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Development of alternative methodology for normalization of the small animals PET scanner of LIM/CDTN

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Abstract: Normalization is a step taken to correct variations in count rates between detection channels of small animals PET scanners. In general, in laboratory practice, normalization is performed using a commercial source of germanium 68. Given the half-life of the Ge-68 isotope, the normalization source must be replaced every two years at most, which generates a significant spent for the Laboratory. The objective of this work was to develop and test an alternative rechargeable source to be used on normalization routine. The results indicated that the rechargeable source (^{18}F-FDG) can be used to replace the commercial source.

Keywords: Normalization, Ge-68 source, ^{18}F-FDG, small animals PET scanner.

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Desenvolvimento de metodologia alternativa para normalização do tomógrafo PET dedicado a pequenos animais do LIM/CDTN

Resumo: A normalização é uma etapa utilizada para corrigir as variações nas taxas de contagem entre os canais de detecção de tomógrafos PET dedicados a pequenos animais. Em geral, na prática laboratorial, a normalização é realizada utilizando-se uma fonte comercial de Ge-68. Dada a meia-vida do isótopo Ge-68, a fonte de normalização deve ser substituída a cada dois anos, no máximo, o que gera um gasto significativo para o Laboratório. O objetivo deste trabalho foi desenvolver e testar uma fonte recarregável alternativa para ser utilizada na rotina de normalização. Os resultados indicaram que a fonte recarregável (^{18}F-FDG) pode ser utilizada em substituição à fonte comercial.

Palavras-chave: Normalização, Fonte Ge-68, ^{18}F-FDG, tomógrafo PET dedicado a pequenos animais.

1. INTRODUCTION

Positron Emission Tomography (PET) is a diagnostic medical modality that evaluates, through images, the functional metabolism of several body tissues, such as bone, muscle, brain and liver.

PET scanners can have thousands of detection channels arranged in blocks. Due to differences in counting sensitivity in each detection channel, it is recommended to use a correction method called *Normalization* [1]. Normalization of the obtained data is performed by uniformly exposing all pairs of detectors to a 511 keV photon source (in general Ge-68 source).

The correction factors are calculated for each pair of detectors by dividing the average of counts of all detector pairs by the individual detector pair count. Thus, the normalization factor for each LOR (Line Of Response) is calculated as

$$F_i = \frac{A_{mean}}{A_i} \tag{1}$$

where F_i is the normalization factor, A_i is the count of all the detector pairs and A_{mean} is the average coincidence counts for all detectors pairs [1].

The Molecular Image Laboratory of the Nuclear Technology Development Center (LIM/CDTN) has a PET scanner dedicated to small animals (described in the section 2. 1). The User's Manual of the PET scanner recommends that the normalization be carried out with a Ge-68 commercial source, which must be replaced at most every two years.

The objective of this work was to develop and to test a cylindrical rechargeable source fillable with 18F-FDG, aiming at the commercial independence of the sources of Ge-68.

2. MATERIALS AND METHODS

2.1. Materials

During the study, the following equipaments were used: (i) a small animals PET scanner, LabPET SOLO 4, available at LIM/CDTN, including a LabPET 1.12.1 software installed, dedicated to the acquisition and reconstruction of PET images; (ii) a simulator for Image Quality tests; (iii) a mouse simulator; (iv) a commercial source of Ge-68.

The LIM/CDTN PET Solo 4 scanner, show in Figure 1, is part of the Triumph™ LabPET platform. This PET scanner is continuously used in studies for the acquisition of metabolic and physiological images of organs and tissues of small animals. The LabPET Solo 4 system consists of a stationary portal and employs 1536 detection channels composed of two different types of scintillators, LYSO – Lutetium Orthosilicate with Yttrium (Lu1.9Y0.1SiO5) and LGSO – Lutetium Orthosilicate with Gadolinium (Lu0.4Gd1.6SiO5), optically coupled to avalanche photodiode detectors (Avalanche Photo Diode - APD) [2]. The set of detectors is arranged in a continuous ring with a diameter of 15.6 cm and an axial Field of View (FOV) of 3.7 cm. PET images are acquired using energy windows in the range of 250-650 keV and coincidence events with a time window of 22 ns. The system can operate in dynamic or static mode.

Figure 1 – LabPET SOLO 4 scanner, dedicated to small animals

The Image Quality (IQ) simulator (Figure 2a) is a device designed to evaluate the image quality of small animal PET scanners. The simulator has a diameter of 3.5 cm and a length of 7.0 cm [3]. This simulator has dimensions of 50 mm length and 30 mm diameter. It possesses a main chamber that communicates with five different diameters auxiliary rods, all of which are expected to be filled with radiopharmaceutical water solution. Thus, activity concentration in any rod is the same that the one in main chamber. In addition, the IQ phantom possess two *cold* chambers - one of them is expected to be filled with air and the other one is expected to be filled with water, both no radioactive [4].

The mouse simulator, also named mouse whole body simulator, has a volume of 10 ml and is intended to obtain images of the whole body for the calculation of the conversion factor (Bq/cps) of the count rate (cps) in activity (Bq). Figure 2b presents the mouse simulator.

The Ge-68 source is typically used for the normalization routine on the PET scanner. Due to its relatively short half-life, must be replaced every two years at most. Figure 2c shows the source inserted in the socket dedicated to the normalization routine. This source was manufactured by Sanders Medical Products INC, certified activity 18MBq in 12/18/2017. The acquisition of a new source was made difficult by the COVID-19 pandemic scenario, then a Ge-68 source was used with the window of activity outside the recommended by the PET manufacturer. To ensure image quality, regular tests are performed on the LIM, as demonstrated in a previous publication [5] which dealt with the tests from March 2017 to March 2019. Important to say that the regular tests performed during this study demonstrates that the IQ parameters obtained using the Ge-68 source are in accordance with the historical values [5] despite the lower activity of the Ge-68 source. To compensate the lower Ge-68 source activity, normalization files are acquired using a bigger acquisition time aiming a comparable total counts values to that of the recommended activity window.

Figure 2: A) Image Quality simulator; B) Mouse Simulator;
C) Ge-68 source positioned in the PET scanner socket.

A) B) C)

2.2. Methods

In this work, an alternative source was developed to replace the commercial Ge-68 source. It is a fillable plastic cylindrical with approximate dimensions of the commercial source (101,1mm height; 3,6mm external diameter). The source was sealed, with ends covered by a flexible film PARAFILM ®, and filled with 1.01ml of ^{18}F-FDG using a 10ml syringe and then positioned in the socket of the equipment. Figure 3 shows the alternative source positioned in the equipment socket. It is important to note that filling the source by different people does not affect the result of the tests, as long as the activity range (40 to 60MBq) and homogeneous filling (without air bubbles) are ensured.

Figure 3: Alternative source positioned in the equipment socket

During the essays, the source was filled with the radiopharmaceutical Radioglic® (^{18}F-FDG) supplied by the Radiopharmaceutical Research and Production Unit (UPPR) of the CDTN. In this way, two normalization files, shown in Table 1, were acquired.

Table 1: Acquired normalizations

NORMALIZATION	SOURCE	ACTIVITY (MBQ)	TURNS
NORM - 1	Ge-68	0,22	1400
NORM - 2	^{18}F-FDG	48,50	180

To verify the feasibility of using the alternative source, images of the simulators were acquired and 3 different essays were performed, shown in Table 2.

Table 2: Image Quality tests

ESSAY	SIMULATORS			
	IMAGE QUALITY		MOUSE	
	ACTIVITY (MBq)	TIME (min)	ACTIVITY (MBq)	TIME (min)
ESSAY-1	3,74	20	8,80	20
ESSAY-2	3,75	20	15,00	20
ESSAY-3	3,75	20	10,50	20

Each PET image of the IQ simulator was reconstructed twice, using previously acquired normalizations, as shown in Table 3.

Table 3: Reconstruction of the PET Images of the IQ simulator

ESSAY	RECONSTRUCTION	NORMALIZATION	ALGORITHM	RESOLUTION	ITERATIONS	FOV
ESSAY-1	E1-R1	NORM 1	MLEM-3D	Standard	20i	60
	E1-R2	NORM 2				
ESSAY-2	E2-R1	NORM 1				
	E2-R2	NORM 2				
ESSAY-3	E3-R1	NORM 1				
	E3-R2	NORM 2				

After the reconstructions, the images were analyzed in the AMIDE software according the NEMA NU-4/2008 [4] tests, (i) Uniformity; (ii) Spill-Over Ratio; (iii) Recovery coefficients.

The Uniformity test consists of evaluating the system's ability to reproduce uniform images of a homogeneous concentration of activity with uniform distribution. In this test we obtain the Average (kbq/ml), Maximum (kBq/ml), Minimum (kBq/ml), Standard Deviation (%) of the activity concentration [6]. To obtain these measurements, a cylindrical VOI (22.5 mm in diameter and 10 mm in height) was positioned in the center of the main chamber, as recommended by NEMA NU 4-2008 [4].

The Spill-Over Ratio (SOR) test indicates scatter correction performance of the system. In this test, three VOI's were positioned in the water, air and center chambers, respectively. In the test we obtain the water and air SOR and their respective standard deviations.

The Recovery Coefficient (RC) test is responsible for quantify the ratio between the average concentration of activity in rods with different diameters (CR) and quantifying the ratio between the average concentration of activity in the rods with different diameters (1, 2, 3, 4 and 5mm) and the concentration activity average in the main chamber, and thus obtain an indication of the spatial resolution of the equipment. For this purpose, five cylindrical

VOI's were designed, one for each rod (diameter: 2.0; 4.0; 6.0; 8.0 and 10.0mm, respectively, and height: 10.0mm), and positioned in the center of the rods.

3. RESULTS AND DISCUSSIONS

Figure 4 illustrates the NEMA tests performed on the obtained PET images. In general, as illustrated in Figure 4, visual inspections of the images obtained in each test did not reveal significant differences between the reconstructed images with different normalizations (commercial Ge-68 or alternative ^{18}F-FDG).

Figure 4: PET Images for different normalizations

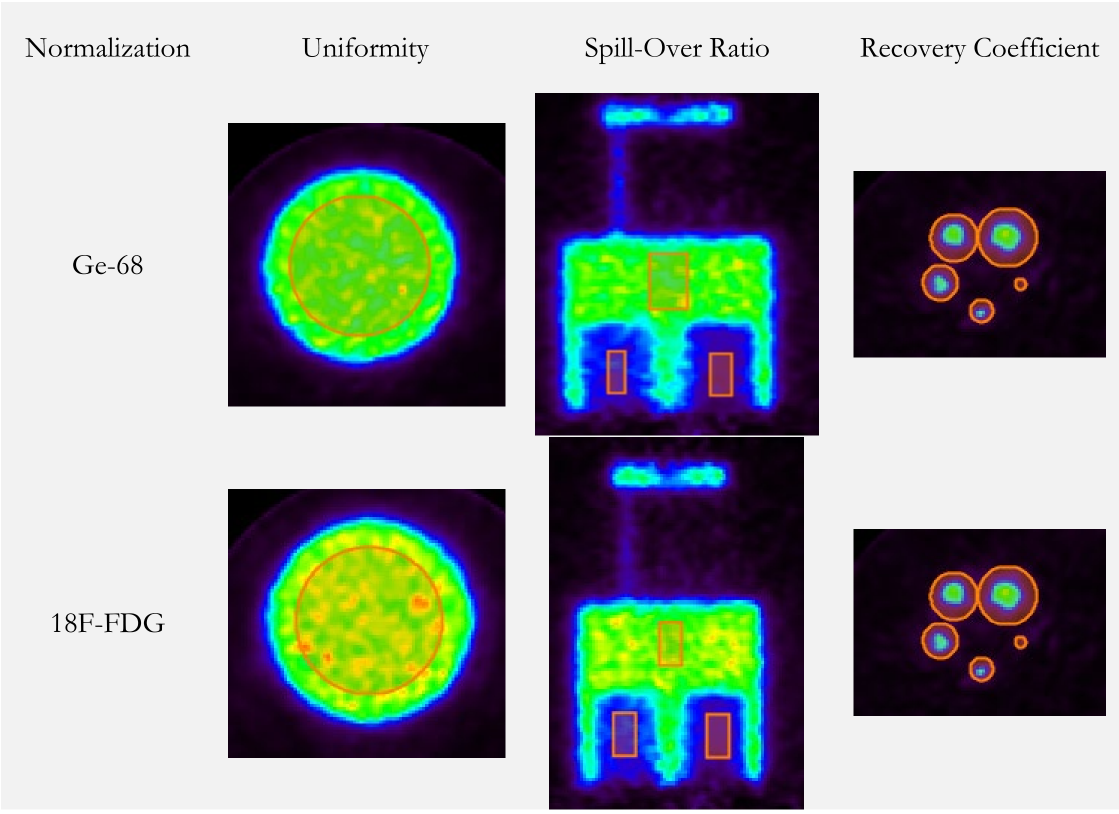


Table 4 presents the results of the NEMA NU 4-2008 Image Quality Test.

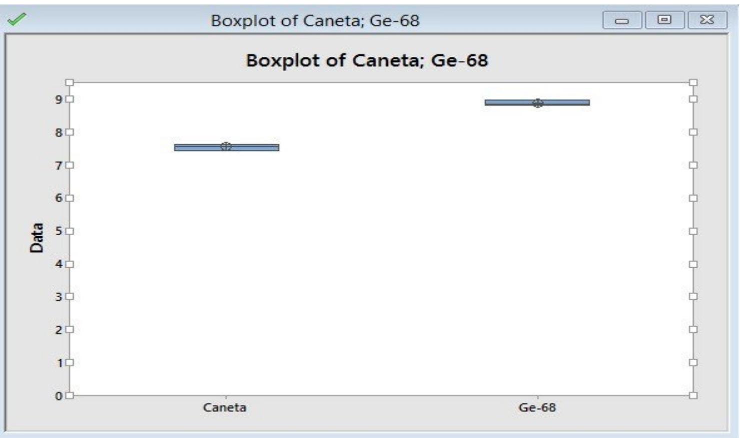
Table 4: Results of the NEMA NU 4-2008 Image Quality Test

TEST		ESSAY1		ESSAY2		ESSAY3	
		18F-FDG	Ge-68	18F-FDG	Ge-68	18F-FDG	Ge-68
Uniformity (kBq/ml)	Mean	207,0	208,5	234,99	234,9	212,1	211,5
	Max	278,6	293,7	311,8	340,1	279,0	317,3
	Min	146,1	138,6	170,9	159,5	160,3	150,8
	SD (%)	7,6	8,8	7,5	8,8	7,4	8,9
RSO	Water	0,30	0,29	0,27	0,27	0,28	0,28
	SD (%)	14,9	14,1	12,3	12,7	12,8	13,2
	Air	0,20	0,19	0,17	0,18	0,18	0,18
	SD (%)	16,8	17,7	16,2	17,8	16,2	17,4
Recovery Coefficients	5 mm	0,91	0,90	0,92	0,91	0,89	0,90
	SD (%)	10,7	15,4	10,5	9,5	8,3	6,8
	4 mm	0,86	0,85	0,89	0,89	0,88	0,86
	SD (%)	9,0	15,1	8,1	8,6	6,8	5,7
	3 mm	0,74	0,78	0,75	0,78	0,75	0,80
	SD (%)	10,7	17,0	8,8	9,1	10,0	7,1
	2 mm	0,51	0,52	0,50	0,49	0,52	0,51
	SD (%)	13,4	18,2	12,0	11,3	12,5	11,9
	1mm	0,09	0,09	0,11	0,11	0,11	0,09
	SD (%)	18,7	15,2	7,3	7,4	5,8	2,8

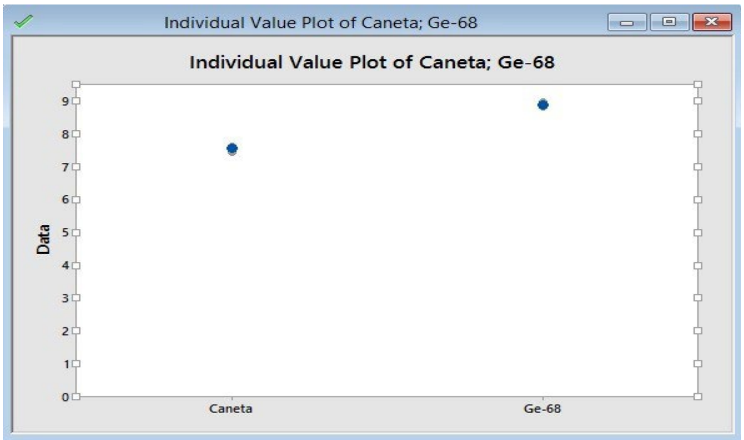
The results of the statistical analysis (Student´s test) of the data shown in Table 4 are presented below. Figure 5 presents the results for the uniformity test, where the roughness values of the image obtained in the reconstructions using normalization with the Ge-68 source and with the alternative source were compared.

Figure 5: Student's t Test for Uniformity
A: Boxplot for Uniformity; B: Individual values for Uniformity.
Images generated in Minitab®

A)



B)



The results shown in Figure 5 demonstrate that the Image Roughness parameter cannot be considered equal to the use of the alternative source detected as the Ge-68 source. This result can be explained by the low activity of the Ge-68 source compared to alternative source activity. Low activity results in a worse count statistic and consequently a higher standard deviation of the activity measure (which is by definition the roughness of the image).

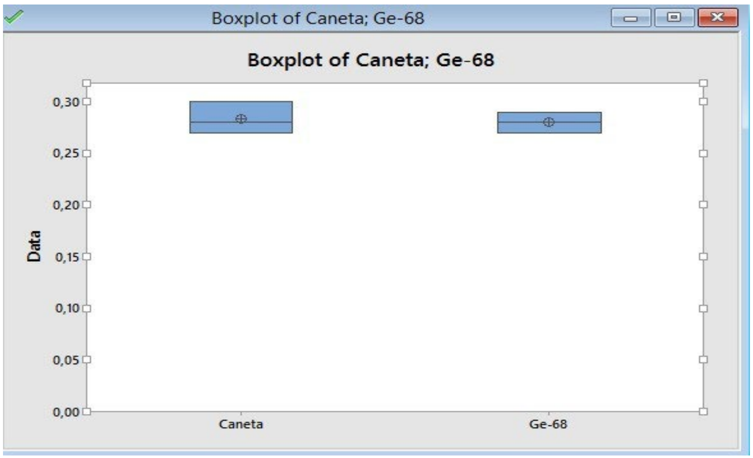
Figures 6 and 7 show the results of the statistical analysis for the Spill-Over ratio test, where the RSO values in water (Figure 6) and in air (Figure 7) of the image treated in the reconstructions using normalization with the source of Ge-68 and with the alternative source.

Figure 6: Student´s Test for Water Spill-Over Ratio

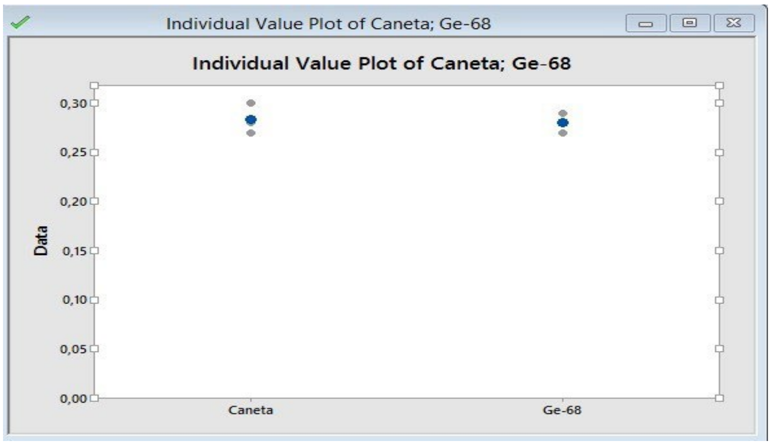
A: Boxplot for Water Spill-Over Ratio; B: Individual values for Water Spill-Over Ratio

Images generated by Minitab®

A)



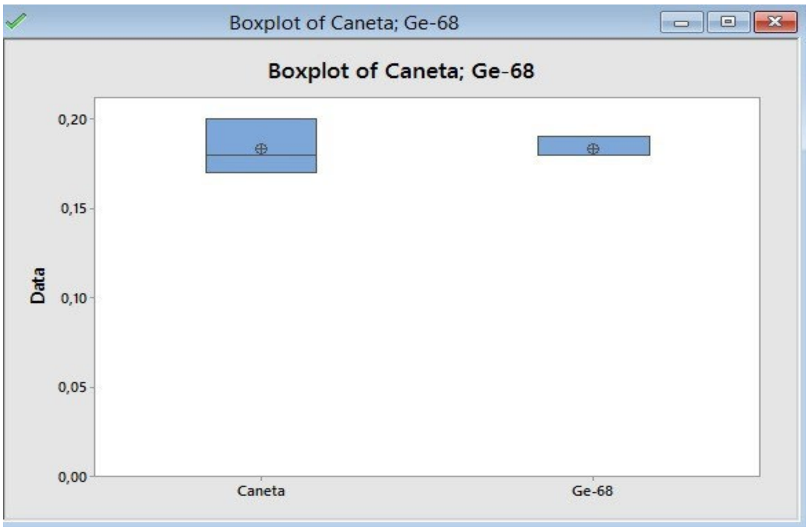
B)



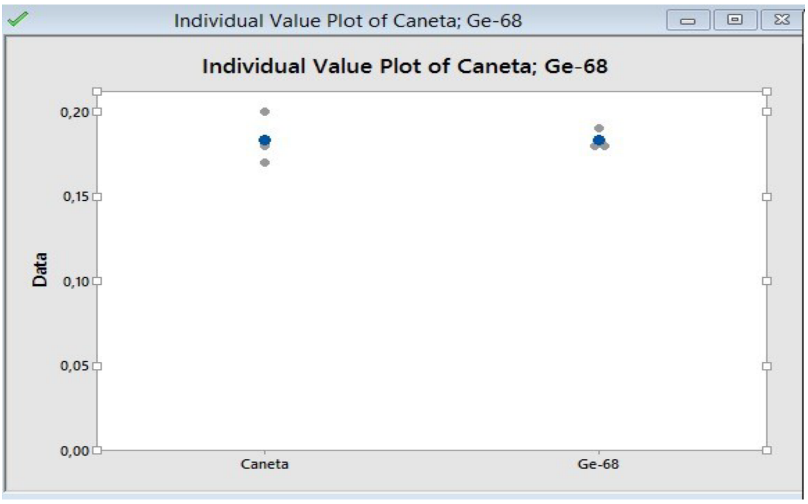
The results shown in Figure 6 reveal that the Water Spill-Over Ratio parameter can be considered equal using the alternative source compared to the Ge-68 source.

Figure 7: Student's t Test for Air Spill-Over Ratio
A: Boxplot for Air Spill-Over Ratio; B: Individual values for Air Spill-Over Ratio.
Images generated by Minitab®

A)



B)



The results shown in Figure 7 reveal that the Air Spill-Over Ratio parameter can be considered equal using the alternative source compared to the Ge-68 source.

The results of the statistical analyzes referring to the recovery coefficients test are shown in Table 5.

Table 5: Results

RC	VALUE P	STATISTICALLY EQUAL	
		YES	NO
5 mm	0,742	X	
4 mm	0,534	X	
3 mm	0,006		X
2 mm	0,768	X	
1 mm	0,519	X	

Student's t test determines that, if the statistical analyzes obtain a value of $P > 0.05$, the hypothesis is null, therefore the measures are equal. Thus, all analyzed recovery coefficients can be considered statistically equal with the use of the alternative source or the germanium source, except for the case of the 3mm rod.

In general, the statistical tests revealed that the images reconstructed with the alternative source and with the germanium source can be considered statistically equal. This fact allows the commercial source of germanium to be replaced in laboratory routine by a rechargeable source using the isotope Fluor-18. The values of Image Quality parameters obtained in this study using the alternative source and also the Ge-68 source are in according with historical values [5]. This fact demonstrates that the use of a “expired” Ge-68 source (with a bigger acquisition time) do not seriously compromised our results and permitted the development of this study to obtain the alternative source to perform normalization. Important to note that in the routine of the laboratory, different personnel manipulating and filling the alternative normalization source does not lead to a different experimental results, since the activity (60 to 80 MBq) and the homogeneity conditions (no air bubbles) are assured. The fact of the alternative source is not sealed is irrelevant to the normalization process – which deal with the global counts rates of the scanner and the counts rates of the individual detection channels.

The cases where the statistics showed differences between the images (uniformity test and recovery coefficient for the 3 mm rod) can be explained by the low count statistics due to the germanium source presenting low activity (0.22MBq) compared to a source new (18.5 MBq) and the alternative source used in the Tests (48.5MBq).

4. CONCLUSIONS

According to PET scanner manufacturer [2], normalization is a procedure taken regularly using Ge-68 source to correct variations in count rates between detection channels of small animals PET scanners. Based on the statistical analysis of the essays carried out, the replacement of the commercial source of Ge-68 by the alternative source proved to be feasible, so that the normalization using the alternative source can be used in the laboratory routine. This work consisted an alternative procedure feasible generating saving public resources in order to thousands of dollars per two years and laboratory independence in relation to the commercial source of Ge-68.

CONFLICT OF INTEREST

The authors declare that they have no competing financial interests or personal relationships that may have influenced the work reported in this study.

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