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Study of emission of radioactive gaseous effluents in the production of ^{18}F-FDG

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ABSTRACT

The number of cyclotron facilities producing radiopharmaceuticals with a half-life less than two hours has increased with the development of PET technology in Brazil. The gaseous waste, or gaseous effluent, is formed in the production of these radiopharmaceuticals such as ^{18}F-FDG (half-life = 109.8 min) or ^{11}C-PIB (half-life = 20.4 min). The International Atomic Energy Agency (IAEA) proposes a methodology to evaluate the dispersion of these gaseous effluents. This evaluation is utmost to guarantee that the overall emitted radioactivity be according to the limits established by CNEN (Nuclear Energy National Commission). This work has retrospectively evaluated the emission of radioactive gaseous effluents as a result of the production of ^{18}F-FDG to delimit yield-values of gaseous-form-radioactive waste in thirty-six ^{18}F-FDG production processes. We also verified the effectiveness and the design of the safety elements of the exhaust system evaluated according to the CNEN and IAEA recommendations.

Keywords: **Radiopharmaceuticals PET, Radioactive Air Contamination, Monitoring air flow, Medical physics.**

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1. INTRODUCTION

Nuclear Medicine is a powerful tool in the evaluation of several pathologies. Recently, the era of molecular imaging has led to the exponential growth of PET (positron emission tomography) technology demand [1]. The number of cyclotron facilities producing 18F-FDG has grown significantly [2][3] to keep up with the advances in PET technology and the increasing demand for nuclear medicine imaging diagnostics. In Brazil, the number of cyclotrons for medical purposes increased from 2 to 15 cyclotrons in 10 years [4].

The waste generation occurs in the solid, liquid, and gaseous form in the production of radiopharmaceuticals such as 18F-FDG or 11C-PIB. Thus, the management of such wastes [5] is imperative. The CNEN regulates the radioactive waste management process [6], and the gaseous effluent cloud scattering can be estimated by models recommended by the IAEA [7]. It is essential for the cyclotron facilities to have the expertise to monitor and manage the radioactive waste systems to guarantee the safety to the population and the critical group, around the facility [8][9][10]. Every cyclotron facility in the world that develop their radioisotope production routes or radiopharmaceutical synthesis should estimate the maximum radioactive gaseous concentration to check whether the planning of the safety elements corroborate to the recommendations and established limits from a competent organization [11][12]. Even if the radioactive concentration information of gaseous form is provided by the manufacturer or technology vendor and the production route/synthesis is already established, the radioactive concentration information must be checked anyway, and it needs to be appropriate to the blueprint of the facility.

The area and the height of the building, as well as the surrounding area of the facility, significantly affects the system planning for gaseous effluents [13][14][15][16]. In this scenario, the safety series study models for gaseous effluent are important for PET radiopharmaceuticals. Thus, this work retrospectively evaluated the emission of radioactive gaseous effluents generated in the production of 18F-FDG. We also achieved the delimited yield-values of radioactive waste in the gaseous form to verify the effectiveness and the safety elements of the exhaust system evaluated according to the CNEN standards and IAEA recommendations.

2. MATERIALS AND METHODS

The Cyclotron PETTrace 880 GE Healthcare (Uppsala, Sweden), the FastLab GE Healthcare (Uppsala, Sweden) and the Hotcell BBS 2 COMECER (Bologna, Italy) were used in this work. The system Medismarts air flow meter (Mishor Yamin, Israel) together with the scintillation detector model PM-11-M was used.

2.1. Gaseous effluents assessment

Thirty-six 18F-FDG batches were evaluated. The cyclotron facility was assessed by determining the characteristics of its building and its surroundings. The exhaustion point height (point of emission of the radioactive cloud) was 18.3 m from the ground. The distance from this same exhaustion point to the limit of the critical group was 42 meters. The critical group refers to the group of citizens in the population, that represents a sample of the ones receiving higher effective doses or equivalent doses due to a radiation source or exposition according to the circumstances [8]. The figure1 (a) and (b) shows the position of the exhaustion point:

Figure 1: *(a) The radial distance (42 meters) between the exhaustion point (center) to the limit of the critical group. (b) Height (18.3 meters) of the exhaustion point of the ducts to the ground.*

Due to such characteristics, we considered the Wake-zone model described in IAEA SS No. 19 [7]. The wind speed in the emission direction was estimated at 1.5 m/s according to the SIMEPAR (Paraná Meteorologic System). In this configuration, the stipulated limit by CNEN (1900 Bq/m3) for 18F radioisotope was conservatively applied at 21.5 m distant from the exhaustion point (approximately half the distance between the exhaustion chimney and the stipulated limit) as shown in figure 2:

Figure 2: *(a) Distance (21.5 meters) between the exhaustion point to the stipulated limit, according to the 1900 Bq/m^3 limit provided by CNEN.*

The total batch process time was 150 min and the activity of 5,000 mCi of 18F- in the End of Bombardment (EOB) or 4,000 mCi in the Start of Synthesis (SOS). The limit of 347 mCi of 18F- in the gaseous form was determined as the maximum possible to be wasted in the evaluated 18F-FDG batches.

For the analysis of thirty-six batches, it was considered that the exhaust system was calibrated according to manufacturer's specifications [17][18]. The Medismarts monitoring software was programmed to monitor the stages of irradiation, transfer, and synthesis and the yield of 18F- of

202 mCi/μA was correctly inputted in the cyclotron operating software [19]. Therefore, the thirty-six irradiation time ranging from 50 min to 100 min, with currents ranging from 50 μA to 119 μA were monitored and stored.

According to the batches evaluated, the produced 18F- was transferred to the established hotcell during the time interval of 3 min for each target at the end of the irradiations. The total activity wasted in gaseous form in this previous step was recorded through the monitoring interface of the software at the end of the transfer. Such processes were repeated for the thirty-five following batches. Through this recorded data and the value of the total activity wasted in the irradiation process, the yield of 18F- was obtained in the gaseous form through equation:

$$R_{waste} = \frac{A_{wasted}}{I*(1-e^{-\lambda t})} \quad (01)$$

Where:

R_{waste}: Batch yield of ^{18}F- in the gaseous form in the irradiation process (mCi/μA).

A_{wasted}: $^{18}F^-$ wasted activity in the irradiation process (mCi).

I: Average beam current during irradiation (μA)

λ: Radioactive disintegration constant of ^{18}F (min^{-1})

t: Irradiation time (min)

According to the batch process in the evaluated cyclotron facility, the 18F- provided to the hotcell was used in the G.E. Healthcare FastLab automatic synthesis module for 18F-FDG production [20]. The entire synthesis period was monitored for all the thirty-six batches. The figure 3 and Figure 4 show the shape of the expected elimination curve in the irradiation, transfer, and synthesis process [21] of the thirty-six productions evaluated:

Figure 3: *System interface for monitoring radiation levels at the maximum production capacity of ^{18}F-FDG*

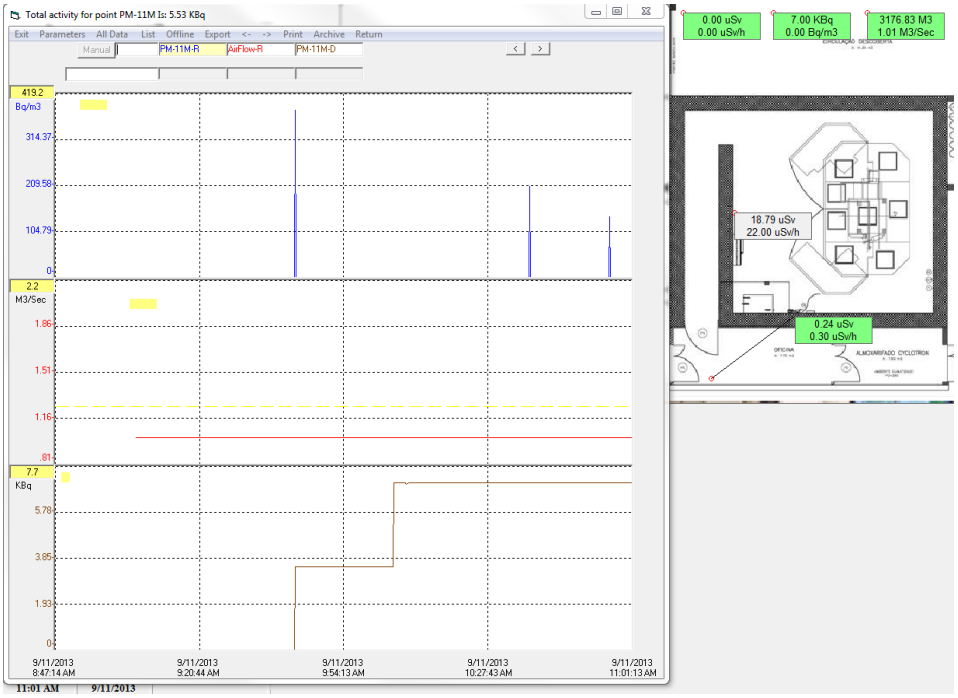
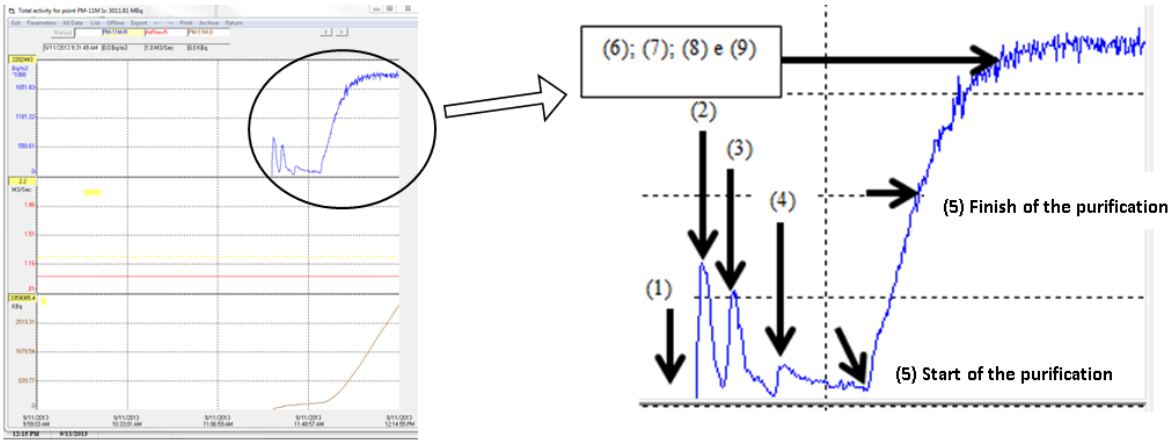


Figure 4: *System interface for monitoring the radiation levels at the maximum production capacity of ^{18}F-FDG after the synthesis and fractionation process. (1) Transfer, (2) ion exchange column, (3) Heating reaction, (4) Hydrolysis, (5) Purification, (6) Fractionation, (7), (8) and (9) Final steps.*



We estimated the percentage of gas emission for each 18F-FDG production with the total waste activity in the synthesis through the graphic interface of the Medismarts software, evaluated by the following expression:

$$A\% = \frac{A_{waste\ in\ synthesis}}{A_{\ initial}} \qquad (02)$$

where:

A%: Percent of gas emission.

$A_{waste\ in\ synthesis}$: gaseous waste activity in the synthesis (mCi).

$A_{initial}$: Activity at the start of synthesis (mCi)

The total activity of $^{18}F^-$ in the gaseous form in the production process, including the irradiation and synthesis was determined by:

$$A_{total\ waste} = A_{waste\ \ in\ the\ radiation} + A_{waste\ in\ the\ synthesis} \qquad (03)$$

Where:

$A_{waste\ total}$: Estimated total activity waste of ^{18}F in the gaseous form (mCi).

$A_{waste\ in\ synthesis}$: Waste activity of ^{18}F in the gaseous form in synthesis process (mCi).

$A_{waste\ in\ irradiation}$: Waste activity of ^{18}F in the gaseous form in the irradiation process (mCi).

To evaluate the safety elements of the exhaust system and its effectiveness, the estimated total activity values were compared with the maximum amount that could be eliminated in the exhaustion point.

3. **RESULTS AND DISCUSSION**

Table 1 shows the thirty-six 18F-FDG batches evaluated in the study of radioactive gaseous effluent. Table 2 shows the values obtained from the effluents in the 18O(p, n)18F irradiation process in all the 18F-FDG batches evaluated.

Table 1: Batch of ^{18}F-FDG.

Batch	Target irradiation position	Average Current (μA)	Time (min)	Produced Activity (mCi)	Activity SOS (mCi)
1	4	50	100	4806	4337
2	1	63	70	4636	4232
3	4	65	70	4779	4365
4	1	50	94	4526	4137
5	4	50	98	4813	4405
6	1	76	10	2000	1477
7	4	35	63	2592	1695
8	4	75	60	5059	2771
9	4	75	81	5716	3392
10	1	79	40	4636	3270
11	1	30	40	800	476
12	1	75	68	5031	3667
13	1	40	95	4696	3080
14	4	60	69	5049	3410
15	4	70	67	5212	3764
16	1	66	68	4607	3756
17	4	60	75	4748	3550
18	1	67	62	4672	3199
19	4	68	59	4361	2999
20	1	75	36	2952	2165
21	4	75	54	4392	3492
22	1	55	99	5126	3666
23	4	69	71	4599	3168
24	1	50	71	4747	3401
25	1	68	71	4685	3459
26	4	78	51	5053	3701
27	1	46	125	4679	3587
28	4	48	115	4882	3668
29	1	65	78	4947	3723
30	4	67	81	4946	3693
31	1	50	82	4807	3579
32	4	63	77	4647	3429
33	1	65	73	4779	3625
34	1	50	101	4526	3352
35	4	50	101	4813	3618
36	1	78	60	4777	3883

Table 2: Gaseous emissions in $^{18}F^-$ batch.

Batch	target	Produced Activity (mCi)	Activity of released ^{18}F (mCi)
1	4	4,806	0.659
2	1	4,636	0.592
3	4	4,779	0.292
4	1	4,526	0.858
5	4	4,813	0.789
6	1	2,000	0.135
7	4	2,592	0.310
8	4	5,059	0.543
9	4	5,716	0.809
10	1	4,636	0.475
11	1	800	0.180
12	1	5,031	0.758
13	1	4,696	0.414
14	4	5,049	0.571
15	4	5,212	0.651
16	1	4,607	0.621
17	4	4,748	0.565
18	1	4,672	0.585
19	4	4,361	0.538
20	1	2,952	0.342
21	4	4,392	0.547
22	1	5,126	0.669
23	4	4,599	0.527
24	1	4,747	0.658
25	1	4,685	0.617
26	4	5,053	0.425
27	1	4,679	0.655
28	4	4,882	0.548
29	1	4,947	0.633
30	4	4,946	0.624
31	1	4,807	0.617
32	4	4,647	0.652
33	1	4,779	0.612
34	1	4,526	0.603
35	4	4,813	0.622
36	1	4,777	0.617
Average		4,503	0.564
The average yield of $^{18}F^-$ in gaseous form			
27.1 µCi/µA			

The results in table 3 show the values obtained in monitoring the effluents in the ^{18}F-FDG batches evaluated:

Table 3: Monitoring of effluents in the ^{18}F-FDG synthesis process

Batch	Activity EOB (mCi)	Activity SOS (mCi)	Eliminated Activity (mCi)	Factor (%)
1	4,806	4,337	193.4	4.5%
2	4,636	4,232	216.2	5.1%
3	4,779	4,365	261.4	6.0%
4	4,526	4,137	131.5	3.2%
5	4,813	4,405	220.3	5.0%
6	2,000	1,477	75.4	4.8%
7	2,592	1,695	80.5	4.7%
8	5,059	2,771	133.4	4.7%
9	5,716	3,392	157.2	4.7%
10	4,636	3,270	155.3	4.7%
11	800	476	23.8	4.7%
12	5,031	3,667	173.2	4.8%
13	4,696	3,080	146.9	4.8%
14	5,049	3,410	162.7	4.8%
15	5,212	3,764	179.1	4.8%
16	4,607	3,756	178.4	4.7%
17	4,748	3,550	168.6	4.7%
18	4,672	3,199	154.0	4.8%
19	4,361	2,999	153.0	4.8%
20	2,952	2,165	104.1	4.7%
21	4,392	3,492	167.2	4.8%
22	5,126	3,666	175.1	4.7%
23	4,599	3,168	150.5	4.8%
24	4,747	3,401	161.5	4.7%
25	4,685	3,459	165.1	4.7%
26	5,053	3,701	175.8	4.8%
27	4,679	3,587	171.3	4.8%
28	4,882	3,668	174.2	4.7%
29	4,947	3,723	176.8	4.7%
30	4,946	3,693	177.1	4.7%
31	4,807	3,579	170.5	4.7%
32	4,647	3,429	163.1	4.8%
33	4,779	3,625	173.1	4.8%
34	4,526	3,352	161.0	4.7%
35	4,813	3,618	169.1	4.8%

36	4,777	3,883	184.4	4.7%
average	4,502.7	3,366.4	160.0	4.7%
Estimated limit activity (mCi)				347 mCi
Total average waste activity in the process (mCi)				160.56
Difference from the calculated limit of 347 mCi				53.7%
Does the exhaust need additional safety device?				No

The monitoring performed in the irradiation process of 18F-FDG batches in Table 1 showed that the system is airtight under normal operating conditions and the yield value of 27.1 µCi/µA of 18F- in gaseous form is extremely low in the process. The elimination of 18F- in the gaseous form only occurs at the end of the irradiation process in the transfer between the cyclotron and hotcell. Comparing the results obtained in the process of irradiation and synthesis, they corroborate with the literature showing that the highest emission rate occurs during the synthesis [21], showed in table 2, and that the average emission value s approximately 4.7% of the activity at the beginning of the synthesis (showed in table 3). The total activity value to be a gaseous waste in the 18F-FDG batch process remained is 53.7% less than the calculated limit according to IAEA SS 19 recommendations. Also, we found that the exhaust system structure of the facility does not require additional elements of safety.

4. **CONCLUSIONS**

We showed that it is possible to obtain reference values for the production of 18F in the gaseous form for each stage of the process (irradiation and synthesis). Our estimation of waste activity was achieved in the maximum production capacity of the evaluated cyclotron facility. The analysis carried out here advocates that the release limit at half the distance between the exhaustion point and the gaseous dispersion (21.5 meters) was effective in radiological protection point-of-view. Our findings corroborate the importance of all cyclotron facility to monitor the radioactive waste generation constantly. This work also encourages further studies to develop new ways of monitoring and new emission models for gaseous effluents to improve the accuracy of evaluation and the safety efficacy of the critical group.

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REFERENCES

[1] Rocha, A. F. G., **Medicina Nuclear: aplicações clínicas**, 1º Ed., Editora Guanabara Koogan. Rio de Janeiro. 1976.

[2] Boschi A, Martini P, Costa V, Pagnoni A, Uccelli L. Interdisciplinary Tasks in the Cyclotron Production of Radiometals for Medical Applications. The Case of 47Sc as Example. **Molecules,** 2019; 24(3):444. Published 2019 Jan 26. doi:10.3390/molecules24030444.

[3] Clarke, B. N, PET Radiopharmaceuticals: What's new, what's reimbursed, and what's next?, **J. Nucl. Med. Technol.**, Published online: February 2, 2018, Doi: 10.2967/jnmt.117.205021.

[4] CNEN, **Comissão Nacional de Energia Nuclear**, Rio de Janeiro, Brazil. Available at:< http://www.cnen.gov.br/index.php/instalacoes-autorizadas-2>. Last accessed: 12 December 2018.

[5] CALANDRINO, R., del VECCHIO, A., TODDE, S., FAZIO, F. Measurement and Control of the Air Contamination Generated In a Medical Cyclotron Facility for PET Radiopharmaceuticals. **The Radiation Safety Journal**, vol.92, suppl. 2, p.70-77, 2007.

[6] CNEN. Comissão Nacional de Energia Nuclear. **Gerencia de Rejeitos Radioativos**. Rio de Janeiro, Brasil: CNEN NN 8.01, 2014.

[7] INTERNATIONAL ATOMIC ENERGY AGENCY . Safety Reports Series Nº 19. **Generic Models for Use in Assessing the Impact of discharges of Radioactive Substances to the Environment**, Viena, 2001.

[8] CNEN. Comissão Nacional de Energia Nuclear. **Diretrizes Básicas de Proteção Radiológica**. Rio de Janeiro, Brasil:CNEN-NN-3.01, 2005.

[9] CNEN. Comissão Nacional de Energia Nuclear. **Licenciamento de Instalações Radiativas.** Rio de Janeiro, Brasil: CNEN-NE 6.02, 1998.

[10] CDTN. **Programa de Monitoração Ambiental do CDTN**. Belo Horizonte: PMA / CDTN, 2008.

[11] INTERNATIONAL ATOMIC ENERGY AGENCY. Technical Reports Series No. 465, **Cyclotron Produced Radionuclides: Principles and Practice**, Viena, 2008

[12] INTERNATIONAL ATOMIC ENERGY AGENCY. Technical Reports Series No. 468, **Cyclotron Produced Radionuclides: Physical Characteristics And Production Methods**, Viena, 2009.

[13] IAEA. International Atomic Energy Agency. **International Basic Safety Standards for protection against ionizing radiation and for the safety of radiation sources**. IAEA, Viena: BSS Safety Series 115, 1996.

[14] IAEA. International Atomic Energy Agency. **Generic procedures for assessment and response during a radiological emergency**. IAEA, Viena: TECDOC 1162, 2000.

[15]INTERNATIONAL ATOMIC ENERGY AGENCY. IAEA RADIOISOTOPES AND

RADIOPHARMACEUTICALS SERIES No. 4, **Cyclotron Produced Radionuclides: Operation And Maintenance Of Gas And Liquid Targets**, Viena, 2012.

[16] CASTELHANO, F. J.; ROSEGHINI, W. F. F. Caracterização da dinâmica dos ventos em Curitiba-PR. **Geousp Espaço e Tempo (Online)**, v. 22, n. 1, p. 227-240, 2018. ISSN 2179-0892.

[17] Manufacturer's guide. **Rotem MediSmarts Stack Monitor**. Calibration Procedure, 2012.

[18] Videira, H.S. **Implantação de um processo comercial de produção de doses do radiofármaco 18F-FDG**. Dissertação apresentada para obtenção do grau de mestre em ciências na área de engenharia. UFPR/PR. 2014.

[19] Manufacturer's guide. PETtrace 800 series, Service Manual – Accelerator-Rev. 20.

[20] IAEA - International Atomic Energy Agency. Cyclotron produced radionuclides: **guidance on facility design and production of [18f] fluorodeoxyglucose (FDG)**. Vienna: IAEA, 2012. (Radioisotopes and Radiopharmaceuticals Series, nº 3).

[21] Kleck JH, Benedict SH, Cook JS, Birdsall RL, Satyamurthy N., Assessment of 18F gaseous releases during the production of 18F-fluorodeoxyglucose, **Health Phys.** 1991 May;60(5):657-60.