

DEVELOPING CARRIER FREE SYSTEMS AND THEIR MAINTENANCE

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ISSUES IN CARRIER-FREE TARGET SYSTEMS THEIR DEVELOPMENT AND MAINTENANCE

a report organized by

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INTRODUCTION

The development of positron emission tomography (PET) has led to the need for ever higher specific radioactivity compounds. The specific radioactivity can be of considerable importance when labeled substances are used for human studies and the compounds are either toxic or have saturable and/or pharmacologically significant receptor sites. Future progress in PET research depends on the availability of radiotracers having high specific radioactivity.

Specific radioactivity is defined as the amount of radioactivity per mass of a labeled compound. The maximum achievable specific radio-activity is a function of its half-life. For short-lived radionuclides commonly used for PET, very high specific radioactivities can be obtained if the dilution of the product with stable isotopes can be avoided.

Radionuclide	T _{1/2} (min)	Maximum Specific Radioactivity		
¹¹ C	20.4	3.4 x 10 ²⁰	Bq/mol	9200 Ci/μ mol
¹³ N	10.0	6.9 x 10 ²⁰	Bq/mol	19000 Ci/μ mol
¹⁵ O	2.05	3.4 x 10 ²¹	Bq/mol	92000 Ci/μ mol
¹⁸ F	109.7	6.3 x 10 ¹⁹	Bq/mol	1700 Ci/μ mol

In practice this can be difficult for the common elements, carbon, nitrogen and oxygen. Traces of the element being produced may already be present in the target gas or may need to be added for efficient operation of the target. Examples of the latter are addition of a small amount of O₂ to an N₂ target when producing O¹⁵O or the requirement for carrier F₂ to efficiently extract ¹⁸F from a neon target. These examples emphasize the need to differentiate between carrier free (a theoretical limiting case), no carrier added, and carrier added preparations.

This report summarizes a discussion of considerations related to the development and maintenance of targets for achieving the highest possible specific radioactivity compounds for the four radionuclides listed above. It covers conceptual aspects of target chemistry and practical issues of target engineering. The latter include, but go far beyond, the general requirements for a leak-tight target body and target handling systems, pure and clean materials for the target body, and pure target compounds free of interfering stable isotopes for the irradiation.

1.2 Oxygen-15

Oxygen-15 labeled radiopharmaceuticals have become increasingly important for PET studies, including oxygen metabolism, blood flow and blood volume. In the preparation of ^{15}O compounds, several toxic gases, CO, nitrogen oxides, and even ozone can be formed in the targets at concentrations that may exceed acceptable limits. This may lead to a concern for patient safety, product specific radioactivity, or interference with subsequent chemical syntheses. Current methodology for production of standard ^{15}O -labeled compounds has been reviewed by Clark et al.¹

Oxygen-15 labeled molecular oxygen, carbon monoxide and carbon dioxide are most commonly and conveniently produced from a $^{14}\text{N}_2$ gas target containing traces of O_2 or CO_2 , respectively, via the $^{14}\text{N}(\text{d},\text{n})^{15}\text{O}$ reaction. For a low energy proton-only accelerator the $^{15}\text{N}(\text{p},\text{n})^{15}\text{O}$ reaction has a high yield, but requires an enriched target gas. The deuteron reaction has a positive Q-value and thus no energy threshold; Q for the proton reaction is -3.5 MeV. The yield of ^{15}O is higher for the $^{14}\text{N}(\text{d},\text{n})^{15}\text{O}$ reaction than for the $^{15}\text{N}(\text{p},\text{n})^{15}\text{O}$ reaction at the same incident particle energy. However, for a low energy proton/deuteron machine the highest yields can be obtained with the (p,n) reaction on enriched $^{15}\text{N}_2$. When only protons >20 MeV are available the $^{16}\text{O}(\text{p},\text{pn})^{15}\text{O}$ reaction can be used. The threshold is 14 MeV and the product is obviously of very low specific radioactivity.

Chemical impurities formed during irradiation of targets to produce ^{15}O are removed by appropriate traps. The chemical and radiochemical purity of the products is usually analyzed by gas chromatography. Methods for the clinical quality control of ^{15}O -labeled products have been described by Strijckmans et al.²

1.2.i. Key issues regarding ^{15}O radiopharmaceuticals:

- (1) What fraction of oxygen is necessary to achieve optimal recovery of ^{15}O , with minimal CO or nitrogen oxides?
- (2) How much carrier CO is present, and how much is acceptable?
- (3) Does anyone routinely measure carrier CO? (or NOx?)

1.2.ii. Summary of discussion

T. Tewson (Univ. of Texas) uses the $^{14}\text{N}(\text{d},\text{n})^{15}\text{O}$ reaction and opened the discussion by presenting his standard irradiation conditions: 8.6 MeV, 15 μA , 4 min, 1% O_2 in N_2 . Direct yield from his target is difficult to measure accurately because he cannot evacuate the target. However, with a standard bombardment he can get >200 mCi of H_2^{15}O . If T. Tewson uses <0.1% O_2 in the target gas then <40% as much ^{15}O is recovered as H_2^{15}O . He is not sure if the remainder is lost in the target or is just not converted to water. He ends up with only 2% conversion to C^{15}O when he irradiates 1% O_2 and then passes it over carbon at 900° C. He has measured the carrier CO by GC with a molecular sieve column and it always gives $\text{N}_2/\text{CO} > 50$. However, as some air always enters the syringe, this is not a precise measurement. Tewson sees no NOx in his ^{15}O products, but there is a NaOH trap upstream from where he samples for quality control, and this should trap all NOx.

G. Robinson (General Electric Medical Systems) has used 6.0 MeV deuterons on high purity N_2 targets at the University of Pennsylvania. A charcoal furnace at 950° C was used for the conversion of O_2 to CO. About 25% of the radioactivity came out of the furnace as C^{15}O . Chemical purity analysis showed <10 ppm CO as measured by gas chromatography using a thermal conductivity detector. Before patient breathing, the radioactive gas was mixed with O_2 .

M. Berridge (Case-Western Reserve) reported his experience in optimizing ^{15}O targets to maximize production of butanol as well as the standard ^{15}O compounds. In order to optimize his yield of

¹⁵O-butanol, M. Berridge lowered the O₂ content of the target gas in his ¹⁴N(d,n)¹⁵O target. He started with a mixture of 2% O₂ in nitrogen and achieved saturation yields per μ amp of beam for ¹⁵O products of 25 mCi for O₂, 20 mCi for H₂O, and 13 mCi for CO. At 2% O₂ the conversion of ¹⁵O to butanol was 50%, with the remainder H₂O. When the target gas was reduced to 1% O₂, a higher conversion was obtained, and at 0.2% the incorporation into butanol reached 80-90%. Unfortunately, at low O₂ (< 1%) in N₂ the yield of both H₂¹⁵O and C¹⁵O fell to about 3 mCi/μA at saturation. The C¹⁵O production was restored to its original yield by reducing the volume of granular carbon in the furnace tube to 8 cm³, about one-half the original amount. Water production could not be brought up to the expected value using Pd/aluminum catalyst, either by reducing the catalyst or raising the temperature; however, it was restored by changing the catalyst to Pt wire. The 20 mCi/μA yield was first obtained at a temperature of 100° C. After a period of use the yield dropped, but raising the temperature to 300° C stabilized the reaction yield, and has now become their standard procedure.

Based on the numbers presented by M. Berridge, T. Tewson speculated that he may not need 1% O₂ in his system for water; although M. Berridge argued that T. Tewson probably does need that much O₂ with his current setup.

J. Clark (MRC Cyclotron Unit, Hammersmith) asked if anyone was measuring CO online. He has tried to measure CO by using a chemiluminescent detector, but found that the detector was too radiation sensitive. G. Robinson was planning on putting a commercially available optical monitor in-line for CO but this was not completed before he left the Univ. of Pennsylvania. M. Berridge reported that the carrier CO dropped with increasing O₂ content of his target and under his standard conditions CO content is about 0.4% by volume. He did not agree that routine measurement of CO was necessary.

J. Nickles (University of Wisconsin) proposed that the "rush hour" level of CO might be a practical acceptable limit for ¹⁵O systems. J. Clark disagreed, but suggested that NOx is the more important chemical carrier to worry about in oxygen-15 targets and radiopharmaceuticals. The general consensus was that we need to be aware of the level of CO in our systems. D. Schlyer (Brookhaven National Laboratory) was less concerned about long term toxic effects, but expressed the concern that he would not want acute physiologic effects from carrier CO to interfere with an imaging study. M. Berridge thought that the rush hour standard might be okay, as "CO leaves the blood quickly, when dealing with small concentrations and breathing clean air afterward." R. Dahl (North Shore University Hospital) thought that we did not need to be so concerned about carrier CO. He has his subjects inhale from about 1 liter of gas containing 50 to 100 mCi of C¹⁵O, such that the subject breathes less than 1 μ mol of CO during the study. Therefore the blood saturation of carboxyhemoglobin remains much less than the 10% level below which symptoms do not normally occur.³ He recommended bolus administration of water or single-breath inhalation of gases, rather than steady state approaches, as a possible way to decrease the amount of CO which a patient inhales.

J. Nickles advocated consideration of oxygen-14, T_{1/2} = 71 sec, from the ¹⁴N(p,n)¹⁴O reaction. Using 11 MeV protons and 400 ppm O₂ in the target, the yield is 2 mCi/μA at saturation. The contaminant ¹¹C can be removed with traps in series of soda lime/I₂O₅/soda lime. The first soda lime trap removes CO₂; the I₂O₅ trap is at 175° C and converts the remaining carbon to CO₂ and the second soda lime trap scrubs this from the system. Addition of a stoichiometric excess of H₂ and passage over a catalyst of Pt/Al₂O₃ in a 200° C furnace makes H₂¹⁴O as the vapor which he traps in acidic water to ensure that any remaining CO₂ is not trapped. There will be some ¹⁵O as a contaminant, produced from the 0.37% natural abundance of ¹⁵N.

1.3 Carbon-11

The most convenient and frequently used nuclear reaction for production of carbon-11 (T_{1/2} = 20.4

min) is the $^{14}\text{N}(p,\alpha)^{11}\text{C}$ reaction with N_2 gas targets. Careful attention to conditions for radionuclide production and precursor preparation is required in order to approach the theoretical maximum of specific radioactivity, owing to the ubiquitous nature of carbon. Other gases may be added in small amounts to the target gas to ensure that the ^{11}C produced will be in the most advantageous chemical form for subsequent synthesis. The amount of stable carbon in the target materials should be minimized to improve the specific radioactivity of the precursor. The earliest report of an attempt to achieve practical yields of high specific radioactivity carbon was by Christman et al,⁴ who achieved 1-2 Ci/ μmol ^{11}CN -EOB. Berger et al⁵ reported 0.4-1.0 Ci/ μmol EOS using $^{11}\text{CH}_2\text{O}$. Fowler et al⁶ have reported a specific radioactivity of 3.8 ± 0.9 Ci/ μmol EOB for $^{11}\text{CN}^-$ used in the synthesis of ^{11}C -spiroperidol. ^{11}C -Methyl iodide has been made at 1-3.5 Ci/ μmol EOB⁷ and, using capillary gas chromatography, $^{11}\text{CH}_4$ was enriched to 20-300 Ci/ μmol .⁸ Wieland et al. have produced $^{11}\text{CO}_2$ at 75 Ci/ μmol with an 11.4 MeV proton beam.⁹

1.3.i. Key issues regarding ^{11}C radiopharmaceuticals:

- (1) Sources of carrier carbon:
target gases, target surfaces, target system materials including vacuum, O-rings, beam entrance foils, cleaning solvents, regulators, reagents, irradiation.
- (2) Manufacturing and cleaning of target systems.
- (3) How should the specific radioactivity be measured?
- (4) In principle, ^{11}CO can be prepared at higher specific radioactivity than $^{11}\text{CO}_2$. Is it worth the effort? Cost in yield? What can be labeled by carbonylation?

1.3.ii. Summary of discussion:

Introduction by S-J. Heselius. Aluminum alloys are usually used for the fabrication of target chambers for production of carbon-11 as well as oxygen-15. The target chamber is usually conical or stepped-wall shaped. Conical target chambers can be easily machined with the help of commercially available conical machining tools. Target entrance foils of havar, stainless steel alloys, or titanium are widely used. Silver, gold, indium, and even PTFE, are used as O-ring materials.

Electrical isolation of the target from stainless steel or other metal transport lines is easily carried out by covering the ends of the input and output lines for the target gas with a larger diameter teflon tubing (e.g. 1/8 in. O.D. by 1/16 in. I.D. fits over 1/16 in. SS.). The teflon tubing is then inserted and tightened into a 1/8 in. Swagelok or other type fitting mounted on the target body. High quality GC-grade stainless steel tubing should be used in the gas transport lines.

Careful cleaning of the targets, the transport lines and the synthesis equipment is of the utmost importance for successful radionuclide production and subsequent radiochemical syntheses. Almost every laboratory has its own protocol for cleaning. B. Langstrom (University of Uppsala)¹⁰ uses the following media in sequence for cleaning targets and chemistry equipment: chloroform, ethanol, distilled water, absolute ethanol, diethyl ether (p.a.); and drying in a vacuum oven at 140° C. Sometimes he also uses dilute nitric acid between the distilled water and absolute ethanol washes. The BNL group¹¹ uses an ultrasonic bath in their target cleaning procedure. Water, 95% ethanol, acetone, cyclohexane, acetone, 95% ethanol, and distilled water are sequentially used. Finally the equipment is dried with filtered nitrogen gas. The use of chloroform and ethanol only for target cleaning has been reported by several groups.

Discussion. In the introduction to the carbon-11 part of this session the manufacture of target chambers and cleaning procedures were discussed. With respect to the manufacturing procedures, J. Nickles asked whether anyone has electropolished target chamber walls, but received no response. He

has used glass bead polish on his target to obtain a matt finish. He then tumbles the target with 1/8 inch case-hardened ball bearings, after which it is cleaned and, if necessary, passivated.

G. K. Mulholland (University of Michigan) asked S. Heselius (Abo Akademi) if using nitric acid as a cleaning agent would pit the target. S. Heselius answered that the dilute nitric acid mentioned in the introduction is not used for cleaning carbon-11 production targets. D. Schlyer stated that one could coat glass surfaces with phosphoric acid¹² and that this coating stops atom/atom recombinations for hydrogen, oxygen and nitrogen. At Brookhaven they use HCl/HBr to wash ¹¹C targets. J. Clark mentioned that he has used phosphoric acid to recondition aluminum for ¹¹C targets, although his current target has not required cleaning in the three years it has been in use. M. Berridge remarked that he had "killed" a carbon target by cleaning it with HNO₃, but when he washed the target with dilute HCl it worked again.

The use of Swagelok SS connectors with NPT threads in the inlet and outlet channels was described in the introduction. J. L. Need (Duke University) suggested that NPT threads are "terrible", and advised the use of other types of threads. He uses nylon fittings for electrical isolation. J. C. Clark mentioned that he isolates his targets with a small piece of Kel-F which is threaded on both sides with 5/16" straight threads to Swagelok brand "O"-seals and asked at the same time whether the nylon fittings suffer from radiation damage. J. Need responded that the nylon fittings are placed away from the radiation field.

B. Wieland (CTI/ Siemens) described their target for production of ¹¹C with 10.4 MeV on the gas. They use an N₂ + 1% O₂ gas mixture directly from the tank without gas purifiers. The conically shaped target chamber has an entrance aperture of 10 μm diameter and a base diameter of 14.5 μm. The length of the target chamber is 100 μm, and the volume is 11.4 cm³. The conical target chamber was machined with a special boring tool using Al 6061T6. He uses an ethylene propylene O-ring and high quality SS valves. With this target they have achieved specific radioactivities of up to 75 Ci/μmol. using 40 μA x 20 min of beam and resulting in 1 Ci of recovered ¹¹CO₂.

D. Schlyer advised that tank gases contain carrier carbon and should be analyzed. When possible one should order gases with certificates of analysis. The experience at Brookhaven is that many high purity gases without certificates do not meet the manufacturer's specifications. He also pointed out the importance of a leak-tight target system in order to avoid carrier carbon compounds, and told about his experience of reducing the amount of carbon traces by a factor of 2.5 when small leaks in the target system were tightened.

T. Ruth (TRIUMF) used an O₂ target chamber to irradiate N₂ and make ¹¹C by the ¹⁴N(p,α) reaction. He observed a clear increase in the amount of CO₂ in the target after irradiation. This target had previously been dedicated to ¹⁵O production via the reaction ¹⁶O(p,pn)¹⁵O. The CO₂ content was measured to be low during no-beam runs. He found the source of the carrier CO₂ was from oxalic acid used to anodize the target.

T. Tewson also advised to order research grade gases that come with analysis certificates. He orders his target gases from Air Products, Inc. He also pointed out that SS high purity non-leaking regulators should be used. G. K. Mulholland orders his target gases from Air Products, Inc. and uses research grade nitrogen, 4 ppm O₂. H. Padgett (CTI/ Siemens) said that he also uses gases from Air Products, Inc.

Measuring the specific activity of carbon: T. Tewson described a sensitive method for measuring the amount of CO₂ present in a target gas. Triphenylmethane reacts with n-BuLi and forms a deeply red complex, triphenyl-C-Li+. Upon reaction with ¹¹CO₂ triphenyl-C-¹¹COOH is formed, which is colorless and easily detected on HPLC. If there is any air, water, oxygen, nitrogen oxides, or probably even ozone in the CO₂ gas stream, it also shows up as a rapid discharge of the red color, but doesn't co-elute on HPLC with the acid formed by the reaction with CO₂. Because the anion is formed from a methylation

reaction of the n-BuLi with triphenylmethane, any products of reaction which occur over time between air (including CO₂) and the stored n-BuLi reagent will not show up in the final products, so it provides a direct measure of the specific radioactivity of the ¹¹CO₂, not the reagents as a whole. Using this system, the specific radioactivity from Tewson's targets has been as high as 15-20 Ci/μmol and the primary factor affecting it is the quality of the target gas. He measured a specific activity of only 0.2 Ci/μmol with N₂ of the same specifications but from a different manufacturer. The question was asked; which reagents decrease specific activity? Lithium aluminum hydride was mentioned. T. Tewson dries it with a Soxhlet apparatus and stores it under argon for up to 14 days.

During a series of comments John Clark pointed out the following aspects:

- Leak tight, non-rubber diaphragm gas regulators should be used.
- Conventional grade tubing is not good enough. High quality GC grade tubing should be used.
- Target chambers are usually made of Al alloys; almost all contain significant amounts of carbon. A careful look at the carbon content of Al used for the fabrication of target chambers is necessary to keep carbon content as low as possible. He suggested quartz as an alternative for target chambers, because O in a plasma is "avid for carbon".

H. Padgett described the method used by CTI for measuring the specific radioactivity of ¹¹CO₂. The ¹¹CO₂ produced in the target is collected in a loop of stainless steel tubing (1/16 in. O.D. x 0.030 in. I.D.) cooled with liquid nitrogen during trapping. With the help of a Valco 8-port valve and two 3-way valves the CO₂ collected into the cold trap could be injected into a gas chromatograph after heating the trap. The total amount of carbon dioxide in the product was analyzed on a pre-calibrated gas chromatograph (Hewlett Packard 5880A). The GC-separation was performed on a column packed with Porapak QS. After passing through the column and the GC-detector, the CO₂ was trapped in soda lime placed in a dose calibrator. The amount of ¹¹CO₂ was quantified using the dose calibrator. Typical values for ¹¹CO₂ were 20 - 75 Ci/μmol. Padgett also mentioned that TFE lines are permeable to CO₂ and should not be used in systems for the production of ¹¹CO₂. He recommended the use of GC grade stainless steel tubing (e.g. Handy & Harman Tube Co., "Chromat I.D.").

S-J. Heselius pointed out that if more exact determinations of the specific radioactivity are needed using the above mentioned technique, one has to be careful with the possible overlapping of CO₂ and nitrogen oxides produced radiolytically in N₂ + O₂ gas mixtures. The difficulties in separation are due to the relatively large gas volume introduced to the GC. On the other hand when mostly non-radioactive nitrogen oxides are in question, as in this case, the possibility of overlapping peaks yields an underestimation of the specific radioactivity as measured with this technique. He is able to measure 2 Ci/μmole specific radioactivity by a method similar to that described by H. Padgett, using a Porapak Q column.

J. Nickles feels that it may be important to keep beam from hitting the target chamber walls in order to achieve high specific radioactivity of the product. In particular, because he has a steel target and worries about carbon from sputtering on the metal and recoil carbons out of the foil. He also wonders about what beam does to local passivation on the walls of fluoride targets. J. Brodack (Washington University) prefers to flush targets with N₂ instead of pumping. If the targets are pumped, he uses only high purity silicone oil in the pumps.

J. Need asked if the measured amount of CO₂ was different between hot (irradiated) and cold (nonirradiated) targets. D. Schlyer has found no change in measured amount of CO₂ with and without beam, using a 140% nominally thick N₂ target. T. Tewson asked if anyone was irradiating boron to produce ¹¹C in order to improve specific radioactivity. G. K. Mulholland had tried but there wasn't much interest in their group in using CO as a reagent. J. Nickles stated that a hot filament could be used to make ¹¹CO in a target but it would be of lower specific radioactivity.

1.4 Nitrogen-13

Targets for production of ^{13}N were not covered in the session on carrier-free systems, but they did come up in discussions later in the week, in reference to the report from K. Mulholland and his colleagues at the University of Michigan. At the St. Louis SNM they described (J. Nucl. Med. 30:926, 1989 abstract, Int. J. Appl. Rad. Isot. in press 1990) a modification of the conventional water target using the $^{16}\text{O}(p,\alpha)^{13}\text{N}$ reaction. Under most irradiation conditions this target has been shown, by several laboratories, to make almost entirely $^{13}\text{NO}_3^-$, with only traces of labeled nitrite and ammonia. Labeled ammonia can then be readily synthesized by one of several chemical reductions of the nitrate in water. In the new procedure, $^{13}\text{NH}_3$ is produced directly in the water target by overpressure with H_2 . The target tested in Ann Arbor was made of silver, volume about 1 mL. At hydrogen pressures >8 atm more than 95% of the ^{13}N in the target was ammonia.

1.5 Fluorine-18

Fluorine-18 can be introduced into organic molecules by either electrophilic or nucleophilic reactions. The nuclear reaction most often used to make electrophilic ^{18}F is $^{20}\text{Ne}(d,\alpha)^{18}\text{F}$ with carrier-added F_2 . Early procedures for introducing ^{18}F into compounds relied almost entirely on this approach, initially with labeled F_2 but recently also with labeled acetyl hypofluorite. This nuclear reaction has a maximum cross section at ~ 6 MeV and typically yields of ~ 350 mCi of ^{18}F as F_2 in a 2 hr irradiation with $15 \mu\text{A}$ of 14 MeV deuterons on the target.^{13,14} Clearly ^{18}F introduced in this way has a specific radioactivity that is orders of magnitude below the theoretical maximum. The only discussion of electrophilic ^{18}F and associated targets at the conference was in a poster presented by B. Wieland using proton irradiation of $^{18}\text{O}/\text{F}_2$ mixtures.

Fluorination via nucleophilic displacement reactions does not require addition of carrier. This route of labeling uses anhydrous fluoride with any one of several good leaving groups, and offers some practical conveniences for preparing ^{18}F compounds. The nuclear reaction requires a target containing enriched ^{18}O , typically as water, and uses the $^{18}\text{O}(p,n)^{18}\text{F}$ reaction. This nuclear reaction has a threshold at 2.5 MeV and a maximum cross section at ~ 5 MeV¹⁵ so that it works well with even very low energy accelerators. It yields 400 mCi ^{18}F in a 30 min irradiation of H_2^{18}O with $20 \mu\text{A}$ of 10 MeV protons.¹⁵ Fluorine produced by this route needs to be separated from the target water before the ^{18}F can be used for labeling. Often the enriched water is recycled for future irradiations.

Fluorine, unlike carbon, nitrogen and oxygen, is not a natural component of most biological molecules. This presents some disadvantages as well as some powerful advantages for the chemist preparing high specific radioactivity ^{18}F compounds. Because F is not ubiquitous in the environment, labeling can be done at very high specific radioactivity, nearer the theoretical maximum than for any of the other positron emitters considered in this report. Because F is not common in the body, the ^{18}F atom is invariably substituted for some other chemical structure, typically hydrogen or hydroxyl. Thus, the radioactive compound will frequently have chemical characteristics that are different from the parent molecule. Nevertheless, the overall advantages offered by the very high specific radioactivity that is reasonably convenient to achieve, and by a half-life that allows the tracer to be used for several hours after synthesis probably means that ^{18}F will be the most important radionuclide for clinical PET.

1.5.i. Key issues regarding ^{18}F radiopharmaceuticals:

- (1) Is the specific activity of ^{18}F radiopharmaceuticals limited by the amount of carrier F in the system, or is the reactivity of the fluoride the major concern?
- (2) What factors affect the specific activity of $^{18}\text{F}^-$? How much carrier F is introduced from reagents, plastic lines, and target water? What is the radiochemical form of ^{18}F directly from water targets?

- (3) What factors affect the reactivity of $^{18}\text{F}^-$? Is there a preferred target material: Ag, Ti, Ta, Ni, Cu, SS, or havar? Is anyone having problems traceable to valves or lines? Is it helpful to degas target water with nonreactive gas?
- (4) Water quality:
Can H_2^{18}O be reused or must we be limited to small target volumes? What is the best procedure to clean the enriched water? What is the value/role of ion exchange traps versus distillation? What is the role of cryptates?
- (5) Is there a useful standard assay for measuring the reactivity of anhydrous $^{18}\text{F}^-$?
- (6) How should you measure the specific radioactivity of ^{18}F compounds?

1.5.ii. Summary of discussion:

Sources of carrier F:

John Clark opened the discussion by emphasizing that if you are working with fluoride in the same laboratory where F_2 is in use, you will find carrier F "everywhere". He asked if there is F^- in commercial ^{18}O -water? J. Nickles commented that there is fluoride in the flux used for silver soldering and D. Schlyer added that there is F in any flux used for soldering. He asked whether anyone used electron beam welding; J. Nickles does, and he also avoids use of Viton O-rings. J. Clark advocated the use of "lock-tite" (a cyano-acrylate compound), which he uses to glue his 1/16" stainless steel lines to his target. T. Tewson uses teflon water lines and redistilled water and cannot measure any carrier F in the water out of his target. Products turn out with $>40 \text{ Ci}/\mu\text{mol}$. He measures carrier fluoride using the reaction of F with tetrabutyl ammonium butyrophene/DMSO $120^\circ \text{C}/\text{K}_2\text{CO}_3/2.2.2$

J. Brodak uses an Orion ion electrode specific for fluoride to measure specific activity. This system is sensitive to 10^{-6} M using 0.5 mL H_2^{18}O + Orion TISAB buffer. He sees a 10x decrease in carrier F when he purifies his ^{18}O -water by passing it through an ion retardation resin instead of distilling it.

Distillation procedures for cleaning or recovering target water:

A poll of the conference attendees revealed a 50/50 split between those reusing H_2^{18}O and those disposing of it.

H. Padgett asked J. Brodak if he distilled from a base; he doesn't. J. Moskwa (University of Michigan) described a pressure increase that was observed in the water target with beam on when using redistilled water. Previously unirradiated water had a pressure of 100 to 115 psi in the target before and during irradiation. When water was redistilled the pressure went from 100 to 200 psi in the same target (before and during irradiation). He has also had some instances of line plugging. In retrospect they ascribed the pressure increase and line plugging to residual acetonitrile in the ^{18}O -water. Their interpretation was that radiolysis of the contaminated water gave off gases which increased the target pressure as well as producing some "tar" in the target and lines. The acetonitrile contamination was the result of valve failure while using acetonitrile in their resin during separation of the $^{18}\text{F}^-$ from the H_2^{18}O . They find it difficult to remove the acetonitrile from the water without decreasing the enrichment. Currently they use fresh water for each run and do not reuse the irradiated water. There were no other reports of similar phenomena. M. Berridge keeps pressure on his target in order to limit bubble formation in the target water from boiling and radiolysis, all of which would make his target thinner. He intentionally introduces a slow leak in the overpressure line of about 0.1 psig every 10 to 15 seconds. If the target lines are tight, the pressure will climb to over 60 psi during a 30 min irradiation.

Overpressure is not a requirement, but it helps, especially if a target does not have a headspace for reflux. M. Berridge has a target with a 0.4 mL beam strike volume and 0.2 mL head space.

M. Berridge has expanded in writing on his experience with several new targets that he has evaluated. These targets used a Ag spacer and double foils, with a head space above the water. Silver foils were used in most cases, with the front one 0.025 μm thick and the back one 0.25 mm thick. Helium or H_2 was used to pressurize the head space to 1.6 bar to prevent the front foil from bowing into the water and thinning the target. New targets were prone to produce fluoride of minimal reactivity (using FDG via the triflate with tetramethyl ammonium hydroxide as a standard reaction). They also were prone to blockage of the 0.1 mm exit tubing. However this situation improved with use, and this could be hastened by thorough cleaning. Stainless steel in the fluid path led to problems from corrosion. M. Berridge believes that traces of machining oils and polishing compounds are likely sources of these problems. They are easy to remove from flat surfaces, but are very difficult to remove from the channels which bring water and gas into the target chamber. In one instance it was necessary to circulate hot concentrated sulfuric acid through the passages to obtain optimum performance. Once an Ag target was well cleaned, the difficulties of clogged lines and low radiochemical yield essentially disappeared. Those problems which occurred were easily traceable to the usual causes such as excess beam on a dry target back or contaminated water. Routine cleaning of these targets was originally performed by polishing with jeweller's rouge. This worked well, but caused severe problems if the rouge was not removed completely. Berridge has found that Na bicarbonate with a little methanol is a good abrasive cleaner and it can be easily removed with water.

B. Wieland uses only 0.3 mL 95% enriched water from Isotec, Inc. in his target with a 0.6 mL overpressure volume. He measures the gases evolved during irradiation using an inverted buret. He has observed 1.3 cc/min gas evolved for the first minute of irradiation and 0.4 cc/min gas evolved by 15 minutes of irradiation. If he re-adds H_2^{18}O to the target during irradiation and repeats the measurement, the gas evolved goes up for a few moments and then settles down to the (0.4 cc/min) previous rate. J. Nickles also observes outgassing during irradiation and 1% radiolysis, which is much greater than would be predicted from the G-value of pure water.

D. Schlyer cautioned that target water can contain Ni and recommended that users have their water analyzed. C. Harris (Duke University) has had an interesting experience with the enriched water from Mound Laboratories which underscores D. Schlyer's warning. One batch he irradiated came out "milky" after irradiation. He stopped using that batch of water and eventually sent it back to Mound Laboratories. He then started using water from Isotec, Inc. In an effort to see what was causing the "milkiness" he sent a sample of the irradiated water for metal analysis. He also sent nonirradiated samples of Mound and Isotec enriched ^{18}O -water for metal analysis. The principal metals found were as follows:

Metal	Nonirradiated water Isotec, Inc. (ppb)** lot NS 0065	Nonirradiated water Mound Labs. (ppb)** order #HH 6-88-007	Irradiated water Mound Labs (ppb)**
Li	59	1	nm
B	110	841	nm
Mg	25	49	nm
Si	424	1640	11000
Ca	172	677	6810
Ti	0.8	64	nm
Cr	<0.29	30	nm
Fe	<1.5	<1.5	nm
Ni	16	1040	42000
Zn	99	252	18000
Br	12	4	nm
Na	327	749	nm
K	168	514	nm
Mn	14	1	42
Co	1	3	nm
Cu	2	6	nm
Sb	10	0.4	nm
I	6	63	nm
Ba	20	156	nm

* nm = not measured.

** All of these water samples were stored in glass vials.

While these data represent only single samples and may not be indicative of the average impurities from these suppliers, he was surprised by the difference in the ion concentration between the two suppliers and speculated that it might be because the preparation of water from the two suppliers was different. As far as he knows, Mound Laboratories distills water from stainless steel and Isotec distills from stainless steel and then from glass. Glass may be a source of carrier fluoride, but unfortunately no fluoride measurements were done on the water. Certainly irradiation of the target introduced the greatest amount of metal ions into the target water.

Issues regarding tubing used for the target and F- drying system:

D. Schlyer is no longer using the electrolytic method to separate $^{18}\text{F}^-$ from H_2^{18}O ,¹⁶ but is using ion exchange for that separation. He uses 30 meter polyethylene/polypropylene lines and routinely changes them about every 6 months. He dries his lines after each run if possible, or at least once each day with helium. T. Tewson uses Teflon lines, both to deliver water to the target and to recover it, and the specific activity of the fluoride is very high (>20 Ci/ μmol). However, these lines start to retain ^{18}F activity and water beads in them after about six months of use and so they have to be replaced.

C. Harris was using 67 feet of 35 mil bore polyethylene tubing, including a 7 foot rise in height, through which the water was moved using nitrogen gas. This system delivered target water, despite lack of cleaning except for blowing with dry nitrogen, for about 80-90 runs without any serious problems. Then delivery of activity became erratic, protracted and broken. Cleaning the tubing with reagent alcohol restored delivery to some extent, but only for a few runs. The tubing was replaced with another of .031" diameter which only lasted a few runs. Polyethylene and teflon tubes of 0.035", 0.042", and 0.045" diameters were tested. The 7 foot rise in tubing was changed to a ramped rise with tubing length increased to 82 feet. Overall he found that tubing internal diameters of less than 0.035" greatly increase the difficulty of delivery. A steep vertical rise of over 3 feet should be avoided if possible; otherwise gentle ramping is preferable. The least pressure that is required to move the bolus should be used. Excessive pressures tend to fracture the water bolus. Delivery lines of polyethylene have a limited life even if cleaned regularly; expect to change them every few weeks. He believes this is due to damage of the polyethylene

which causes it to swell. Teflon lines have a longer lifetime, which would not be predicted by radiation sensitivity.

J. Link (University of Washington) asked if anyone filters their $H_2^{18}O$ to assure sterility and remove bacteria? What might the filters introduce? J. Brodak found that pieces of septa from his $H_2^{18}O$ vial were getting into his target and clogging his lines. He tried using filters a few times to remove the septa particles and found that both the amount of $^{18}F^-$ recovered and the reactivity of the fluoride decreased. He now redistills his water in glass, transfers it to glass and uses a glass syringe and has not seen a change in his specific radioactivity in over a year. D. Schlyer has looked at filters and especially likes one which uses propyleneglycol. M. Berridge filters after recovery and then stores the water under Ar to inhibit bacterial growth. K. Mulholland uses water from Isotec, Inc. and only uses sterile needles to draw up water from the vial.

C. Harris uses vials with tear-off tops, to prevent septum puncture and contamination of the ^{18}O -water.

Target materials:

Y. Jongen (IBA, Belgium) strongly prefers tantalum because of its chemical inertness and no activation at low proton energies. He has compared Ta with Ti, Cu/Ni, and Ni to reach this conclusion. T. Tewson has found that with extended use Ni/Cu targets drop to <10% recovery of fluoride. With silver targets his recovery has stayed above 90%. When you irradiate a target containing water, some metal inevitably dissolves in the water, even with Pt, so Tewson advocates using target metals that won't reduce labeling yields. Berridge gets high yields with Ag foils and argued that they are easier than tantalum to seal.

J. Need and C. Harris have had success with a Ni plated Cu target. When they switched to a Ag target of the same design, they observed no significant difference in the recovery of $^{18}F^-$ from their target. R. Dahl has had success with titanium and silver under a range of conditions, although Ti windows get highly activated. Both materials result in successful FDG labeling, which he felt was the most important test of the quality of $^{18}F^-$. Everyone agreed that we need to compare yields for a specific synthesis in order to evaluate the quality of fluoride from different targets, but there was no consensus on what would be the optimum synthesis to use for this purpose.

Cryptates

No one commented on the role of cryptates in alleviating the problems of metal ion contamination. K. Mulholland asked how one removes 2.2.2 from a product compound. M. Berridge's experience is that more 2.2.2/carbonate requires more triflate-- up to 2-4 times that recommended by Hammacher, but the ratio of reagents should be held constant. He routinely uses 10 mg triflate per synthesis. He finds typical yields for FDG are 30-50% with either Ag or Ti. Both foil materials last about 20 runs ($15 \mu A \times 15$ min.) before they need changing. Berridge argues that Ag foils are less activated and easier to seal.

C. Harris reported that adding K_2CO_3 stoichiometrically increases his FDG yield.

Standardized assay for quality of anhydrous fluoride:

D. Schlyer has studied yields by a standard assay using dinitrobenzene + CsF ---> fluoronitrobenzene (submitted to Int. J. Appl. Rad. Isotop.)

T. Tewson recommended that a "standard" FDG procedure from the literature could be used by individual labs to compare their fluoride, he feels that the Julich synthesis would be best. Clark questioned whether this was a good test system because "every condition works." This comment is probably most true for the cryptate system, which is very forgiving. Glassware may even be the most important variable. J. Brodak reported that yields for the Hammacher synthesis of FDG were higher when a Pt crucible was used, versus glass, to dry the fluoride. Vacutainers don't work for him. M. Berridge washes his FDG glassware, which is used for drying the fluoride, with KOH/isopropanol, but does not soak it for very long. He then washes it with nitric acid and finds that it works. He stores it dry containing 2.2.2 and carbonate ready for use.

FDG synthesis is probably useful to test whether fluoride is reactive, but it is not a very sensitive test for the reactivity or specific radioactivity of fluoride. M. Berridge reported after the conference that if he makes FDG with tetramethyl ammonium hydroxide instead of 2.2.2/ K_2CO_3 , the sensitivity of the test improves. The TMAH is roughly stoichiometric with target garbage at the failure point (nominally 5-100 μ mol). A 50% yield with TMAH indicates good quality fluoride. To have a sensitive test, one must use the fluoride from a full target load and long irradiation.

Assays for specific radioactivity of final ^{18}F product:

Has anyone compared specific radioactivity assayed by HPLC versus a biochemical binding assay? For receptor ligands a competitive radiometric receptor binding assay may provide a more meaningful measure of "mass" in radiopharmaceutical preparations. These assays do not measure mass directly, but rather the quantity of receptor binding components in the preparation, both the radiopharmaceutical itself and any receptor binding contaminants which may be present. Although this "effective" specific radioactivity may include receptor binding material other than that of the intended radiopharmaceutical, for in vivo receptor studies, it is the effective specific radioactivity of the radiopharmaceutical, rather than the actual mass specific radioactivity, that is important. Conventional methods to estimate receptor competing mass, based on peak areas from HPLC, can underestimate mass if the sample contains co-eluting receptor binding components with weaker chromophores or if the column is "bleeding" substantial quantities of highly retained receptor binding impurities. However, in a chemically pure preparation of a radiopharmaceutical, the effective specific radioactivity and the mass specific radioactivity should be the same. For preparations where Katzenellenbogen and Welch have determined both the mass and effective specific radioactivities, there has been good agreement between the two values.¹⁷

J. Katzenellenbogen (University of Illinois) provided an account of how effective specific radioactivity is determined from a competitive radioreceptor assay using a decayed sample of a radiopharmaceutical. The assay requires a tritiated tracer ligand (e.g. estradiol for the estrogen receptor, R5020 for the progesterone receptor, R1881 for the androgen receptor, or aldosterone for the mineral corticoid receptor), a nonradiolabeled sample of the tracer ligand, an authentic standard of the pharmaceutical, and an appropriate receptor preparation. By comparing the position of the competition curve (Hill plot) for the decayed radiopharmaceutical with that of the authentic unlabeled standard, one can determine the quantity of receptor binding substance in the unknown sample in terms of mass equivalents of the standard, the effective mass. The effective specific radioactivity is the ratio of the radioactivity present in this sample at the end of synthesis, divided by the effective mass of the decayed radiopharmaceutical.

An example demonstrating the determination of effective specific radioactivity for 16α - ^{18}F fluoroestradiol (^{18}F FES) is shown below. This particular assay used lamb uterine cytosol containing approximately 1 nM of estrogen receptor, tritiated estradiol as the tracer, and unlabeled

estradiol (E_2) and FES as reference ligands. Serial dilutions of the ligands were incubated with the protein and tritiated tracer at 0° C for 18 hrs, and treated with dextran coated charcoal to remove unbound ligand before liquid scintillation counting. For a complete description of the binding protocol, see reference.¹⁸ Comparison of the 50% competition points shows the [^{18}F]FES sample to have 0.0012 of the binding mass present in the known sample of FES. Correcting for dilutions gives 7.75×10^{-7} M of receptor-binding equivalents in the decayed sample. From this and the concentration of radioactivity present at the end of synthesis (0.965 mCi/mL), an effective specific radioactivity of 1.24 Ci/ μ mol can be calculated for this preparation of [^{18}F]FES.

1.6 Conclusions

The conference and this report set out to understand and describe those parameters, both chemical and engineering, that result in an optimal target system. Such an ideal system would be characterized by high yields of maximal specific radioactivity isotopes and would be robust to changes in irradiation and labeling conditions that seem to be normal reality in the radiochemistry laboratory. Toward that goal we have been only modestly successful. Too many things remain a mystery in target chemistry, but for those who spent their midsummer '89 in Vancouver, there are surely fewer mysteries.

Further progress is needed in developing the chemistry and engineering of targets. Too often the knowledge gained by one group is difficult for others to apply because of the permutations in target systems due to differences in target materials, shapes, sizes, conditioning, supply lines and valves as well as differences in irradiation conditions and analytical techniques. We are working to describe our target systems with a common set of variables, as presented in a questionnaire. We have also suggested some assay procedures for characterizing the radiochemical quality of products from targets. With these accomplishments, progress in understanding the radiochemistry of targets and precursors should accelerate. However, as each PET radiochemistry laboratory becomes increasingly consumed with feeding insatiable tomographs, it may be easy to live with our targets at their current level of (non)performance. It's hard to argue with the approach that "if it isn't broken, don't fix it." But carefully documented and systematic changes in targetry and precursor chemistry will surely lead to improvements that will make the next workshop even more useful.

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