Vacuum ultraviolet photon–mediated production of $[^{18}\text{F}]\text{F}_2$

Anna Krzyczmonik$^1$ | Thomas Keller$^1$ | Anna K. Kirjavainen$^1$ | Sarita Forsback$^{1,2}$ | Olof Solin$^{1,2,3}$

1 Radiopharmaceutical Chemistry Laboratory, Turku PET Centre, University of Turku, Turku, Finland
2 Department of Chemistry, University of Turku, Turku, Finland
3 Accelerator Laboratory, Åbo Akademi University, Turku, Finland

Correspondence
Olof Solin, Turku PET Centre, University of Turku, Kiinamyllynkatu 4-8, FI-20520 Turku, Finland.
Email: olof.solin@abo.fi

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The chemistry of $\text{F}_2$ and its derivatives are amenable to facile aliphatic or aromatic substitution, as well as electrophilic addition. The main limitation in the use of $[^{18}\text{F}]\text{F}_2$ for radiopharmaceutical synthesis is the low specific activity achieved by the traditional methods of production. The highest specific activities, 55 GBq/μmol, for $[^{18}\text{F}]\text{F}_2$ have been achieved so far by using electrical discharge in the post-target production of $[^{18}\text{F}]{\text{F}}_2$ gas from $[^{18}\text{F}]\text{CH}_3\text{F}$. We demonstrate that $[^{18}\text{F}]\text{F}_2$ is produced by illuminating a gas mixture of neon/$\text{F}_2/[^{18}\text{F}]\text{CH}_3\text{F}$ with vacuum ultraviolet photons generated by an excimer laser. We tested several illumination chambers and production conditions. The effects of the initial amount of $[^{18}\text{F}]\text{F}_2$, amount of carrier $\text{F}_2$, and number of 193-nm laser pulses at constant power were evaluated regarding radiochemical yield and specific activity. The specific activity attained for $[^{18}\text{F}]\text{F}_2$–derived $[^{18}\text{F}]\text{NFSi}$ was 10.3 ± 0.9 GBq/μmol, and the average radiochemical yield over a wide range of conditions was 6.7% from $[^{18}\text{F}]\text{F}_2$. The production can be improved by optimization of the synthesis device and procedures. The use of a commercially available excimer laser and the simplicity of the process can make this method relatively easy for adaptation in radiochemistry laboratories.

KEYWORDS
$[^{18}\text{F}]\text{F}_2$, $[^{18}\text{F}]\text{NFSi}$, electrophilic $^{18}\text{F}$, excimer laser, fluorine-18, PET, radiochemistry, specific activity

1 | INTRODUCTION

Positron emission tomography (PET) is a diagnostic technique, which allows the study of biological processes in living subjects. $^{18}\text{F}$ is the most commonly used radionuclide in the production of PET tracers and can be introduced into a molecule by nucleophilic or electrophilic methods. Nowadays, most $^{18}\text{F}$-labelled tracers are made by a nucleophilic approach because of the ready availability of nucleophilic $[^{18}\text{F}]\text{F}_2$, which is produced in high specific activity (SA) by the $^{18}\text{O}(p,n)^{18}\text{F}$ nuclear reaction in an $^{18}\text{O}$-enriched water target. In contrast, electrophilic $[^{18}\text{F}]\text{F}_2$ is only produced by $\text{F}_2$ carrier-added methods, which lower the SA. Despite this limitation, some tracers such as $[^{18}\text{F}]\text{CFT}$ and $[^{18}\text{F}]\text{EF5}$ are made$^2$ by electrophilic fluorination.

Electrophilic fluorination is a fast way of introducing a fluorine atom into organic molecules. While $\text{F}_2$ can be directly used for electrophilic substitution, it can also be easily transformed into milder fluorination reagents. Presently, there are various electrophilic $^{18}\text{F}$ labelling reagents with different reactivities, which can be used for PET tracer production. These include $[^{18}\text{F}]\text{XeF}_2$, $[^{18}\text{F}]\text{CH}_3\text{COOF}$, $[^{18}\text{F}]\text{N}$-fluorobenzenesulphonimide ($[^{18}\text{F}]\text{NFSi}$), $[^{18}\text{F}]\text{N}$-fluoropyridinium salts, and $[^{18}\text{F}]\text{Selectfluor bis}(triflate)$. The use of $\text{F}_2$ and its derivatives allows aliphatic or aromatic substitution, as well as electrophilic addition to be performed.

Anna Krzyczmonik and Thomas Keller contributed equally to this study.
The main limitation in the use of \(^{18}\text{F}\)F\(_2\) for tracer synthesis is the low SA achieved by the traditional methods of production. There are 2 practically useful approaches for the cyclotron production of \(^{18}\text{F}\)F\(_2\) gas: \(^{20}\text{Ne}(d,\alpha)^{18}\text{F}\) and \(^{18}\text{O}(p,n)^{18}\text{F}\), which lead to SAs of 0.1 GBq/\(\mu\)mol\(^8\) and 1.3 GBq/\(\mu\)mol\(^9\), respectively. In 1997, Bergman and Solin reported a method for the post-target production of \(^{18}\text{F}\)F\(_2\) gas from \(^{18}\text{F}\)CH\(_3\)F. They applied a high-voltage discharge to perform the \(^{19}\text{F}/^{18}\text{F}\) isotopic exchange and obtained \(^{18}\text{F}\)F\(_2\) with a SA of 55 GBq/\(\mu\)mol\(^1\). Since that time, this method has been used at Turku PET Centre in the production of different tracers such as 6-\(^{18}\text{F}\)fluoro-DOPA, \(^{18}\text{F}\)CFT, and \(^{18}\text{F}\)EF\(_5\)\(^{1}\) for clinical use. However, the discharge method has its limitations. The high-voltage discharge (25-30 kV) creates a harsh environment in the reaction chamber resulting in the consumption of F\(_2\) gas. Furthermore, this method requires specialized equipment, which can be difficult to install.

We propose that by using a gentler source of excitation, such as vacuum ultraviolet (VUV) photons generated by an excimer laser, we can reduce the amount of carrier F\(_2\) gas needed for the \(^{18}\text{F}\)F\(_2\) production and this might, in turn, result in higher SA. Since the bond-dissociation energies for fluoromethane (CH\(_3\)F) to tetrafluoromethane (which are present in the chamber during isotopic exchange) are in a range of 260 to 219 nm\(^1\), the energy of the ArF excimer laser (193 nm) is sufficient to break the C–F bond. Herein, we report the proof-of-principle for the VUV illumination method for the production of \(^{18}\text{F}\)F\(_2\).

## 2 | EXPERIMENTAL

### 2.1 | General

All organic solvents were high-performance liquid chromatography (HPLC) grade and purchased from Sigma-Aldrich (Steinheim, Germany). Potassium carbonate was also purchased from Sigma-Aldrich. Kryptofix 222 [4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane] was purchased from Merck KGaA (Darmstadt, Germany). \(^{18}\text{F}\)-N-fluorobenzenesulfonimide was used as a model compound for the identification of the \(^{18}\text{F}\)F\(_2\) synthesized during the experiment due to its straightforward preparation (Figure 1) and identification (Figure 2). Sodium dibenzenesulfonimide (\(^{18}\text{F}\)NFSi precursor) was supplied by Prof Gouverneur’s Group (University of Oxford, Oxford, United Kingdom).

18O-enriched water for the production of \(^{18}\text{F}\) was purchased from Rotem Industries Ltd (Arava, Israel). Gases were supplied by AGA, Linde group (Espoo, Finland).

For HPLC analysis, a Merck Hitachi LaChrom 7000 system with Hitachi D-7000 HPLC System Manager software (version 3.1.1) was used. Analyses were performed using a Waters Atlantis dC18, 3.9 x 150-mm column (Waters Corp, Milford, Massachusetts) with a gradient of H\(_2\)O and MeCN starting from 95% water to 20% water over 10 minutes with a flow of 1.5 mL/min. A wavelength of 254 nm was used for the UV detector. Radioactivity was detected with a NaI (TI) scintillator detector (2 x 2 in; Bicron, Newbury, Ohio) placed on the HPLC column outlet.

The illumination chambers were custom made to our specifications by Finnish Special Glass Oy (Espoo, Finland). The TiO\(_2\) reflective paint (BC-620) was purchased from Saint-Gobain Crystals (Nemours, France).

### FIGURE 1

Synthesis of \(^{18}\text{F}\)F\(_2\) from \(^{18}\text{F}\)F\(_2\)aq and subsequent synthesis of \(^{18}\text{F}\)-N-fluorobenzenesulfonimide. Yields 1 to 3 represent the respective synthesis step yields. n and m denote the respective molar amounts. As described in Bergman and Solin\(^1\), the exchange process can be simulated by a Monte Carlo model. When the molar amount of carrier F\(_2\) gas is in large excess compared to that of \(^{18}\text{F}\)CH\(_3\)F (ie, n >> m) and assuming that all the bonds of the molecules in the gas mixture are broken, the exchange reaction will produce (n-3 m) moles of \(^{18}\text{F}\)F\(_2\).
The gas chromatography column (id 0.8 cm, length 30 cm) was filled with HayeSep Q 60-80 mesh (Sigma-Aldrich, Steinheim, Germany).

2.2 | Laser

The ArF Excimer XS laser (Coherent, Gottingen, Germany) was installed outside the hot cell. A hole was drilled in the hot cell wall, and a metal tube was used to transfer the laser beam in a helium atmosphere to the illumination chamber (Figure 3). The laser is operated in pulse mode, with 15 000, 30 000 or 60 000 pulses being used, depending on the experiment. The repetition rate (200 Hz) and energy (11-12 mJ/pulse) were kept constant for all the experiments.

2.3 | F₂ titration

The amount of carrier F₂ used in the synthesis of [¹⁸F]F₂ was determined by iodometric titration. The mixing chamber (Figure 3A) was filled with a known pressure of Ne/0.5% F₂ gas and further filled with neon to a total pressure of 5 bar. The mixing chamber was opened to the illumination chamber, and the pressure was allowed to equilibrate.

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**FIGURE 3**  
A. Schematic diagram of the apparatus for converting [¹⁸F]CH₃F to [¹⁸F]F₂ using the vacuum ultraviolet laser. B. A photograph depicting the setup of the apparatus in the laboratory, from left to right: hot cell containing synthesis device, laser housed in adjacent fume hood, and the user interface.
for 1 minute. The gas mixture in the illumination chamber was bubbled through 1 mL of 1M KI solution, and the chamber was flushed 3 times with neon. The resulting solution was titrated with 0.01M Na$_2$S$_2$O (when the solution color turned very pale yellow, starch indicator, 0.5 mL, was added). The amount of carrier F$_2$ gas was calculated from the total amount of Na$_2$S$_2$O used for titration.

### 2.4 Radionuclide production by cyclotron

$[^{18}F]$F$_{aq}$ was produced via the $^{18}$O(p,n)$^{18}$F reaction. $^{18}$O-enriched water (800 μL) was irradiated with a beam of 17 MeV, 10 μA protons using the MGC-20 cyclotron for 5 minutes (Efremov Scientific Research Institute for Electrophysical Apparatuses [NIIEFA], Saint Petersburg, Russia). For the reactions with high activity, $[^{18}F]$F$^-$ was produced using the TR-19 cyclotron (Advanced Cyclotron Systems Inc Richmond, British Columbia, Canada) by irradiating $^{18}$O-enriched water (3.6 mL) for 1 hour with a 19 MeV, 100 μA proton beam. An aliquot (1 mL) of the irradiated water was transferred to the synthesis apparatus for the reaction.

### 2.5 Production of $[^{18}F]$CH$_3$F

The irradiated water containing the $[^{18}F]$F$_{aq}$ was transferred to a reaction vessel containing K$_2$CO$_3$ (6-8 mg), Kryptofix 222 (22-28 mg), and 1 mL of MeCN. Azeotropic distillation was conducted at 100°C for 4 minutes. Following this, a further 1 mL of MeCN was added and the drying was continued for 4 minutes. CH$_3$I (1.5 mmol) in 1 mL MeCN was added to the dry $[^{18}F]$KF/K$_{222}$ complex, and the reaction was conducted for 40 seconds at 100°C.

The resulting $[^{18}F]$CH$_3$F was transferred to a 60-mL syringe and injected onto the gas chromatography column for purification. Neon was used as a carrier gas. The gas chromatography column was held at RT. A Geiger-Muller radioactivity detector, placed on the outlet of the column, monitored the elution of $[^{18}F]$CH$_3$F. The purified product was collected in a stainless steel loop (od 1/16", id 0.5 mm) submerged in a liquid nitrogen trap. Upon collection, the stainless steel loop was allowed to warm to room temperature for 90 seconds. Subsequently, the Ne/F$_2$ gas mixture, premixed to a total pressure of 5 bar as described earlier (see Section 2: F$_2$ titration), was used to transfer the $[^{18}F]$CH$_3$F to the illumination chamber (Figure 3A). The final pressure of the gas mixture in the illumination chamber was 2.5 bar.

### 2.6 $[^{18}F]$F$_2$ production and $[^{18}F]$NFSi labelling

The chamber, previously filled with $[^{18}F]$CH$_3$F/F$_2$/Ne, was illuminated with the laser beam, and the resulting gas mixture

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**TABLE 1** Properties of illumination chambers used for the experiments

| Chamber | Chamber material | Chamber shape and dimensions | Volume, cm$^3$ | Chamber coating |
|---------|------------------|-----------------------------|---------------|----------------|
| A       | Glass with quartz windows on ends | ![Diagram A](image) | 10.3 | TiO$_2$ |
| B       | Quartz           | ![Diagram B](image) | 9.8 | Al |
| C       | Quartz           | ![Diagram C](image) | 4.1 | Al |

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was bubbled, at a flow of 20 to 25 mL/min, through the solution of the NFSi precursor in 0.9 mL of MeCN and 0.1 mL of H2O. The remaining volatile radioactive compounds were trapped in a waste bottle. 

[18F]NFSi was not purified. The crude solution of [18F]NFSi was analyzed by analytical radioHPLC. The reported HPLC yield is an integrated yield based on the area of radioactive product peak compared to the total area of all radioactive peaks. The SA values of [18F]NFSi (SA_{[18F]NFSi}) were calculated from the analytical radioHPLC chromatograms as follows: The UV detector response was calibrated with known amounts of NFSi. The [18F]NFSi fraction was collected from the HPLC outlet, the radioactivity was measured, and the area of the UV peak corresponding to NFSi was determined. The areas of the NFSi peak in the calibration and area of that in the analytical chromatogram were compared, and the amount of NFSi was calculated based on the [18F]NFSi UV peak area.

During the initial screening reactions, 3 different illumination chambers were tested (Table 1). All of the chambers were coated with either an opaque layer of aluminum metal by vacuum evaporation or with TiO2 reflective paint. In each case, a small uncoated window was left as the laser beam inlet. On chamber A, only the terminal quartz glass window was coated with paint. The chambers were connected with stainless steel Swagelok ¼” fittings and teflon ferrules.

[18F]CH3F was synthesized as described and transferred to the illumination chamber, and a known quantity of carrier F2 was added (Table 2). The mixture was illuminated with 30 000 laser pulses, and the produced gas was immediately used for the synthesis of [18F]NFSi. The chamber providing the highest SA_{[18F]NFSi} and HPLC yield was subsequently used to determine optimal number of laser pulses to promote the isotopic exchange reaction. Thus, the effect of varying the amounts of carrier F2 was investigated, keeping all other conditions unchanged.

The screening reactions were conducted with low starting activity (A_{[18F]F} = 3.25 ± 0.54 GBq). The conditions that resulted in the highest SA_{[18F]NFSi} were further used for reactions with high A_{[18F]F} (36 ± 2 GBq) to obtain high SA_{[18F]NFSi}.

2.7 | Statistical methods

The results are reported as means ± SD of n = 3-5. All statistical analyses were performed using Microsoft Excel 2010. Differences between the HPLC yields and SA_{[18F]NFSi} obtained using different conditions were tested using the unpaired t-test. Differences were considered statistically significant if \( P < .05 \).

3 | RESULTS

[18F]F2 was successfully produced and subsequently used to label [18F]NFSi, which was identified by analytical HPLC (Figure 2). Analysis of the crude reaction mixture showed some UV-active impurities that separated well from the product peak. Two radioactive impurities with retention times of 1 and 8.5 minutes were also observed.

3.1 | Chamber shapes and amount of laser pulses

The investigation of chamber shapes (Table 2) showed that use of the chamber A resulted in the highest HPLC yield of [18F]NFSi, and hence, this chamber was chosen for all further experiments. The comparison of different coating materials (chambers B and C) (Table 2) indicated that

| Chamber | nF2 (nmol) | A_{[18F]F} (GBq) | A_{crude} (MBq) | SA_{[18F]NFSi} (GBq/μmol) | [18F]NFSi HPLC Yield (%) |
|---------|-----------|----------------|----------------|--------------------------|---------------------------|
| A       | 1260      | 3.15           | 142            | 0.04                     | 36                        |
| A       | 1260      | 3.15           | 360            | 0.15                     | 34                        |
| B       | 1280      | 3.75           | 352            | 0.04                     | 15                        |
| B       | 1280      | 2.76           | 608            | 0.12                     | 15                        |
| C       | 1280      | 3.30           | 451            | 0.04                     | 9                         |
| C       | 1280      | 2.88           | 618            | 0.10                     | 5                         |
| C       | 1280      | 3.60           | 498            | 0.09                     | 5                         |
| D       | 1090      | 3.06           | 393            | 0.05                     | 13                        |
| D       | 1090      | 3.12           | 333            | 0.04                     | 9                         |

Abbreviation: [18F]NFSi, [18F]-N-fluorobenzenesulfonimide; HPLC, high-performance liquid chromatography; SA_{[18F]NFSi}, SA values of [18F]NFSi.
The values are corrected to end of synthesis (EOS), except for the A_{[18F]F}, which was measured at the start of synthesis. nF2 = amount of carrier F2.
aluminum is the better reflective material; however, the aluminum layer was also easily destroyed during the laser illumination. A comparison of the amount of laser pulses used to promote the isotopic exchange demonstrated that 30 000 pulses gave a higher yield and SA_{18}^{18}FNFSi than 15 000 pulses. However, increasing the number of laser pulses to 60 000 did not give significantly different results for either SA_{18}^{18}FNFSi (P = .16) or HPLC yield (P = .051) of [18F]NFSi (Table 3). Hence, subsequent reactions were conducted with 30 000 laser pulses.

3.2 | Amount of carrier F2 gas

Decreasing the amount of carrier F2 led to an increase of SA_{18}^{18}FNFSi. In the experiments starting with low A_{18}^{18}FF, the highest SA_{18}^{18}FNFSi (1.2 ± 0.6 GBq/μmol) was obtained with 190 nmol of carrier F2 (Table 4). Lowering the amount of carrier F2 to 95 nmol did not increase the SA_{18}^{18}FNFSi. The correlation between the total radioactivity of the the crude [18F]NFSi solution (A_{crude}) and the SA_{18}^{18}FNFSi is shown in Figure 4.

No significant difference in the HPLC yield was observed when decreasing the amount of carrier F2 from 1720 to 1180 nmol (P = .96). As the quantity of carrier was decreased from 1180 to 95 nmol, a gradual decrease in HPLC yield was observed (Table 4).

The best trial conditions (chamber A, 30 000 laser pulses and 190 nmol of carrier F2) were used in experiments with high A_{18}^{18}FF. These provided a SA_{18}^{18}FNFSi of 12.7 ± 1.2 GBq/μmol and a [18F]NFSi HPLC yield of 13 ± 3%.

### TABLE 3 Results of the experiments conducted with different amounts of pulses

| Pulses   | A_{18}^{18}FF (GBq) | A_{crude} (MBq) | SA_{18}^{18}FNFSi (GBq/μmol) | [18F]NFSi HPLC Yield (%) | N |
|----------|---------------------|----------------|------------------------------|--------------------------|---|
| 15 000   | 3.2 ± 0.5           | 420 ± 100      | 0.19 ± 0.12                 | 10 ± 5                   | 4 |
| 30 000   | 3.6 ± 0.5           | 640 ± 330      | 0.66 ± 0.41                 | 23 ± 5                   | 4 |
| 60 000   | 3.0 ± 0.2           | 260 ± 24       | 0.40 ± 0.08                 | 17 ± 1                   | 3 |

Abbreviation: [18F]NFSi, [18F]-N-fluorobenzenesulfonimide; HPLC, high-performance liquid chromatography; SA_{18}^{18}FNFSi, SA values of [18F]NFSi.

All experiments were done with 380 nmol of carrier F2. The values presented are corrected to end of synthesis (EOS), except for the A_{18}^{18}FF, which was measured at the start of synthesis.

### TABLE 4 A comparison of the experiments performed with different amounts of carrier F2

| Entry | nF2 (nmol) | A_{18}^{18}FF (GBq) | A_{crude} (MBq) | [18F]NFSi HPLC Yield (%) | SA_{18}^{18}FNFSi (GBq/μmol) | N |
|-------|-----------|---------------------|----------------|--------------------------|-------------------------------|---|
| 1     | 1720      | 3.0 ± 0.5           | 380 ± 160      | 29 ± 2                   | 0.07 ± 0.05                   | 5 |
| 2     | 1180      | 3.5 ± 0.6           | 570 ± 230      | 31 ± 3                   | 0.16 ± 0.07                   | 4 |
| 3     | 380       | 3.6 ± 0.5           | 640 ± 330      | 23 ± 5                   | 0.66 ± 0.41                   | 4 |
| 4     | 190       | 2.9 ± 0.4           | 500 ± 180      | 13 ± 6                   | 0.93 ± 0.43                   | 4 |
| 5     | 95        | 3.1 ± 0.5           | 430 ± 78       | 5 ± 2                    | 0.57 ± 0.37                   | 3 |
| 6     | 190       | 35.8 ± 1.9          | 4100 ± 2400    | 13 ± 3                   | 10.3 ± 0.9                    | 3 |

The values presented are corrected to end of synthesis (EOS), except for the A_{18}^{18}FF, which was measured at the start of synthesis. Entries 1 to 5 were conducted with a constant amount of A_{18}^{18}FF and a varied amount of carrier F2. Entry 6 was conducted with 10 times higher A_{18}^{18}FF than the other entries.
Figure 5 shows the linear correlation between the SA$_{18^\text{F}}$\(\text{NFSi}\) and the theoretical maximum SA, which was calculated by dividing the initial [\(18^\text{F}\)]fluoride activity, decay corrected to end of synthesis (EOS), by the amount of unlabelled carrier F$_2$ used in the reaction. Hence, the slope of the trendline presented on the graph (0.067, $R^2 = 0.9997$) corresponds to the average radiochemical yield of 6.7% (decay corrected to EOS) of [\(18^\text{F}\)]F$_2$ from [\(18^\text{F}\)]F for all the data sets that fit the trendline. This yield corresponds to the overall yield for the entire synthesis of \([18^\text{F}]\text{NFSi}\) from \([18^\text{F}]\)fluoride and represents a combination of yields 1, 2, and 3, as shown in Figure 1. If all of these yields were 100%, the SA$_{18^\text{F}}\text{F}2$ would be the same as the activity of the [\(18^\text{F}\)]fluoride (A$_{18^\text{F}}\text{F}$) introduced divided by the molar amount of carrier (nF$_2$) added, ie, the units of the horizontal axis in Figure 5, and the slope of the trendline would be unity.

Since the scaling of the SA$_{18^\text{F}}\text{F}2$ from low to high radioactivity experiments, at a constant amount of carrier, mirrors that of the A$_{18^\text{F}}\text{F}$ (Table 4), it is confirmed that the total molar amount of CH$_3$F is essentially the same in all of the experiments. Hence, using the presented conditions, the only variable that the SA$_{18^\text{F}}\text{F}2$ depends upon is the amount of A$_{18^\text{F}}\text{F}$.

5 | CONCLUSION

Vacuum ultraviolet photons were successfully used for the production of [\(18^\text{F}\)]F$_2$. This proof-of-concept study resulted in the production of [\(18^\text{F}\)]F$_2$ with a highest SA of 10.3 ± 0.9 GBq/μmol (decay corrected to EOS), a value that would be sufficient for the production of tracers such as \([18^\text{F}]\)fluoro-DOPA, \([18^\text{F}]\text{CFT}\), or \([18^\text{F}]\text{EF5}\). The use of a commercially available excimer laser and the simplicity of the process will facilitate the application of this method in different radiochemistry laboratories.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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