half life of ^{211}At. The short half life of ^{211}At also explains why the dose per unit injected activity to the thyroid from ^{211}At is higher than that from ^{131}I at 1 hour after injection (530 mGy/MBq combared to 170 mGy/MBq). The reason why ^{131}I delivers a higher absorbed dose per unit injected activity than ^{125}I is the higher amount of energy emitted per disintegration for ^{131}I. For the other organs and tissues ^{211}At delivers a higher dose per unit injected activity in general, which is expected considering the higher accumulation in general of ^{211}At compared to radioiodide found in the biodistribution studies.

For radioiodine, only the energy deposited by electrons was included in the dose calculations. This results in an underestimation of the dose caused by ^{131}I in particular. Including the photons in the calculations would require a more exact calculation of the cross-absorbed fractions. By estimate this underestimation is about 10 % for the thyroid gland (for a γ-energy of 380 keV).

The self-absorbed fraction was set to 1 for all emitted particles (electrons and α-particles) for all three radionuclides. This approximation should be valid for ^{211}At on account of the short range of α-particles, but results in an overestimation of the dose from radioiodine, particularly ^{131}I which has a higher energy per β-particle than ^{125}I (the maximum β range in tissue is about 2 mm for ^{131}I and 0.012 mm for ^{125}I [1]).

5 Conclusions

Results show that the biodistribution of free ^{211}At are different to those of ^{125}I and ^{131}I. The thyroid gland accumulates both radioiodide and astatine selectively, although only about one-fifth of the activity concentration of radioiodide was found for ^{211}At. Furthermore ^{211}At is selectively accumulated in the stomach and small intestine. This could not be seen for radioiodide (except for ^{125}I in small intestine). Absorbed dose calculations showed that ^{211}At in general gave the highest dose per unit injected activity, although the highest dose per unit injected activity to the thyroid emanated from ^{131}I. Further studies are needed to properly investigate the biodistribution of ^{125}I, ^{131}I and free ^{211}At in thyroid and other normal tissue in rats. This is important for the research on thyroid disorder treatments as well as studies on thyroid stunning, due to the fact that, to our knowledge, only one paper (from 1953) has presented biodistribution data from radioiodine and ^{211}At in rats. These further studies should be based on the results in this work. Changes should be made in the measurement corrections and absorbed dose calculations to improve the results. Further attempts should also be made to properly investigate the effects of a reduced iodine diet.

Acknowledgements

I would like to express my gratitude to those without whom this work would not have been completed.

First of all I would like to thank my supervisors Nils Rudqvist and Eva Forssell Aronsson who have taken the time and trouble to teach, tutor and motivate me throughout the project and have helped me with solving problems along the way.

I would like to thank Lilian Karlsson for helping me with the syringe- and animal-handling and organ extraction procedures.

I also wish to thank to Sture Lindegren, Jörgen Elgqvist and Sofia Frost for supplying me with radionuclides and for giving me helpful tips regarding labwork.

I am also thankful for the help, support and comments I have received from my fellow students.

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