

Specific Activity of ^{11}C -Labelled Radiotracers: A Big Challenge for PET Chemists

Vanessa Gómez-Vallejo¹, Vijay Gaja¹, Jacek Kozirowski² and Jordi Llop¹

¹Molecular Imaging Unit – CIC biomaGUNE

²Herlev University Hospital

¹Spain

²Denmark

1. Introduction

Non-invasive *in vivo* molecular imaging using radionuclides is based on the Radiotracer Principle of G. von Hevesy and the magic bullet concept by Ehrlich (1990). Both principles require administration of a radioactive tracer (a molecule labelled with a radioactive isotope which when injected into a living object can be traced by external radiation detection devices) and require that the quantity is in sub-pharmacological amounts, i.e. that minimal mass is injected, which in radiopharmaceutical terms means high specific activity.

1.1 Specific activity: The concept

According to the more updated terminology that is going to be recommended by the IUPAC, the concept of specific activity (A_s) is defined as the activity of a radionuclide divided by the mass (or molar amount) of the sum of all radioactive and stable nuclides (present in the same chemical and physical form) isotopic with the element involved (Bonardi, 2003). Thus, if one thinks of an injectable solution of, for instance, 3,5-dichloro-*N*-[[[(2*S*)-1-ethylpyrrolidin-2-yl]methyl]-2-hydroxy-6-([^{11}C]methoxy)benzamide or [^{11}C]Raclopride (a post-synaptic D_2 receptor antagonist which is used for the quantification of D_2 -like dopamine receptors (Elsinga et al., 2006) with different clinical applications, e.g. distinction of multiple system atrophy from Parkinson disease (Van Laere et al., 2010)), what one has in solution before administration to the patient is a mixture of different (chemically identical) species (A+B+C+D in Figure 1).

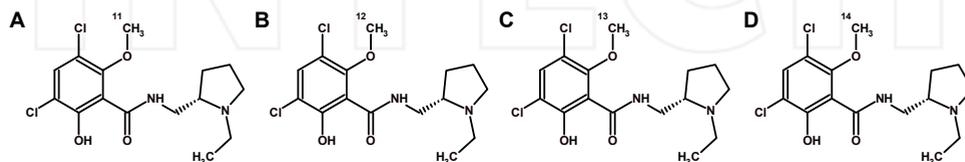


Fig. 1. Chemical structure of [^{11}C]Raclopride and chemically identical species which co-exists with the radioactive species. All carbon atoms whose mass number is not specified are ^{12}C , ^{13}C or ^{14}C .

The A_S of the radiotracer can thus be expressed as the ratio between the amount of radioactivity (given by the number of molecules containing a Carbon-11 atom, A in Figure 1) and the number of molecules (expressed as mass or molar quantity) containing Carbon-11 or other (stable and unstable) isotopes of Carbon (A+B+C+D in Figure 1).

In the context of radiopharmaceuticals, other definitions have been described for different situations that occur when analyzing the final radioactive product. Thus, the term *effective specific activity* is used to describe the mass or molar quantity of a single species radiotracer relative to the total mass or molar quantity of the radiotracer and non-radioactive compound(s) that have similar biochemical properties. For instance, proteins can be labelled with positron emitters (e.g. ^{68}Ga) by (covalently) attaching a bifunctional chelator to introduce later on the metallic radioactive atom. The chemical structure of the labelled (C in Figure 2) and unlabelled (B in Figure 2) species are very similar (although not identical) and thus it can be anticipated that both compounds will have very similar biochemical properties. Isolation of the labelled compound is not (usually) feasible and *effective specific activity* is defined as the ratio between the amount of radioactivity (given by the number of molecules containing a gallium-68 atom, C in Figure 2) and the number of molecules (expressed as mass or molar quantity) with similar biochemical properties (B and C in the Figure). This concept is mainly applied in the context of macromolecules (e.g. labelled proteins, antibodies, peptides, polymers), nanostructures (nanoparticles, nanotubes) and also when, in smaller molecules, undesired contaminants (which cannot be separated from the labelled structure but have similar biochemical properties) are present in the final solution.

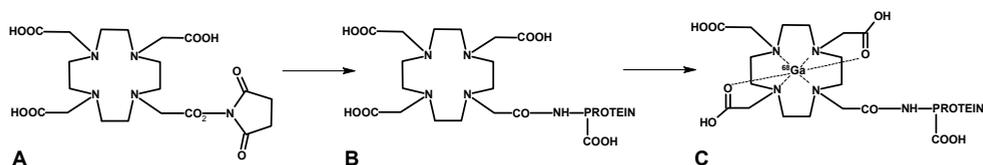


Fig. 2. Schematic reaction pathway for the introduction of a positron emitter (^{68}Ga in the example) in a macromolecule (protein). The labelled and unlabelled structures (B and C) are almost identical and have similar (if not identical) biochemical properties.

When *in vivo* imaging studies are performed, the amount of radioactivity to be administered is somehow fixed within a range: It has to be sufficiently high to allow acquiring good quality images but low enough to prevent saturating of the radio-detectors and, eventually, damage to the organism due to radiation exposure. Thus, the A_S will definitely determine the molar amount of radiotracer. In some applications such as the study of the behaviour of bioactive or toxic molecules, dose exposure studies and the visualization of low density receptors in the brain, the concept of A_S becomes especially relevant, provided that the quantity of injected tracer can definitely produce undesired pharmacodynamic or toxicological effects, as well as target (e.g. receptor) saturation. In some cases, when the injected compound is endogenous and normally found in μM or higher concentrations in the body (e.g. [^{15}O]water, [^{11}C]acetate, [^{11}C]glucose) or that the target or function is not saturated easily (e.g. glucose metabolism - [^{18}F]FDG, hypoxia - [^{18}F]FMISO, enzyme

activity; thymidine kinase 1 - [^{18}F]FLT) specific activity is not crucial. For macromolecules it is known that the highest specific activity is not necessary the optimal one. This has been reported for peptides (de Jong et al., 1999; Bernhardt et al., 2003; Schuhmacher et al., 2005; Velikyan et al., 2010) and antibodies (Pandit-Taskar et al., 2008).

Although theoretical A_S values for PET isotopes are very high (e.g. 341.1 TBq/ μmol for Carbon-11, 63.3 TBq/ μmol for Fluorine-18) these values are usually very far (10-10000 times higher) from those values obtained once the radiotracer has been synthesized. This decrease in A_S is due to a dilution process with the non radioactive isotope, usually occurring during radionuclide production and/or manipulation and preparation of the radiotracer. This fact is well known among the scientific community; however, the number of factors contributing to the introduction of stable isotopes during the production process is very high and usually difficult to be controlled. These potential sources of stable isotopes become relevant when simple calculations are performed. For instance, in 37 GBq of [^{11}C]CO₂ (a radioactive precursor typically used for the preparation of ^{11}C -labelled radiotracers) the number of molecules (when A_S is the theoretical value, 341.1 TBq/ μmol) is only 6.53×10^{13} (0.108 nmol). The introduction of (only) 1 or 100 nmol of non radioactive CO₂ will decrease A_S by a factor of 10 or 1000, respectively.

Despite the dramatic consequences of incorporation of minute amounts of non radioactive carbon on A_S , the number of systematic approaches for the study of contamination sources reported in the literature is scarce, and syntheses under (apparently) identical experimental conditions might lead to immense differences in A_S values of the final radiotracer. These facts have led to perpetual discussions among scientists regarding the optimal procedures to be followed to improve A_S , especially in the case of Carbon-11 labelled radiotracers.

1.2 Carbon-11: A challenging isotope

Among all radionuclides, only a few of them have the adequate physical properties to become suitable candidates for the preparation of radiotracers. In the particular case of positron emitters, there are four radionuclides which have been historically used: Carbon-11, Nitrogen-13, Fluorine-18 and Oxygen-15. The wide historical use of these isotopes is due to (i) they can be produced in relatively high yields in commercially available cyclotrons, (ii) they can be easily introduced in biomolecules, (iii) their decay mode is close to 100% positron emission (see table 1) and (iv) their stable isotopes are present in all organic molecules; this last statement is not true in the case of fluorine, but in many cases the substitution of an hydroxyl group (or hydrogen atom) by a fluorine atom does not significantly alter the biological behaviour of the molecule; thus fluorine can be used to prepare analogues of molecules with specific biological characteristics.

Among these four PET isotopes, Fluorine-18 is probably the most widely used, especially for clinical applications. Fluorine-18 forms strong covalent bonds with carbon atoms and can be incorporated into a large variety of organic molecules; on the other hand, substitution of a hydrogen atom by a fluorine atom causes little steric alterations in the molecule; in some particular cases, the biological properties of the radiotracer are even improved with respect to the original molecule. Moreover, Fluorine-18 has a small positron range and its half-life is relatively long (109.8 minutes) allowing the preparation of complex molecules with

acceptable radiochemical yields. Finally, the relatively long half-life permits the commercialization of radiotracers as diagnostic tools in the clinical environment.

Radionuclide	Half-life (min)	Decay mode	Max. Energy (MeV)
Fluorine-18	109.8	97% β^+ + 3% EC*	0.69
Carbon-11	20.4	100 % β^+	0.96
Nitrogen-13	9.98	100 % β^+	1.19
Oxygen-15	2.05	100 % β^+	1.70

Table 1. Physical characteristics of Fluorine-18, Carbon-11, Nitrogen-13 and Oxygen-15. *EC: Electron capture.

Out of the above mentioned clinical environment, Nitrogen-13 and Oxygen-15 can be also potentially used for the synthesis of radiotracers. However, the manufacturing process of radiotracers with these positron emitters presents some difficulties because of their short half-life (9.98 and 2.05 min, respectively) and distribution of radiotracers from one centralized production centre to surrounding centres is not feasible.

Despite the widespread use of these isotopes (which is reflected in a high number of scientific publications in which the preparation and putative applications of ^{18}F -, ^{13}N - and ^{15}O - labelled radiotracers are described) the most challenging and exciting positron emitter is probably Carbon-11, which in general terms cannot be transported from manufacturing centres to surrounding hospitals and thus began to receive increasing attention in the sixties due to the widespread installation of cyclotrons in hospitals and research centres.

There are two main reasons to consider Carbon-11 as the most exciting and challenging PET isotope. First, carbon is present in all organic compounds, and thus a Carbon-11 analog (identical to the unlabelled structure) of any specific organic molecule could be potentially prepared, and second, Carbon-11 can be produced with good yields in two different chemical forms ($[^{11}\text{C}]\text{CH}_4$, obtained by irradiating N_2/H_2 mixtures; and $[^{11}\text{C}]\text{CO}_2$, obtained by irradiation of N_2/O_2 mixtures (Christman et al., 1975)) which can be easily transformed into other radioactive precursors via well established labelling strategies to perform different types of chemical reactions. Thus, Grignard-type reactions to yield [carbonyl- ^{11}C]carboxylates can be carried out by using directly cyclotron generated $[^{11}\text{C}]\text{CO}_2$; the latter can be also converted into $[^{11}\text{C}]\text{CO}$ through the reduction over zinc or molybdenum in an on-line process and further used to produce (e.g. via the palladium-mediated $[^{11}\text{C}]$ carbonylation of olefins, alkynes and organic halides) carboxylic acids (Itsenko et al., 2006), amides (Rahman et al., 2003) and imides (Karimi et al., 2001), among others. $[^{11}\text{C}]\text{CO}_2$ can be also transformed into $[^{11}\text{C}]\text{CH}_3\text{OH}$ via reduction with LiAlH_4 ; the latter can be further reacted with hydriodic acid to yield $[^{11}\text{C}]\text{CH}_3\text{I}$ which is by far the most commonly used radioactive precursor for introducing Carbon-11 into organic molecules via nucleophilic substitution using amines (Mathis et al., 2003), amides (Hashimoto et al., 1989), phenols (Ehrin et al., 1985) or thiol groups (Langstrom & Lundqvist, 1976). Eventually, $[^{11}\text{C}]\text{CH}_3\text{I}$ can be passed in gas phase through a silver triflate column at high temperature to yield $[^{11}\text{C}]$ methyl triflate (Jewett, 1992), which can be used as a highly reactive methylating agent when reactivity of $[^{11}\text{C}]\text{CH}_3\text{I}$ is not sufficient. On the other hand, $[^{11}\text{C}]\text{CH}_4$ can be also

converted into $[^{11}\text{C}]\text{CH}_3\text{I}$ through a gas-solid iodination reaction at high temperature. In this case, the iodination step is carried out in a quartz tube which contains I_2 vapour at high temperature (Prenant & Crouzel, 1991; Larsen et al., 1997).

This versatility of Carbon-11 as a synthetic tool has led to an immense number of publications in the scientific literature in which the synthetic strategies and optimization steps are described. As a result, nowadays there is a large variety of well established processes that can be followed when the radiosynthesis of a new radiotracer is approached. However, depending on the final application of the tracer, one strategy can be more appropriate than others, and one of the big challenges for radiochemists consists not only of synthesizing the radiotracer with good radiochemical yield and high radiochemical purity but also with a sufficiently high A_s for a particular application.

In this chapter, an exhaustive analysis (based on bibliographic data) of the typical values of A_s obtained for ^{11}C -labelled radiotracers and the main factors affecting this parameter will be performed. Experimental protocols to improve specific activity of ^{11}C -labelled radiotracers will be described and discussed on the basis of bibliographic data and personal experience of the authors.

2. Specific activity in ^{11}C -labelled radiotracers

2.1 Modulation of specific activity

According to IUPAC definition (see above) and in the context of radiopharmaceuticals, specific activity can be expressed using equation (1):

$$A_s = \frac{A_i}{n_i} \quad (1)$$

Where A_i is the activity (expressed in Bq) of the radiopharmaceutical specie and n_i is the molar amount of the sum of all radioactive and stable forms of the radiopharmaceutical. Usually, A_s is expressed, in the case of ^{11}C -labelled radiopharmaceuticals, in $\text{GBq}/\mu\text{mol}$. From the equation, it is clear that specific activity can be increased either by (i) increasing the amount of radioactivity and/or (ii) decreasing the amount of stable forms.

In the specific case of cyclotron produced ^{11}C , the increase in the amount of radioactivity can be achieved, obviously, by producing higher amounts of radioactive precursor (e.g., $[^{11}\text{C}]\text{CO}_2$ or $[^{11}\text{C}]\text{CH}_4$). However, increasing the dose (integrated current) or the beam intensity does not always result in a higher amount of radioactivity and consequently in a higher specific activity of the final radiopharmaceutical. In other occasions, increasing the beam time increases also the incorporation of impurities. For instance, it has been reported that the in-target specific activity of $[^{11}\text{C}]\text{CO}_2$ peaked at 20-25 minutes of beam time and decreased with longer irradiations, due to incorporation of contamination into the target gas, which was faster than the net production of carbon-11 (Mock, 2006). However, in a certain range and in general terms, increasing irradiation time results in an increase of A_s . In Figure 3, a set of experiments performed by the authors of this chapter (results not published before) are shown. Carbon-11 was produced by irradiation (target current=22 μA , 1-8 μAh) of a gas N_2/H_2 mixture (95/5, filling pressure=16 bar) with high energy (~ 16 MeV)

protons. The resulting $[^{11}\text{C}]\text{CH}_4$ was allowed to react with iodine at 720°C to form $[^{11}\text{C}]\text{methyl iodide}$ in a gas circulating process, to be further reacted with phenol in the presence of a base to yield $[^{11}\text{C}]\text{anisole}$. As can be seen, higher specific activity values were obtained with increasing beam time. Although the curve seems to reach a plateau, the presence of a peak as previously reported (Mock, 2006) was not found, probably because no longer irradiation times were investigated.

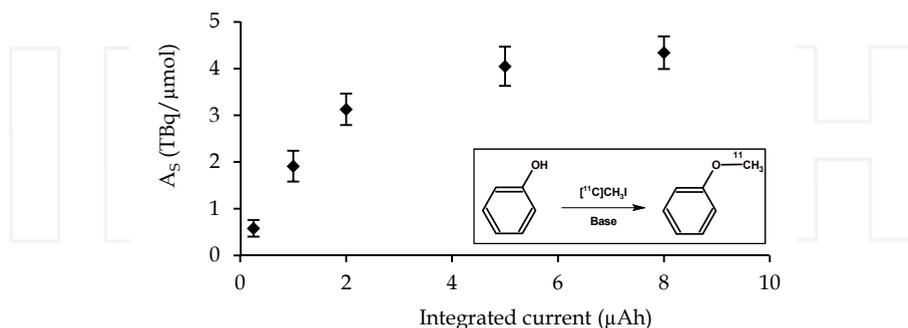


Fig. 3. Specific activity of $[^{11}\text{C}]\text{anisole}$ (corrected to EOB, end of bombardment) produced using different irradiation times.

Besides increasing the amount of radioactivity, the other possibility to increase specific activity consists of decreasing the amount of stable forms, or in other words, to prevent the introduction of stable isotopes of carbon (mainly ^{12}C) in any of the processes followed for the preparation of the radiopharmaceutical, from the production of ^{11}C in the cyclotron till the final formulation of the radiopharmaceutical. These non radioactive carbon sources might potentially contaminate the reaction environment during radiopharmaceuticals preparation processes, thus decreasing the final specific activity. Actually, some of these sources have been known for a long time. During production of the radioactive precursor (irradiation), impurities in the target gas, impurities coming from the valves, pressure regulators, seals, target body, target windows or even residues from hydrocarbon solvents used to clean metal pieces after manufacturing might affect the final specific activity (Dahl & Schlyer, 1985). During radiotracers synthesis, incorporation of contaminants from the atmosphere, or release of undesired chemicals from tubes, reactors, etc. or even the presence of stable carbon in some of the reagents could also contribute to the decrease of final A_S .

These non radioactive sources will have different effects on the final specific activity depending on the particular configuration of the different equipment at each site. The effects will also vary depending on the synthetic process followed and the chemical structure of such impurities. Thus, every specific scenario should be investigated individually. However, the discussion of all specific scenarios and configurations is beyond the scope of this chapter, and only a few synthetic routes, namely, methylation reactions starting from cyclotron produced $[^{11}\text{C}]\text{CO}_2$ and $[^{11}\text{C}]\text{CH}_4$ (which are considered by the authors the most frequently used in Carbon-11 radiochemistry) will be discussed. Still, most of the concepts introduced in the following pages can be applied (or extrapolated) to the preparation of ^{11}C -labelled radiotracers by following other routes.

2.2 Interpretation of specific activity: Are reported values always comparable?

If one has a solution of, for instance, [^{11}C]Raclopride, and specific activity is not the theoretical value, species A, B, C and D (Figure 1) are co-existing. The specific activity will be given by equation (2):

$$A_S = \frac{A_A}{n_A + n_B + n_C + n_D} \quad (2)$$

Where A_A is the amount of radioactivity due to the presence of specie A, and n_A , n_B , n_C and n_D are the molar amounts of A, B, C and D, respectively. When the specific activity of a radiotracer is the theoretical value (341.1 TBq/ μmol for Carbon-11), n_B , n_C and n_D are zero, and the value of A_S value is not changing over time, because both the amount of radioactivity (A_A) and the molar amount of A (n_A) are decreasing with the same rate.

On the other hand, when the specific activity is far from its theoretical value, then:

$$n_B + n_C + n_D \gg n_A \quad \text{thus,} \quad \frac{A_A}{n_A + n_B + n_C + n_D} \sim \frac{A_A}{n_B + n_C + n_D}$$

As $(n_B + n_C + n_D)$ is (almost) constant (due to the long half life of ^{14}C) then A_S decreases at the same rate as A_A does. In other words: Every half life, the value of A_S is decreased by a factor of 2. Therefore, in real scenarios the values of A_S have to be reported at a given time point. In the literature, and in the particular case of ^{11}C -labelled radiotracers, authors usually report A_S at the end of synthesis (EOS), end of bombardment (EOB) or end of transfer (of the activity, from the cyclotron to the hot cell where the radiosynthesis takes place). Values at EOB are usually easier to compare, because they do not depend on synthesis time and offer a direct estimation of the amount of stable carbon contributing to the dilution (and consequent decrease in A_S). In some occasions, where systematic studies are performed to search for the sources of contamination, the total amount of carrier (which can be directly compared to previously published values) is reported.

3. Specific activity of ^{11}C -labelled radiotracers produced following methylation

Methylation reactions consist of attaching a CH_3 - group (using e.g. CH_3I or CH_3OTf) to a nucleophile (usually an oxygen, nitrogen or sulphur atom) via the $\text{S}_{\text{N}}2$ reaction pathway. When ^{11}C -labelled radiotracers are prepared by following this route, [^{11}C] CH_3I cannot be produced directly in the target in large amounts (Wagner et al., 1981) and has to be synthesized from other synthetic precursors, namely [^{11}C] CO_2 or [^{11}C] CH_4 . Both schemes will be discussed separately.

3.1 Methylation reactions starting from cyclotron produced [^{11}C] CO_2

3.1.1 [^{11}C] CO_2 production

The irradiation of nitrogen gas at sufficient beam (proton) energies yields large amounts of [^{11}C] CO_2 . During irradiation, ^{14}N is converted into ^{11}C via the $^{14}\text{N}(\text{p}, \alpha)^{11}\text{C}$ nuclear

reaction, with the highest cross-section at 7.5 MeV. According to Christman and co-workers, it is unnecessary to add oxygen to the nitrogen gas, because trace amounts of oxygen already present in the nitrogen (~1 ppm) are sufficient for the oxidation reaction to occur. They reported that, when oxygen was added to the system, copious amounts of nitrogen oxides were produced in addition to the desired $[^{11}\text{C}]\text{CO}_2$, from the reaction $^{16}\text{O}(p, \alpha)^{13}\text{N}$ and from radiolysis processes. According to previous reports (Ache & Wolf, 1968) the primary products resulting from the reactions of “hot” carbon atoms with nitrogen-oxygen mixtures at low radiation doses are cyanide and carbon monoxide. The oxidation of these two primary products as a function of the radiation dose by the proton beam are not fully known, but in any case, the final product obtained from this system was shown to be over 90 per cent $[^{11}\text{C}]\text{CO}_2$, without the incorporation of any chemical oxidation.

Currently, $[^{11}\text{C}]\text{CO}_2$ is still produced in similar targets to those described by Christman et al., although 0.5-2% oxygen is added to the target gas and some improvements have been incorporated; it was demonstrated (Ferrieri et al., 1993) that the interaction between beam and target walls (independently of the material used for the manufacture of the target) produced the release of non radioactive carbon into the target gas mixture, decreasing thus specific activity. Thus, the use of targets with minimal surface exposure to beam is preferred. Also, and due to multiple scattering suffered by the beam through the foil window and in the gas, a conical-shaped target (a cylindrical target was used in previous experiments conducted by Christman’s group) was proposed (Schlyer & Plascjak, 1991). The conical target is still the standard model supplied with some commercial cyclotrons.

3.1.2 $[^{11}\text{C}]\text{CH}_3\text{I}$ production and methylation

The general reaction pathway followed for the preparation of ^{11}C -labelled radiopharmaceuticals via methylation using $[^{11}\text{C}]\text{CH}_3\text{I}$ (or $[^{11}\text{C}]\text{CH}_3\text{OTf}$) produced from $[^{11}\text{C}]\text{CO}_2$ (historically named the “wet method”) can be summarized in 6 steps:¹ (i) $[^{11}\text{C}]\text{CO}_2$ is generated in a cyclotron via the $^{14}\text{N}(p, \alpha)^{11}\text{C}$ nuclear reaction by bombarding a N_2/O_2 mixture with high energy protons; (ii) the target content is transferred to a hot cell and trapped in a molecular sieve column (Mock et al., 1995) at room temperature or in a cold trap (liquid nitrogen); (iii) the reactor is prefilled with lithium aluminium hydride solution; (iv) $[^{11}\text{C}]\text{CO}_2$ is released by increasing the temperature of the trap and bubbled (with the help of an inert gas) in the reactor; (v) After complete trapping, solvent is evaporated to dryness and hydriodic acid (aqueous solution) is added to generate $[^{11}\text{C}]\text{CH}_3\text{I}$ which is distilled by heating under continuous nitrogen flow and (vi) $[^{11}\text{C}]\text{CH}_3\text{I}$ is trapped in a reactor prefilled with the adequate precursor, where methylation takes place. Along this process, the formation of the non-radioactive specie (this is, $[^x\text{C}]\text{CH}_3\text{I}$, where ^xC is any stable isotope of carbon) is due to the presence, incorporation and/or *in situ* generation of $[^x\text{C}]\text{CO}_2$ before the treatment with hydriodic acid. The specific sources of such ^xC in real scenarios and the individual contribution of each one to the decrease of final specific activity have been historically profoundly discussed.

¹ $[^{11}\text{C}]\text{CH}_3\text{I}$ can be also produced from $[^{11}\text{C}]\text{CO}_2$ via reduction over a nickel catalyst at high temperature and further reaction with I_2 (“gas phase” method). This reaction pathway will be considered later on.

3.1.3 Search for the sources of ^{12}C in methylation reactions starting from $[^{11}\text{C}]\text{CO}_2$ via the wet method

In one of the first reviews in which different sources of carrier carbon were considered (Crouzel et al., 1987) practical recommendations to attain molar activities of 75–175 GBq/ μmol routinely were suggested. These recommendations included: (i) using (small and properly washed) aluminum targets with Havar, stainless steel or titanium foils, (ii) using high purity target gases with a purification trap installed between the target and the gas supply, (iii) using metal (stainless steel or copper) tubing between the gas supply and target, (iv) performing short irradiations with as high a beam current as possible and (v) using the smallest possible amount of LiAlH_4 , preferably dissolved in dry (distilled from sodium or potassium) THF. The authors suggested that most of the stable CO_2 was coming from the target under irradiation conditions.

One of the first systematic studies searching for the sources of carrier carbon in ^{11}C -labelled radiotracers produced from $[^{11}\text{C}]\text{CH}_3\text{I}$ synthesized from cyclotron generated $[^{11}\text{C}]\text{CO}_2$ was performed 1 year later (Iwata et al., 1988). Although the authors suspected in a first step that LiAlH_4 (solution in THF) was the main source of carrier (LiAlH_4 can absorb CO_2 from the environment when not stored/prepared under rigorous inert atmosphere), the total carrier amount was not so much reduced as expected with decreasing the concentration of LiAlH_4 solution. This fact led them to postulate that a significant amount of carrier might come from the $[^{11}\text{C}]\text{CO}_2$ production system (the target), although no significant correlation between the total carrier amount and the volume of the target gas was observed. Finally, they concluded that carrier carbon dioxide was mostly originated in the methanol formed from a trace of THF remaining in the LiAlH_4 after the evaporation step, and could be decreased significantly (up to a certain limit) by reducing the amount and concentration of the $\text{LiAlH}_4/\text{THF}$ solution. They concluded that it might be very difficult to overcome this limit, and thus increasing starting ^{11}C -activity and shortening the synthesis time were proposed to be the most adequate solution to achieve higher specific activities.

In a more recent work (Matarrese et al., 2003) another systematic study of the different factors introducing carrier carbon was performed. Although the authors concluded that the critical point to obtain high specific radioactivity was the minimization of lithium aluminum hydride quantity (see table 2 for relation of A_5 and quantity of LiAlH_4 solutions obtained by Matarrese's group), different modifications were also introduced to the commercial Synthesizer to improve the specific activity. The original reaction vessel design was modified and the tube inlets were accomplished by standard male-luer fittings with disposable needles, while carrier gas flows (the purge gas lines leading to reaction vessels and to dispensing vessels and solid phase extraction unit) were separated, thus allowing the use of different gases for these two purposes. Besides, several routine operations were included before syntheses, mainly: (i) the target was flushed with the target gas mixture (at least 10 target volumes) prior to bombardment; (ii) a leak-test was performed on the liquid nitrogen loop, $[^{11}\text{C}]\text{CO}_2$ trapping reaction vessels and connecting tubes; (iii) reaction vessels and liquid nitrogen trap were dried at 150 °C for 30 minutes by a continuous argon flow (100 mL/min); (iv) the PTFE $[^{11}\text{C}]\text{CO}_2$ delivery lines connecting the target with the module were continuously flushed with a stream of helium during bombardment and (v) the metallo-organic trapping solution ($\text{LiAlH}_4/\text{THF}$) was added into the reaction vessel

immediately before unloading the $[^{11}\text{C}]\text{CO}_2$ target with the sample-lock gas-tight syringe. As can be seen in the table, good specific activity values were reached, especially when the optimal amount of LiAlH_4 solution was used, although such values were reported at EOS and synthesis time was not reported; therefore, recalculation at EOB is not possible.

Radioligand	Yield EOB (%)	A _s EOS (GBq/μmol)	LiAlH ₄ (μmol)
$[^{11}\text{C}](\text{R})\text{-MDL-100907}$	55 ± 10	70 ± 30	10
$[^{11}\text{C}](\text{R})\text{-MDL-100907}$	60 ± 20	315 ± 89	7
$[^{11}\text{C}](\text{R})\text{-MDL-100907}$	54 ± 10	392 ± 166	6
$[^{11}\text{C}](\text{R})\text{-MDL-100907}$	53 ± 10	322 ± 181	5

Table 2. Relation between specific radioactivity of $[^{11}\text{C}](\text{R})\text{-MDL-100907}$ and quantity of the $\text{LiAlH}_4/\text{THF}$ solutions.

Five years later (Ermert et al, 2008), a different strategy for the preparation of $[^{11}\text{C}]\text{CH}_3\text{I}$ (in which $[^{11}\text{C}]\text{CO}_2$ from the target chamber was reduced by a lithium aluminum hydride solution, and the methanol obtained on-line was converted using triphenylphosphine diiodide) was reported. $[^{11}\text{C}]\text{CH}_3\text{I}$ was transformed into $[^{11}\text{C}]\text{MeOTf}$ via on-line conversion to synthesize $[^{11}\text{C}]\text{TCH346}$. Six batches of this radiotracer were prepared within 10 days and specific activity values of 40, 330, 1700, 280, 770 and 5700 GBq/μmol for syntheses 1-6, respectively, were obtained. All syntheses were carried out using the same flask of commercially available lithium aluminum hydride solution repetitively; as the specific activity increased during the course of the synthesis campaign, the authors concluded that essential dilution by stable carbon via the LiAlH_4 -solution could nearly be excluded, or at least equally important carbon sources appeared to be the target chamber and the penetration of ambient air into the target line and the synthesis unit. In any case, the aforesaid specific activities are higher than those earlier reported and are probably the highest values ever reported for ^{11}C -labelled radiotracers prepared by following this synthetic approach.

Almost simultaneously to the paper reported by Ermert and co-workers, and encouraged by this historical disagreement suggesting that the sources of contamination were extremely dependent on the particular configuration of the systems involved in the production process of each particular site (e.g. quality of the reagents and irradiated gases, target material, synthesis box, etc.) an exhaustive analysis of the potential sources of non radioactive carbon and their individual contribution to the final specific activity was carried out by some of the authors of this chapter (Gómez-Vallejo et al., 2009). In these studies, four synthetic scenarios were defined: (a) syntheses were carried out by executing steps (iii) and (v) of the previous general procedure; (b) syntheses were run by executing steps (iii), (iv) and (v); (c) syntheses were run by executing steps (ii), (iii), (iv) and (v) and (d) syntheses were run by executing all steps included in the general procedure. To assess also the effect of bombarding time on the final amount of $[^{11}\text{C}]\text{CH}_3\text{I}$, different experiments were carried out at different integrated currents (1, 2, 3 and 10 μAh; scenarios d₁-d₄, respectively).

Under Scenario (a) (where the contribution to the production of stable methyl iodide should come from the presence of CO_2 absorbed in LiAlH_4 solution, methanol formed from THF

remaining in the LiAlH_4 after evaporation step and/or direct CO_2 incorporation from the atmosphere during the synthesis process due to the lack of tightness of the synthesis module) only 15.5 ± 2.7 nmol of non-radioactive CH_3I were generated (Figure 4B). Under scenario (b) conditions (where the contribution of absorbed CO_2 in the molecular sieve was also considered), 45.8 ± 11.7 nmol of CH_3I were generated. Under scenario (c) conditions (where also the contribution from loading and unloading the target was considered, thus CO_2 should come from carbon dioxide absorbed either in the target chamber or in the stainless-steel tubing connecting the target with the synthesis box, and present as an impurity in the target gas), 78.5 ± 12.3 nmol of CH_3I were detected (Figure 4B). Under scenario (d), 537.9 ± 197.5 , 832.8 ± 56.3 , 907.4 ± 28.2 and 1067.2 ± 59.3 nmol of methyl iodide were obtained for integrated currents of 1, 2, 3 and 10 μAh , respectively (scenarios d_1 - d_4 , Figure 4B). These results show that the generation of stable methyl iodide under scenarios (a), (b) and (c) is minor when compared to the contribution of bombarding processes during irradiation (see Figure 4A for individual contribution of the sources considered at each scenario). On the other hand, there is a non-linear trend between the increase in the amount of $^{11}\text{C}\text{CO}_2$ and the increase in integrated current in the target (Figure 4A), suggesting that the decrease in specific activity is probably due to the presence of carbon carrier contamination which undergoes combustion (High temperature, estimated around 260°C and pressure, around 38 bar, are reached into the target chamber during bombardment) mainly during the first minutes of irradiation. This effect of beam integrated current on the amount of stable carbon was also reported by other authors (Mock, 2006).

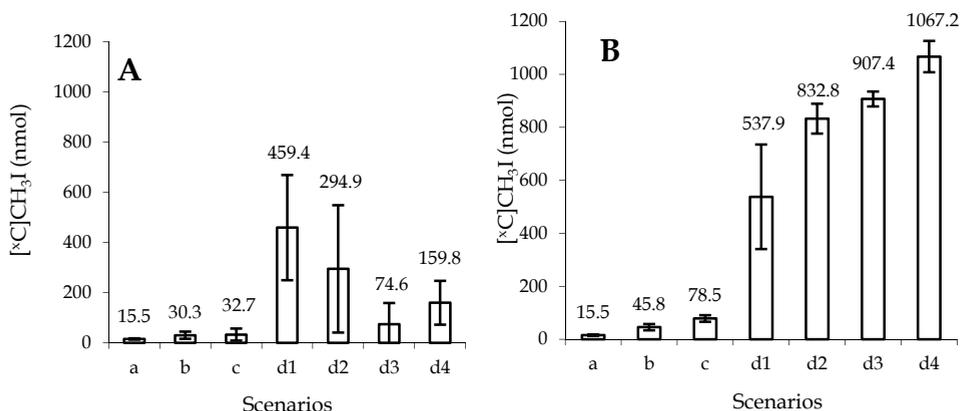


Fig. 4. Amount (in nmol) of $^{11}\text{C}\text{CH}_3\text{I}$ generated under scenarios (a), (b), (c) and (d). Individual contribution of the factors considered in each scenario (A) and cumulative contribution (B).

In view of these results, some general procedures (which should help to improve the specific activity of Carbon-11 labelled compounds synthesized by the wet method) were suggested,

including: i) loading/unloading (through transfer line into the molecular sieve) the target several times (with the aim of transferring all CO₂ contamination present in the target chamber and/or the transfer line into the molecular sieve); ii) loading/bombarding (integrated current = 1 μAh, target current = 24 μA)/unloading (to waste) the target three times (to “burn” all carbon compounds presumably present in the target chamber); iii) preconditioning (t = 60 minutes, T = 250°C, continuous N₂ flow = 50 mL/min) the molecular sieve column (to eliminate CO₂ from the molecular sieve); iv) cleaning (ethanol/acetone/diethyl ether) and drying (N₂) the synthesis box and keeping the system pressurized after drying to avoid atmospheric contamination; v) using commercially available LiAlH₄/THF solution and vi) minimizing the amount of LiAlH₄/THF solution used per run; furthermore, keeping the target loaded (P = 21 bar) between two consecutive productions and periodical inspection of general connections and tubing should help in the prevention of external contamination in the target chamber, the transfer line and the synthesis box.

Although by implementing these steps moderate specific activity values could be achieved in the preparation of e.g. [¹¹C]Raclopride (23.2 ± 11.7 GBq/μmol at EOS, 128 ± 64 GBq/μmol at EOB (Catafau et al., 2009)), such values were still far from those reported by Ermert and coworkers in 2008. This is probably due to the fact that the purity of the gases was not considered in the study conducted by Gomez-Vallejo et al., and no purification steps before loading the target were implemented. Also, no specific cleaning of the target chamber was performed before the experiments. In any case, the values obtained by Ermert’s group are very far from average specific activities reported in the literature (see table 5); thus, a profound analysis of the specific configuration (and preparation procedures) used by this group could help to get more consistent conclusions related to the sources of non radioactive carbon and the protocols to be followed in order to increase A_S.

One of the last works focused in improving specific activities in [¹¹C]CO₂ production was reported recently (Eriksson et al., 2009). Three consecutive test periods were carried out with a standard IBA aluminum target, using 4 different configurations: a) Previously not irradiated target body, using a new window foil with nitrile o-ring; b) used foil with silver o-ring; c) new foil with silver o-ring and d) same basic build as (c) but with nickel plating on the aluminum surface. For configurations (a), (b) and (c) an increase in A_S of 2.4-2.5 GBq/μmol per μAh was observed for second and third production of a series of consecutive runs (results that are consistent with those reported by Gómez-Vallejo et al.), while for (d) the increase was significantly faster (5.4 GBq/μmol per μAh). After several irradiations, a plateau was found for all configurations, but (d) gave better specific activities (2540 ± 190 GBq/μmol) than (a) and (c) (2010 ± 310 GBq/μmol and 1920 ± 220 GBq/μmol, respectively).² The specific activity obtained with (d) could be even improved by connecting the helium line (used for activity transfer from cyclotron) only to the ¹¹C target (values up to 5400 ± 1700 GBq/μmol). Thus, nickel plating on the aluminum surface and using high purity gases (isolated from atmosphere or potential contamination sources) seem to have a positive effect on specific activity values obtained when the wet method is used.

² Configuration (b) developed a target leak before the plateau was established.

3.2 Methylation reactions starting from cyclotron produced $[^{11}\text{C}]\text{CH}_4$

3.2.1 $[^{11}\text{C}]\text{CH}_4$ production

The irradiation of nitrogen/hydrogen gas mixtures at sufficient beam (proton) energies yields large amounts of $[^{11}\text{C}]\text{methane}$ (Christman et al., 1975). During irradiation, ^{14}N is converted into ^{11}C via the $^{14}\text{N}(p, \alpha)^{11}\text{C}$ nuclear reaction (Epherre and Seide, 1971). From the reaction of hot recoil carbon atoms with nitrogen molecules, $[^{11}\text{C}]\text{CN}$ and $[^{11}\text{C}]\text{CN}_2$ can be produced (Dubrin et al., 1964), and of these $[^{11}\text{C}]\text{CN}$ is the most probable final stable species. Upon the addition of small amounts of hydrogen to the target gas, a second (and very fast) reaction gives $[^{11}\text{C}]\text{HCN}$ (Ache & Wolf, 1968), which is readily reduced via a radiation induced mechanism to yield $[^{11}\text{C}]\text{CH}_4$. Unfortunately, increasing the beam current and irradiation lengths results in a significant drop in the amount of $[^{11}\text{C}]\text{CH}_4$, probably due to beam-wall interactions and high probability of the radioactive species sticking in the target walls, resulting in a reduction in recoverable yield. Due to these observed interactions with the target walls, large volume targets (flow through design in some cases) where beam wall interactions are less likely, produce results more in line with theory. Thus, the choice of target material in small- to medium-sized targets is therefore proposed to be one of the most important factors for optimizing $[^{11}\text{C}]\text{methane}$ yields (Koziorowski et al., 2010). Buckley et al. (2004) explored the viability of using a niobium target chamber with a cylindrical shape (15 mm in diameter and 120 mm in length, energy of the proton beam = 12 MeV) for the production of $[^{11}\text{C}]\text{CH}_4$ from a gas mixture of N_2/H_2 ; 95/5 and 90/10. In table 3, the amount of radioactivity (in GBq) and saturation yields (in GBq/ μA) for 20 μA irradiations are shown.

Time (min)	Yield (GBq)*	Saturation Yield (GBq/ μA)
5	12.47	3.66
10	20.02	3.29
20	32.19	3.18
30	39.22	3.03
40	43.81	2.92
60	48.47	2.78

Table 3. Target yields in GBq and production rate at saturation in GBq/ μA for the production of $[^{11}\text{C}]\text{CH}_4$ at 20 μA for the Nb chamber (loaded with N_2/H_2 ; 90/10). Nominal target loading pressure was 2067 kPa.

When beam was performed on 5% hydrogen at 20 μA for 20 min, 26.94 GBq (EOB) were produced (saturation yield of 2.70 GBq/ μA). These results are not as good as the 10% values (32.19 GBq, 3.18 GBq/ μA) but comparable to 10% results reported for the aluminum target chamber. Although the yields from the niobium target chamber were found to be better than those from the aluminum target chamber, the production rate was found to diminish with time.

In a recent work, the use of quartz as a target material (due to its chemical inertness) was proposed (Koziorowski et al., 2010); the use of such material should also improve the

specific activity of produced $[^{11}\text{C}]\text{CH}_4$ due to its low carbon content and the fact that it is manufactured without the use of any potential carbon sources, such as lubricants. In this work, the authors designed and constructed a target based on an aluminum body fitted with a quartz liner. A mixture N_2/H_2 (90/10) was used (filling pressure = 26 bar). As previously reported, an increasing deviation from theoretical yields with increased irradiation dose (μAh) was seen (see Figure 5), both when irradiation time and irradiation current were increased. The authors concluded that this drop in yields should be explained by the presence of radioactive species adsorbed to the target, although the underlying mechanism(s) of this phenomenon has yet to be elucidated.

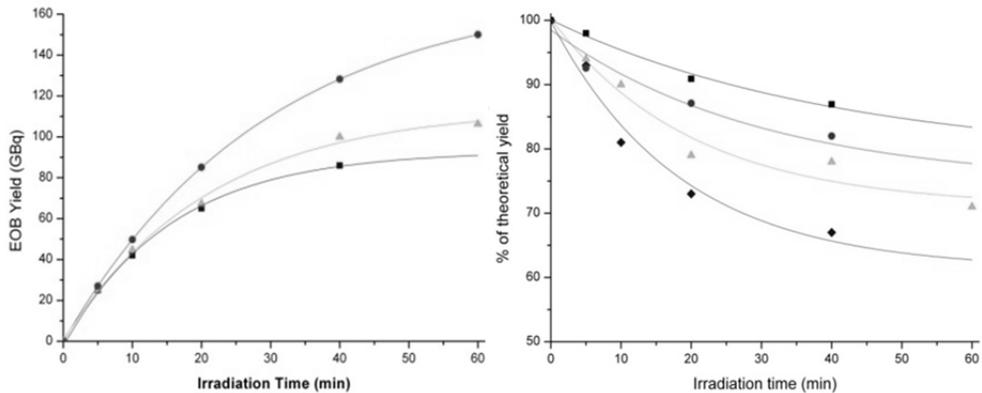


Fig. 5. (A) Theoretical and production yields expressed as GBq at EOB with a beam current of 25 μA . Theoretical yield (\bullet); target with quartz insert (\blacktriangle); target without quartz insert (\blacksquare); (B) Production yields expressed as percentage of the theoretical yield for 10 μA with (\blacksquare) and without quartz insert (\bullet) and for 25 μA with (\blacktriangle) and without quartz insert (\blacklozenge).

Buckley et al. (2004) had previously proposed an exponential equation which target production data could be fitted to:

$$Y = A e^{-at} I SF \quad (3)$$

Where Y is the decay-corrected yield (mCi), A the fitted pre-exponential term (mCi/ μA , term representing production rates in the target), a the fitted exponential term (min^{-1} , representing losses due to activity retained in the target), I the beam current, t the irradiation time (min) and SF the saturation correction factor ($1 - e^{-\lambda t}$).

The results obtained after fitting the data obtained by Kozirowski and coworkers are shown in Table 4, and compared to those previously obtained with the niobium target (Buckley et al., 2004). As can be seen, the quartz-lined target chamber performs well compared with the niobium target chamber, while the pure aluminum chamber performs slightly less well.

Target chamber	A	a (x 10000)
Niobium cylinder [†]	95 ± 2	40 ± 4
Quartz-lined aluminum cylinder [‡]	170 ± 6	45 ± 11
Aluminum cylinder*	168 ± 10	85 ± 26
Aluminum cone*	78 ± 9	135 ± 44
Nickel cone*	65 ± 9	527 ± 67
Stainless Steel cylinder*	71 ± 11	64 ± 62
Large Aluminum cylinder*	70 ± 9	180 ± 52

Table 4. Fitted parameters *A* and *a* for targets used for production of $[^{11}\text{C}]\text{CH}_4$. [†]Buckley et al., 2004; [‡]Koziorowski et al., 2010; * Buckley et al., 2000.

3.2.2 $[^{11}\text{C}]\text{CH}_3\text{I}$ production and methylation

The general reaction pathway followed for the preparation of ^{11}C -labelled radiopharmaceuticals via methylation using $[^{11}\text{C}]\text{CH}_3\text{I}$ (or $[^{11}\text{C}]\text{CH}_3\text{OTf}$) produced from $[^{11}\text{C}]\text{CH}_4$ can be summarized in 5 steps: (i) $[^{11}\text{C}]\text{CH}_4$ is generated in a cyclotron via the $^{14}\text{N}(p,\alpha)^{11}\text{C}$ nuclear reaction by bombarding a N_2/H_2 mixture with high energy protons; (ii) the target content is transferred to a hot cell and trapped in Carbosphere 60/80 at low T (approximately -140°C); (iii) $[^{11}\text{C}]\text{CH}_4$ is desorbed by heating (~80°C) and allowed to react with iodine at 720°C to form $[^{11}\text{C}]\text{methyl iodide}$ in a gas circulating process. At this step, due to the low efficiency of the iodination reaction, $[^{11}\text{C}]\text{methyl iodide}$ is selectively retained in a trap (PorapakTM Q, 50-80 mesh) at room temperature, while unreacted $[^{11}\text{C}]\text{CH}_4$ is allowed to recirculate until reaction is complete (~80% conversion). (iv) After several recirculations, the PorapakTM Q trap is heated (~190°C) and $[^{11}\text{C}]\text{methyl iodide}$ is distilled under continuous inert gas flow (20 mL/min); (v) the gas stream is directed to a reactor pre-filled with a solution of the precursor and methylation reaction takes place. A single pass gas phase method (where $[^{11}\text{C}]\text{CH}_4$ is not recirculated but reacted with I_2 in a single step) was first reported (Prenant & Crouzel, 1991). Later the method was improved by changing the single-pass to recirculation, starting with either cyclotron produced $[^{11}\text{C}]\text{CO}_2$ (converted to $[^{11}\text{C}]\text{CH}_4$ by hydrogen reduction in the presence of a nickel catalyst) or $[^{11}\text{C}]\text{CH}_4$ (Larsen et al., 1997) reporting yields up to 83%, decay corrected.

3.2.3 Search for the sources of ^{12}C in methylation reactions starting from $[^{11}\text{C}]\text{CO}_2$ and $[^{11}\text{C}]\text{CH}_4$ via the gas phase method

When the latter procedure (reduction of $[^{11}\text{C}]\text{CO}_2$ with a catalyst to produce $[^{11}\text{C}]\text{CH}_4$) is used, the same problems associated to the introduction of carrier carbon as in the case of producing $[^{11}\text{C}]\text{CH}_3\text{I}$ from $[^{11}\text{C}]\text{CO}_2$ via the wet method can be found: (i) CO , CH_4 and other carbon sources in the target gas can be transformed into CO_2 during irradiations and (ii) CO_2 absorbed on the inner surface of the target chamber or transfer lines can be released to the reaction environment. By using this method, Mock (2006) reported a maximum in specific activity of ~925 GBq/ μmol , by using a RDS-111 Eclipse cyclotron and bombarding N_2/O_2 ; 99/1 mixture. The amount of carrier in the irradiated gas increased with irradiation time and also when the target remained pressurized (even without irradiation). Moreover, specific activity dropped for irradiations > 20 μAh due to excessive carrier release from the target.

To overcome the problems associated to the use of $[^{11}\text{C}]\text{CO}_2$ at any step of the synthesis, an automated synthesis device using the single pass I_2 method coupled with the in situ $[^{11}\text{C}]\text{CH}_4$ production method (irradiation of N_2/H_2 ; 95/5) was developed, and the experimental conditions for the production of ultra high specific activity $[^{11}\text{C}]\text{CH}_3\text{I}$ were optimized (Noguchi & Suzuki, 2003). The target body (aluminum A5056, metallic seal, length 150 mm, inlet aperture 20 mm, outlet aperture 30 mm) was carefully machined without oil and polished with sandpaper AA-400. All the parts for the target assembly were washed with HCl, Milli-Q water and acetone, and dried at 350°C under vacuum. The target chamber was then assembled quickly in an air-tight glove box filled with pure N_2 gas and connected to the production line. The production route was cleaned carefully by sweeping it under heating with a target gas or helium. Before irradiation for the production of radiotracers, the target chamber was loaded/unloaded a few times without irradiation and three times with irradiation (20 μA , 5 minutes). By following this procedure, specific activities of $4700 \pm 2500 \text{ GBq}/\mu\text{mol}$ (2900-9700 $\text{GBq}/\mu\text{mol}$) were achieved. However, as reported later (Zhang & Suzuki, 2005), an immediate decrease of such values was occasionally encountered. The authors analyzed the sources of carrier carbon in the previously developed system, assuming that some organic reagents (contaminants in the synthetic line) may react with I_2 vapor to yield CH_3I in the heated quartz tube, resulting in a significant decrease of the specific activity of $[^{11}\text{C}]\text{CH}_3\text{I}$. The authors found that traces of organic reagents, such as acetone, methanol, silicone oil and paraffin, reacted with I_2 to yield CH_3I in the heated quartz tube, resulting in a significant decrease of the specific activity of $[^{11}\text{C}]\text{CH}_3\text{I}$. Therefore, prior to production, sufficient washing and drying of the device components and sufficient flushing of the synthetic lines with a pure inert gas were suggested to improve specific activity. In this sense, Kozirowski & Gillings (2010) found that when specific activity of (cyclotron generated) CH_4 was measured by on-line conversion to HCN , values higher than 13000 $\text{GBq}/\mu\text{mol}$ were encountered. These results suggest that the A_5 of ^{11}C -labelled radiotracers synthesized by the gas phase method is lowered downstream from the target, i.e. during $[^{11}\text{C}]\text{CH}_4$ to $[^{11}\text{C}]\text{CH}_3\text{I}$ conversion, which is consistent with the results of Zhang & Suzuki (2005).

Recently, a quartz-lined aluminum target for the production of $[^{11}\text{C}]\text{methane}$ was developed (Kozirowski et al., 2010). On top of producing $[^{11}\text{C}]\text{CH}_4$ in excellent yields and reducing losses of radioactivity significantly (when compared with the aluminum target), the authors were able to produce radiopharmaceuticals with specific radioactivities up to 9000 $\text{GBq}/\mu\text{mol}$ at end of bombardment (EOB). In Figure 6, the values of specific activity obtained by Kozirowski's group are depicted. These values were initially (already) a factor of four to five higher compared with the conical, aluminum 750 mL volume target. By installing an inline gas purifier, the specific activities further increased. Additionally, specific activity was seen to increase with repeated irradiations and radiosyntheses on the same day. This fact (which can be attributed to a conditioning effect) has been seen also by the authors of this chapter in a recently performed set of experiments with an Aluminum target (Unpublished results). Seven consecutive 0.25 μAh irradiations were performed in an aluminum target filled with N_2/H_2 ; 95/5 ($P = 16 \text{ atm}$) at 22 μA . As can be seen in Figure 7A, the specific activity (corrected to EOB) increased from $\sim 61 \text{ GBq}/\mu\text{mol}$ (beam number 1) up to $\sim 571 \text{ GBq}/\mu\text{mol}$ (beam number 7) within one day. When experiments were performed the following day, the same pattern was obtained. A plateau seems to be achieved after 4 runs, which is a clear indication that contamination in the surface of the target

walls/window is accumulated while the target is not used (it is maintained unpressurized) and is slowly released as the number of experiments increase. In a second set of experiments, three consecutive irradiations (under the experimental conditions stated above) were performed but the target was kept pressurized ($P = 16$ bar, N_2/H_2 ; 95/5) overnight to prevent contamination from the atmosphere. Higher values of A_S were obtained even in the first irradiation of the day (~ 557 GBq/ μmol) and were maintained in consecutive runs (Figure 7B). Although the performance of the target was not (apparently) affected in terms of amount of activity obtained at the end of the synthesis, more experiments are still required to assess the potential degradation of the target due to long term exposure of Aluminium to the N_2/H_2 mixture.

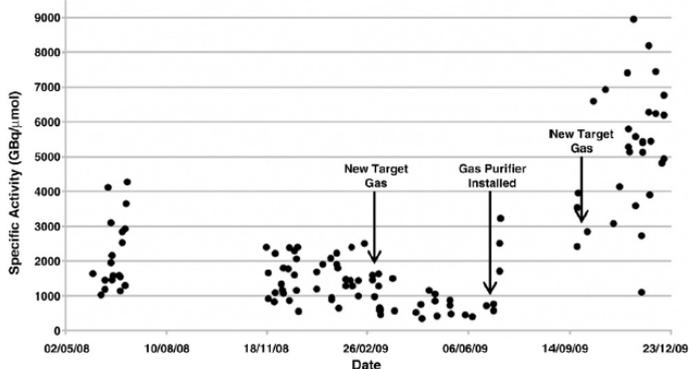


Fig. 6. Specific activities of ^{11}C radiopharmaceuticals (EOB) produced from ^{11}C methane.

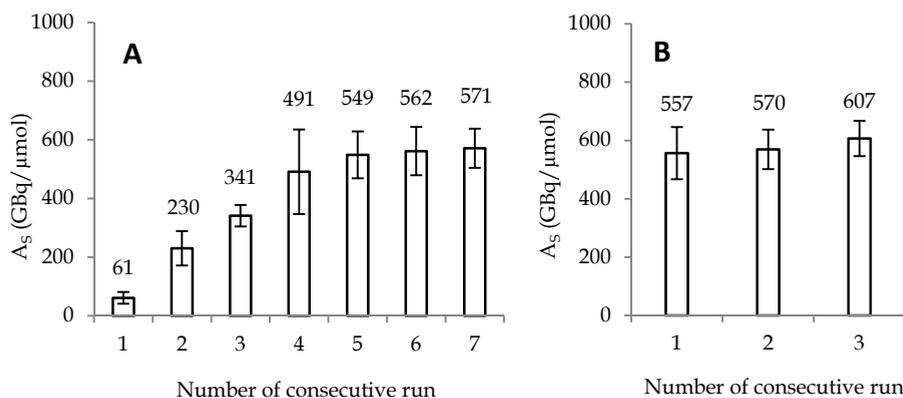


Fig. 7. (A) Specific activities of ^{11}C anisole (EOB) produced from ^{11}C methane within 1 day (integrated current = 0.25 μAh , beam intensity = 22 μA , filling pressure = 16 atm, aluminium target). (B) Specific activities of ^{11}C anisole (EOB) produced from ^{11}C methane within 1 day (same irradiation conditions, target filled with N_2/H_2 overnight).

4. General discussion and conclusions

As can be concluded from all the previous works, the discussion regarding the origin of non radioactive carbon and the procedures to minimize contamination effects (independently of the production process followed to generate carbon-11 and the reaction pathway followed afterwards) have been lasting for years. Although different sources have been encountered and their individual contribution somehow quantified, it seems clear that the final specific activity of ^{11}C -labelled radiotracers is extremely dependent of site-specific configuration and minimal alteration of experimental conditions can lead to considerable effects on specific activity values, especially when such specific activities are high.

Tables 5 and 6 show specific activity values reported in the literature for syntheses of ^{11}C -labelled radiotracers synthesized either from cyclotron generated $[^{11}\text{C}]\text{CO}_2$ or $[^{11}\text{C}]\text{CH}_4$ using either the wet method or the gas phase method. It is absolutely impossible to include every single reported value, and thus a selection has been performed while trying to include representative data. In order to get comparable results, values at EOB are shown, although values at EOS are also included. In the case that one of the values was not reported in the original publications but synthesis time was included, decay corrected values have been calculated and included in the tables.

As can be seen in table 5, specific activity values (EOS) are in the range 5.92-357 GBq/ μmol (except for entrance 16, where extremely and unusually high A_S values were obtained, as discussed above). In most cases where high values (relative to average) were reported, specific procedures to prevent external contamination were applied. Thus, Matarrese and co-workers (2003) obtained high A_S values at EOB (217-357 GBq/ μmol) by optimizing the amount of LiAlH_4 solution, flushing the target with gas several times before beam, checking (and correcting) leaks, carefully cleaning and drying the synthesis system and flushing the lines from the cyclotron to the synthesis boxes continuously during irradiations. However, no special actions were taken with the target itself. When these results are compared to those included in table 6, it can be concluded that higher specific activity values are obtained (in general terms) when the gas phase method is used, independently of the radioactive specie generated in the cyclotron (62-740 GBq/ μmol for $[^{11}\text{C}]\text{CO}_2$, 74-5479 GBq/ μmol for $[^{11}\text{C}]\text{CH}_4$), although higher values are obtained when cyclotron generated $[^{11}\text{C}]\text{CH}_4$ is used. This is due, partially, to the high concentration of CO_2 in the atmosphere which constitutes an important source of contamination. For instance, by switching from $[^{11}\text{C}]\text{CO}_2$ target to the $[^{11}\text{C}]\text{CH}_4$ target and using the gas phase method in both cases, a 6-17 fold increase of specific activity was found in the preparation of some ^{11}C -labelled radiotracers ($[^{11}\text{C}]\text{Raclopride}$, $[^{11}\text{C}]\text{MADAM}$, $[^{11}\text{C}]\text{PE2I}$ and $[^{11}\text{C}]\text{FLB457}$ (Andersson et al., 2009)). In this case, the authors attributed this finding to $[^{11}\text{C}]\text{CO}_2$ being more sensitive to isotopic dilution from CO_2 in the air, than what the influence of environmental contamination of CH_4 is likely to have on the specific activity. Considering that the concentration of CO_2 and CH_4 in air are 365ppm and 1745ppb, respectively, a 200 times higher specific activity would be expected when using $[^{11}\text{C}]\text{CH}_4$. As long as the mentioned 200-fold increase is never found in real conditions, one can conclude that specific activity is lowered by carbon introduced not only from the air, but also from the system, all the way from the target gas to the reaction vessel. This is consistent with all previous works that have been referenced all along this chapter.

Entry	Radiotracer	A_S EOB (GBq/ μmol)	A_S EOS (GBq/ μmol)	Cyclotron	Reference
1	[^{11}C]DMT	13.32 \ddagger	3.4	18 MeV	Iwata et al., 1988
2	[^{11}C]MPTP	5.92 \ddagger	1.51	18 MeV	Iwata et al., 1988
3	Dilthiazem	8.51 \ddagger	2.17	18 MeV	Iwata et al., 1988
4	[^{11}C]YM-09151-2	37 \ddagger	9.44	18 MeV	Iwata et al., 1988
5	[^{11}C]CH ₃ I	219 \pm 88	185 \pm 74	CTI-RDS-112	Matarrese et al., 2003
6	[^{11}C]m-hydroxyephedrine	357 \pm 103	152 \pm 44	CTI-RDS-112	Matarrese et al., 2003
7	[^{11}C]Flumazenil	304 \pm 43	129.5 \pm 18.5	CTI-RDS-112	Matarrese et al., 2003
8	[^{11}C]PNU 167760	217 \pm 87	92.5 \pm 37	CTI-RDS-112	Matarrese et al., 2003
9	[^{11}C]VC-195	258 \pm 103	92.5 \pm 44	CTI-RDS-112	Matarrese et al., 2003
10	[^{11}C](R)MDL-100907	-	392 \pm 166	CTI-RDS-112	Matarrese et al., 2003
11	^{11}C -labelled Adrenoceptor antagonists	70	-	Scanditronix RNP 16	Balle et al., 2004
12	^{11}C -labelled (S)-thionisoxetine	74-111	22-33	IBA 18 MeV	Filannino et al., 2007
13	[^{11}C]CH ₃ I	42 \ddagger	30	IBA 18 MeV	Gómez-Vallejo et al., 2009
14	[^{11}C]DAC	37-170	-	CYPRIS HM18	Yui et al., 2011
15	[^{11}C]Verapamil	100-170	-	CYPRIS HM18	Yui et al., 2011
16	[^{11}C]TCH346	40-5700		GE PETtrace*	Ermert et al., 2008
17	[^{11}C]SKF 75670	86-305	26-92	Scanditronix MC 17	Da Silva et al., 1996
18	^{11}C -labelled 1-methyl-4-piperidyl-4'-fluorobenzoate	-	26	TCC CS30	Bormans et al., 1996
19	[^{11}C]ketamine	13-17	3.3-4.2	Not specified	Shiue et al., 1997
20	[^{11}C]SKF 82957	115	37	Scanditronix MC 17	Da Silva et al., 1999

Entry	Radiotracer	A _S EOB (GBq/μmol)	A _S EOS (GBq/μmol)	Cyclotron	Reference
21	[¹¹ C]MeNER	82-153	35-65	Scanditronix MC 17	Wilson et al., 2003
22	[¹¹ C]DAA1106	191-331	90-156	CYPRIS HM18	Zhang et al., 2003
23	¹¹ C-labelled MAO-B imaging agents	145	37	Not specified	Vasdev et al., 2011
24	[¹¹ C]DACA	163	41.5	Not specified	Brady et al., 1997
25	[¹¹ C](L)-deprenyl	37	-	Japan Steel works 41-inch	Ferrieri et al., 1999
26	¹¹ C-labelled flutamide derivatives	-	148	Not specified	Jacobson et al., 2006

Table 5. Specific activity values reported in the literature for ¹¹C-labelled radiotracers synthesized from [¹¹C]CO₂ and wet method. †corrected to end of transfer of activity, transfer time 3-12 min. *Modified target gas according to Qaim et al., 1993.

Entry	Radiotracer	Precursor†	A _S EOB (GBq/μmol)	A _S EOS (GBq/μmol)	Cyclotron	Reference
1	[¹¹ C]MHED	[¹¹ C]CO ₂	444	360	13 MeV	Link et al., 1997
2	[¹¹ C]Ro-15-4513	[¹¹ C]CH ₄	4700 ± 2500	2000 ± 1060	HM18 cyclotron	Noguchi & Suzuki, 2003
3	[¹¹ C]Raclopride	[¹¹ C]CH ₄	74-370	-	TR13	Buckley et al., 2004
4	[¹¹ C]Flumazenil	[¹¹ C]CH ₄	5730	2440	CYPRIS HM18	Zhang & Suzuki, 2005
5	[¹¹ C]HOMADAM	[¹¹ C]CO ₂	221.1	28.5	Siemens RDS 112	Jarkas et al., 2005
6	[¹¹ C]Raclopride	[¹¹ C]CH ₄	4880 ± 2360	1690 ± 818	CYPRIS HM18	Noguchi et al., 2008
7	[¹¹ C]raclopride	[¹¹ C]CO ₂	124	36,27	GEMs PETtrace	Andersson et al., 2009
8	[¹¹ C]raclopride	[¹¹ C]CH ₄	2335	784,67	GEMs PETtrace	Andersson et al., 2009
9	[¹¹ C]MADAM	[¹¹ C]CO ₂	162	50,74	GEMs PETtrace	Andersson et al., 2009
10	[¹¹ C]MADAM	[¹¹ C]CH ₄	2332	836,53	GEMs PETtrace	Andersson et al., 2009
11	[¹¹ C]PE2I	[¹¹ C]CO ₂	183	59,31	GEMs PETtrace	Andersson et al., 2009

Entry	Radiotracer	Precursor†	A _s EOB (GBq/μmol)	A _s EOS (GBq/μmol)	Cyclotron	Reference
12	[¹¹ C]PE2I	[¹¹ C]CH ₄	1097	683,54	GEMs PETtrace	Andersson et al., 2009
13	[¹¹ C]FLB457	[¹¹ C]CO ₂	176	61,07	GEMs PETtrace	Andersson et al., 2009
14	[¹¹ C]FLB457	[¹¹ C]CH ₄	1313	439,28	GEMs PETtrace	Andersson et al., 2009
15	Not specified	[¹¹ C]CH ₄	5479 ± 1735	-	Scanditronix MC 32	Koziorowski et al., 2010
16	[¹¹ C]DAC	[¹¹ C]CH ₄	3670-4450	-	CYPRIS HM18	Yui et al., 2011
17	¹¹ C-labelled styryl dyes	[¹¹ C]CO ₂	173.76-260.65	74-111	CTI 11 MeV Siemens	Wang et al., 2009
18	¹¹ C-labelled tetrahydroisoquinoline derivatives	[¹¹ C]CO ₂	148-222	63-94.54	CTI 11 MeV Siemens	Wang et al., 2007
19	¹¹ C-labelled tetrahydroisoquinolinium derivatives	[¹¹ C]CO ₂	62-123.50	37-74	CTI 11 MeV Siemens	Gao et al., 2008

Table 6. Specific activity values reported in the literature for ¹¹C-labelled radiotracers synthesized via gas phase method (starting either from [¹¹C]CH₄ or [¹¹C]CO₂).

Although (as previously discussed) the sources of contamination are extremely dependent on the particular configuration of the systems involved in the production process of each particular site, and despite the everlasting discussion among scientists to find out (and control) the main factors contributing to a decrease in the specific activity of ¹¹C-labelled radiotracers, there are general procedures that, independently of the employed radioactive precursor and the synthetic route, might help to improve specific activity. However, it has to be taken into account that contamination can come at any step of the synthesis process, and therefore precautions should be taken at each single step.

1. Generation of the radioactive precursor in the cyclotron; at this step, the purity of the gases, the material of the target chamber, the windows and the o-rings (and the procedure followed for their machining and polishing), the size of the target chamber and the quality of the irradiated gas have been found to have important effects on the introduction of carrier carbon. Beam time and beam current should also be considered. The use of high purity gases (with a purification column between the gas source and the target), careful cleaning of the target chamber components, the use of metallic o-rings

and recovering the target chamber with materials which minimize beam-wall interactions lead usually to improvement in A_s . Increasing beam time and/or current (up to a certain level) offers usually satisfactory results. Preparation protocols have been also historically used, e.g. loading and unloading the target before irradiation, discarding the first 1-3 irradiations of the day and keeping the target under pressure between runs.

2. Transfer of the irradiated gas to the synthesis box; increasing time decreases specific activity, and thus minimizing transfer time leads to higher specific activity values. The material of transfer lines (pipes and connections) and the carrier gas (if used) could also introduce non radioactive carbon into the reaction environment. This should be considered when choosing dimensions (i.e inner diameter; ID) for the transport line: the smaller the ID the less the material, but longer emptying/delivery time. Keeping the lines pressurized with high purity gases and avoiding carbon-rich materials should help, thus, to increase A_s .
3. Synthesis process; at this step, the use of high purity reagents is the most important factor. All traps can be activated before synthesis, and reagents should be prepared and stored under adequate inert conditions to prevent contamination from the atmosphere. Reagents and solvents should be used in minimal amounts, especially in those cases where they are supposed to be potential sources of carrier carbon (e.g. LiAlH_4 in the wet method). Special attention should be paid to the purity of the non radioactive precursor, which could be contaminated (*ab initio*) with the methylated species. The synthesis box should be also cleaned and dried thoroughly and kept isolated from atmosphere; traces of solvents and direct contact with air contribute to decreased A_s .

5. References

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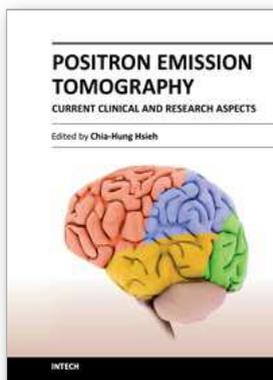
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This book's stated purpose is to provide a discussion of the technical basis and clinical applications of positron emission tomography (PET), as well as their recent progress in nuclear medicine. It also summarizes current literature about research and clinical science in PET. The book is divided into two broad sections: basic science and clinical science. The basic science section examines PET imaging processing, kinetic modeling, free software, and radiopharmaceuticals. The clinical science section demonstrates various clinical applications and diagnoses. The text is intended not only for scientists, but also for all clinicians seeking recent information regarding PET.

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University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
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InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821