^{18}F Production

Bert Windhorst
Radiopharmaceutical scientist
VU University Medical Center Amsterdam

Outline

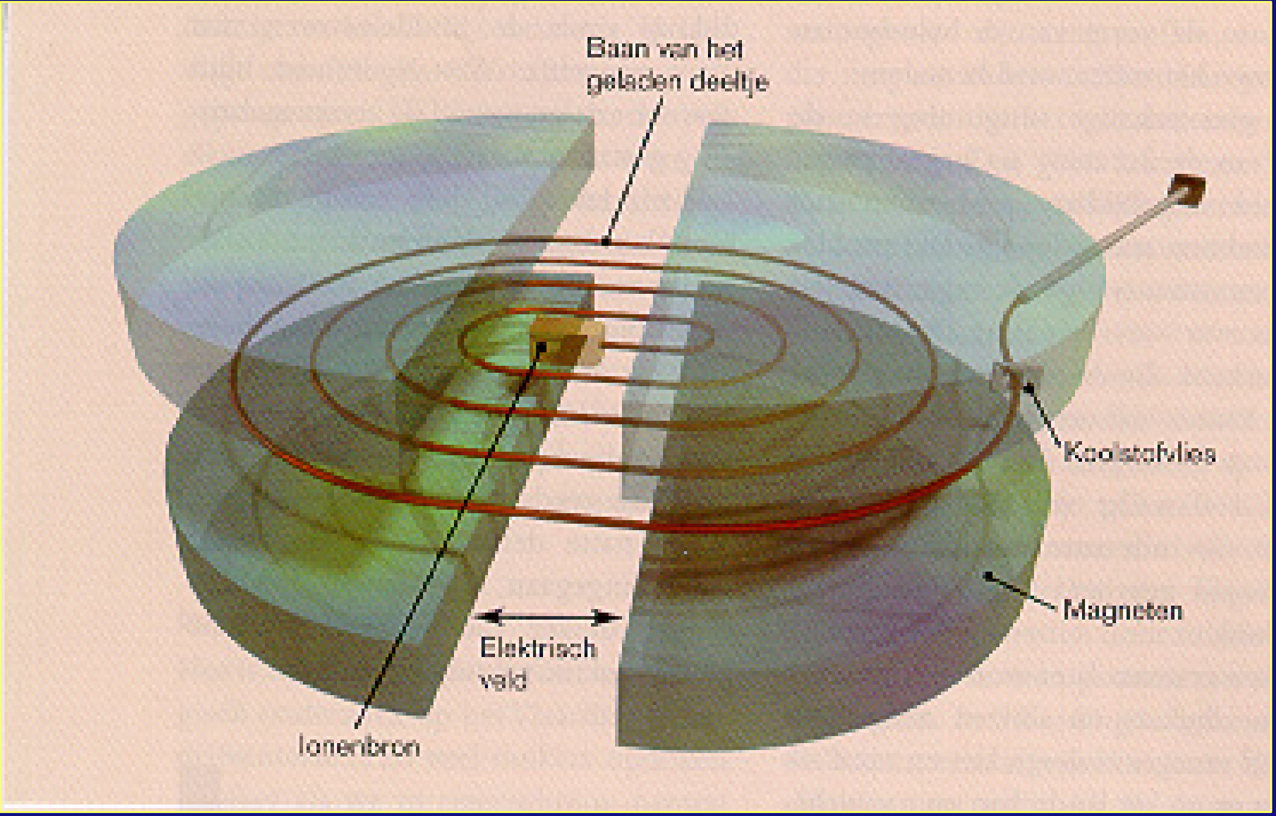
Cyclotron technique

^{18}F targetry : Fluoride and Fluorine production

Main PET Isotopes

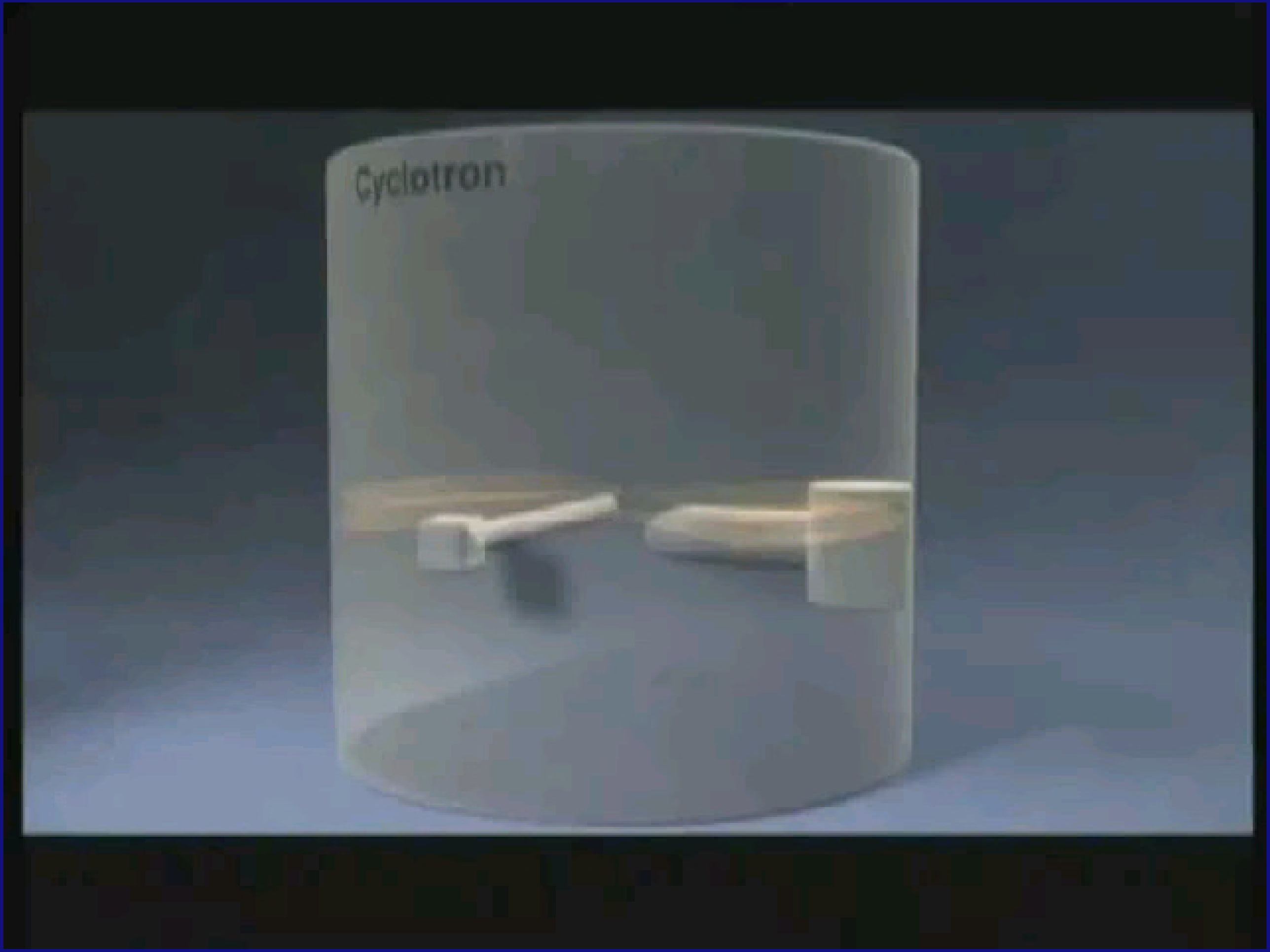
^{11}C	:	20 min,	β^+ (970 KeV),	$^{14}N(p,\alpha)^{11}C$
^{13}N	:	10 min,	β^+ (1190 KeV),	$^{16}O(p,\alpha)^{13}N$
^{15}O	:	2 min,	β^+ (1720 KeV),	$^{14}N(d,n)^{15}O$
^{18}F	:	110 min,	β^+ (635 KeV),	$^{18}O(p,n)^{18}F$

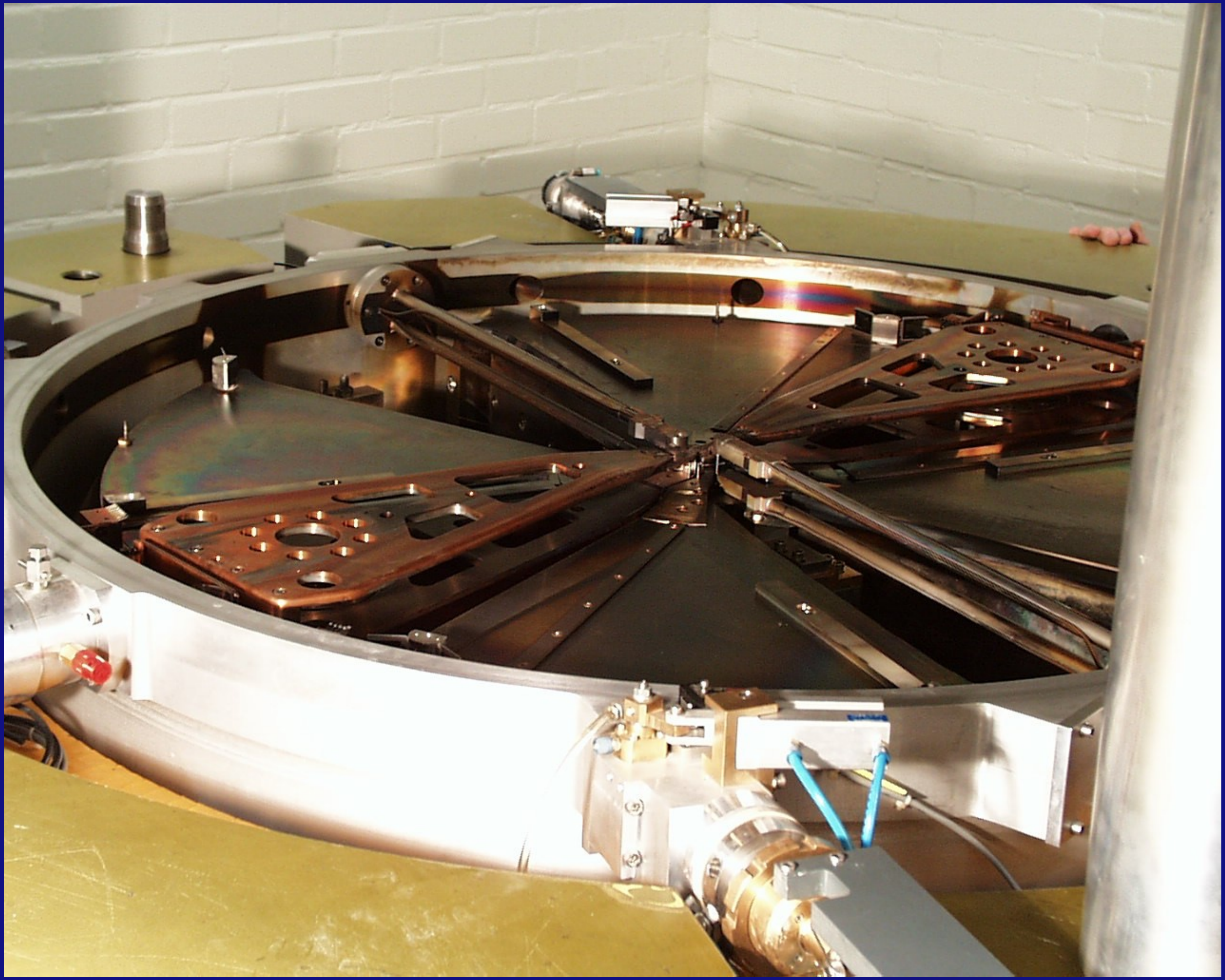
Cyclotron production



30.000 volt between D's
300 circles, 600 accelerations of 30.000 volt = 18 MeV

Cyclotron





IBA 18/9

^{18}F : 2,3 ml $H_2{}^{18}O$ in nuobium
^{11}C : 60 ml N_2 + 0,5% O_2 in aluminium
^{13}N : 2,3 ml H_2O in nuobium
^{15}O : 60 ml N_2 in aluminium

^{18}F Fluoride production

Nuclear reaction

$^{18}O(p,n)^{18}F$, obtained as Fluoride in water

Proton energy from 10 MeV

Side reaction

$^{16}O(p,\alpha)^{13}N$, obtained as nitrates in water

Side products

no nuclear side reactions

^{18}F Fluoride production

Nuclear reaction

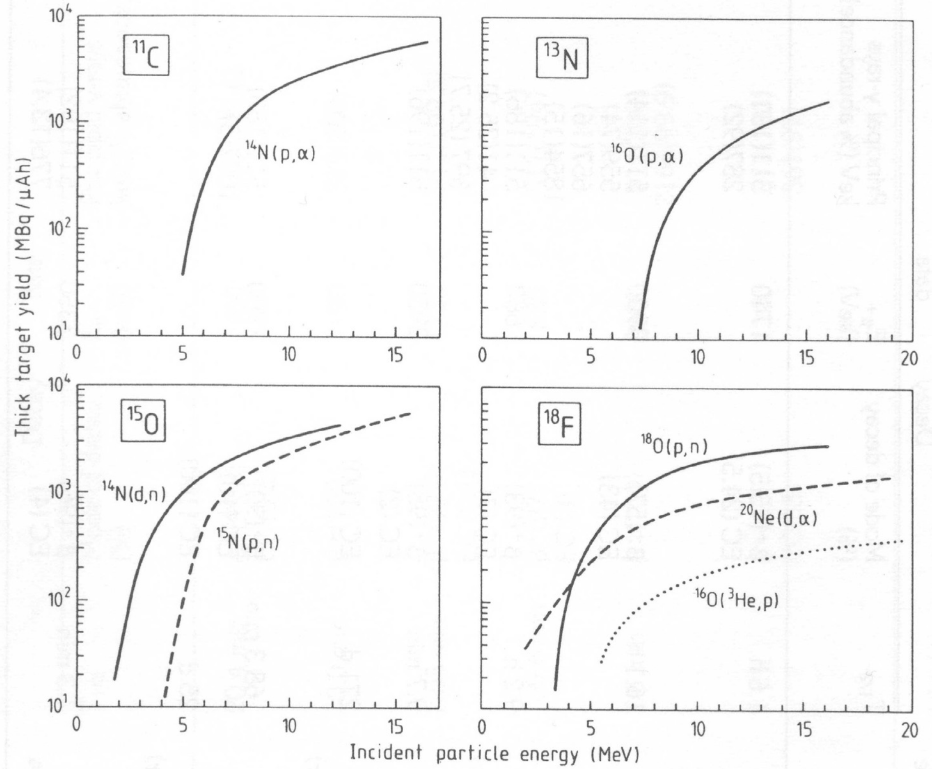
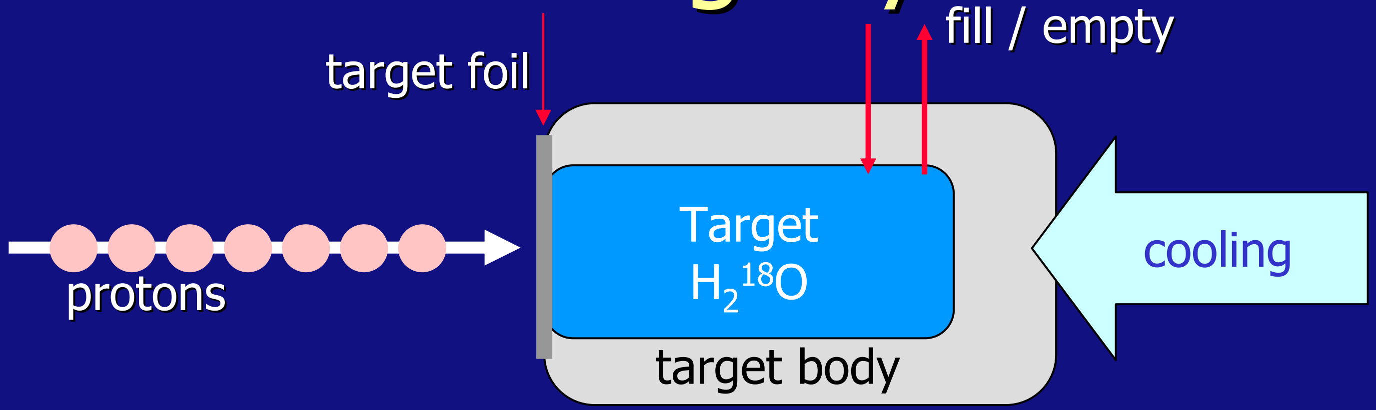


Figure 1. Integrated thick target yields of some commonly used positron-emitters expected from the most common production routes, plotted as a function of incident particle energy. Data were calculated using the measured excitation functions (for reference see text).

^{18}F Fluoride targetry



Important chracteristics for target body material:

- Heat capacity coefficient
  - (limiting factor for high beam currents: high pressure in target)
- Radionuclidic side products
- Chemical purity of [^{18}F]Fluoride from target

^{18}F Fluoride target body material

Silver

Advantage:
- high heat capacity (max ± 40 μA)
- no long lived radio isotopes

Disadvantage:
- Silver particles

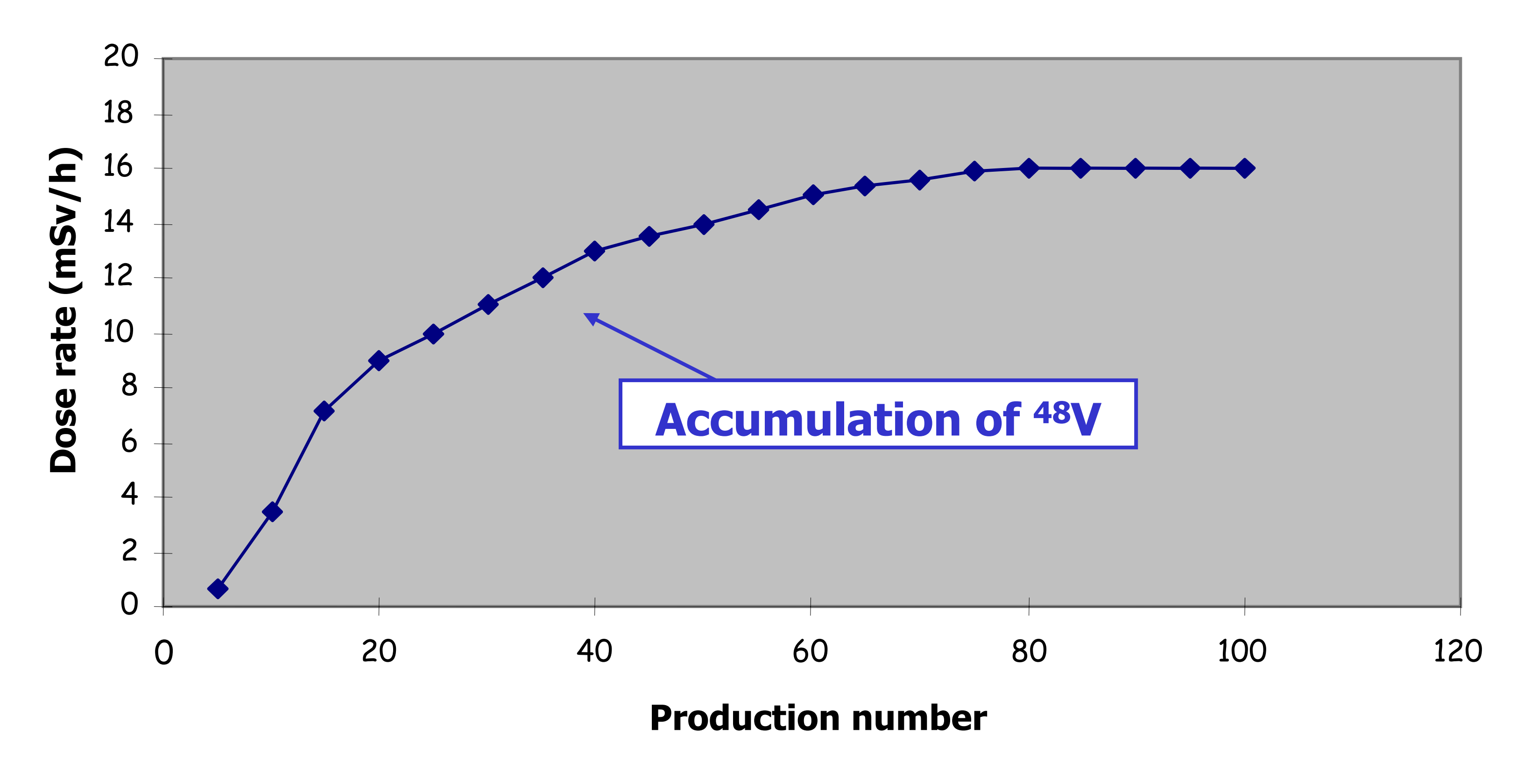
^{18}F Fluoride target body material

Titanium

Advantage: - clean ^{18}F solution

Disadvantage: - low heat capacity (max ± 30 μA)
- ^{48}V as side product

Activation of Titanium



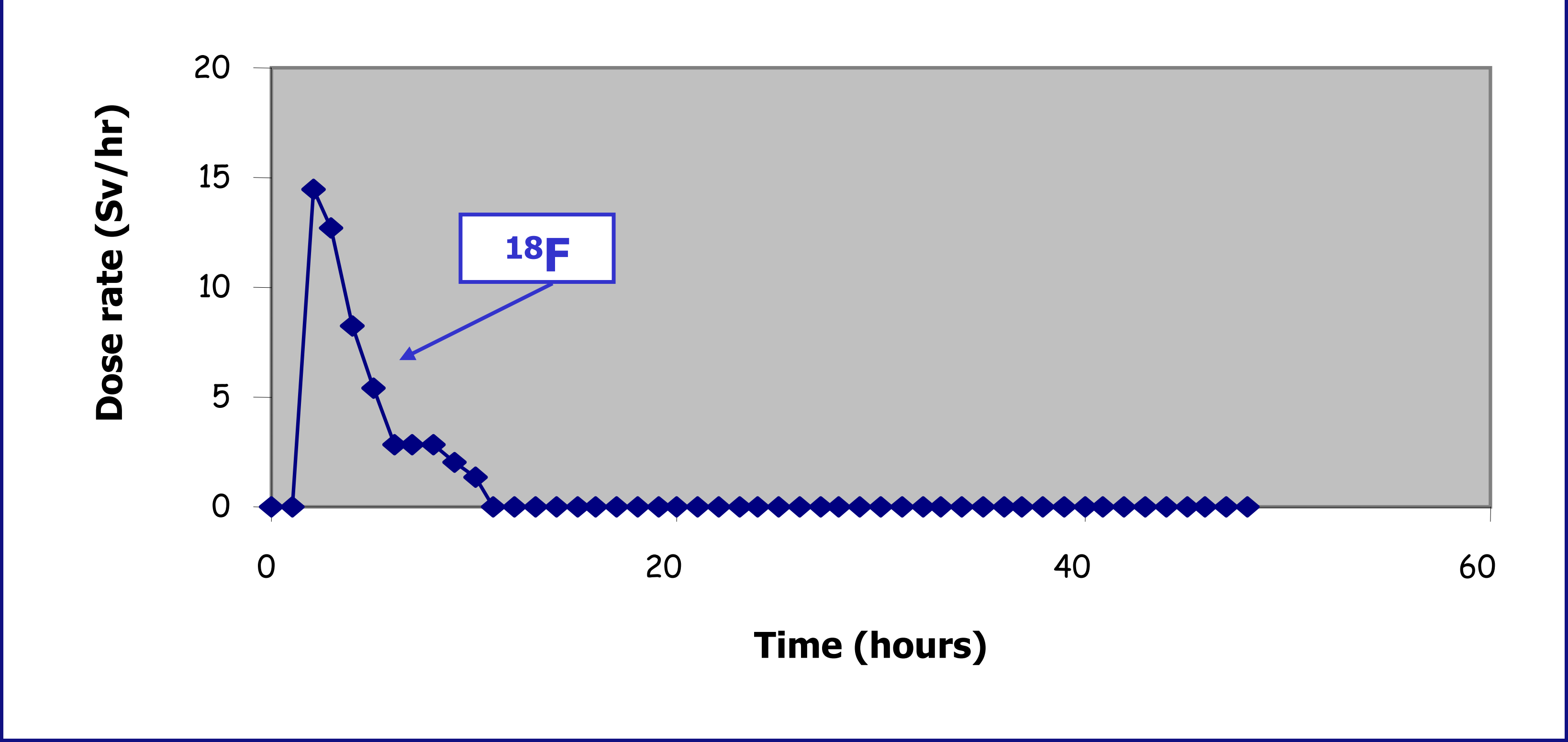
^{18}F Fluoride target body material

Niobium

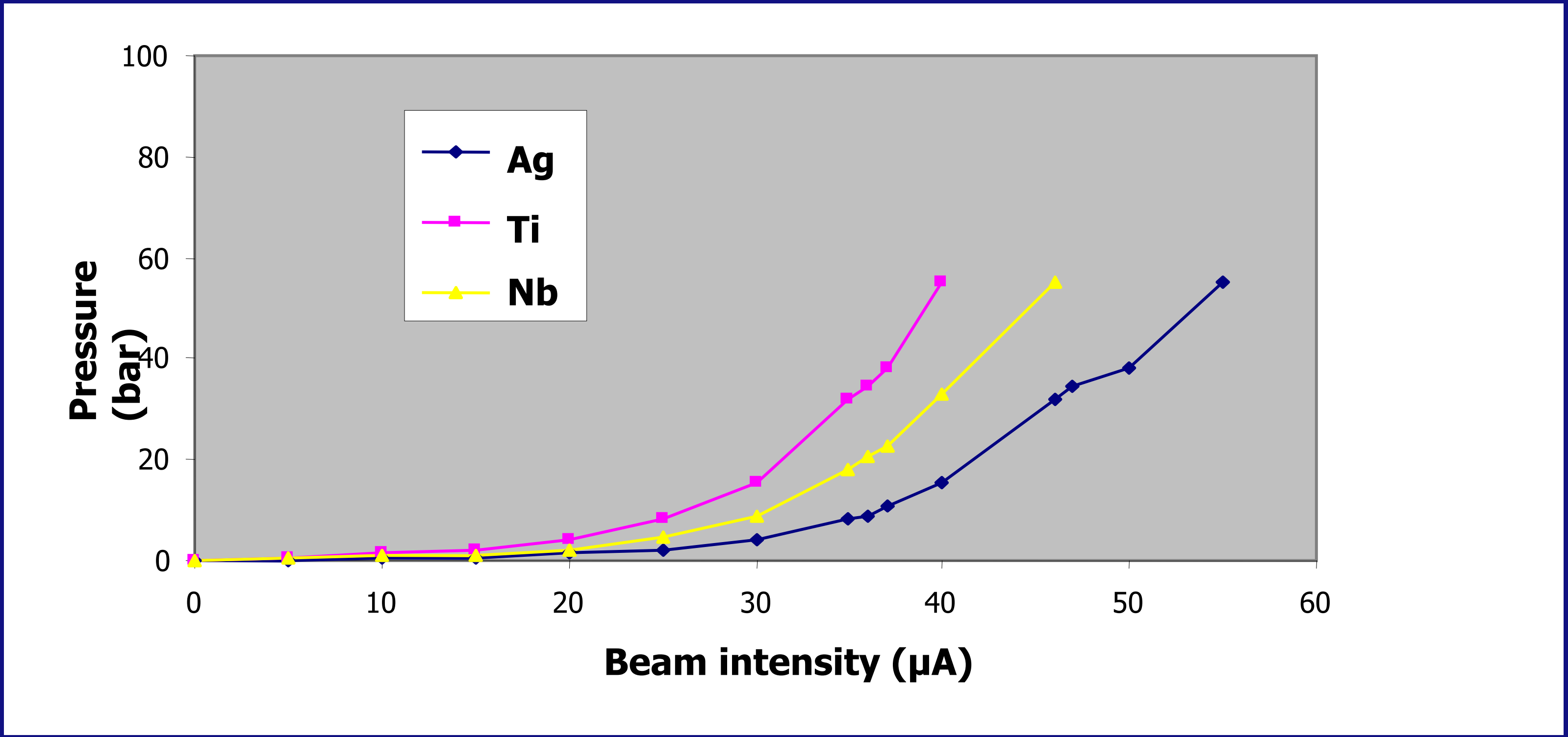
Advantage:
- clean ^{18}F solution
- no long lived radio isotopes
- high heat capacity (max ± 40 μA)

Disadvantage:
- ?

Nuobium activation



Pressure in different materials



Results different target materials

Summary of the results after 120 minutes irradiation

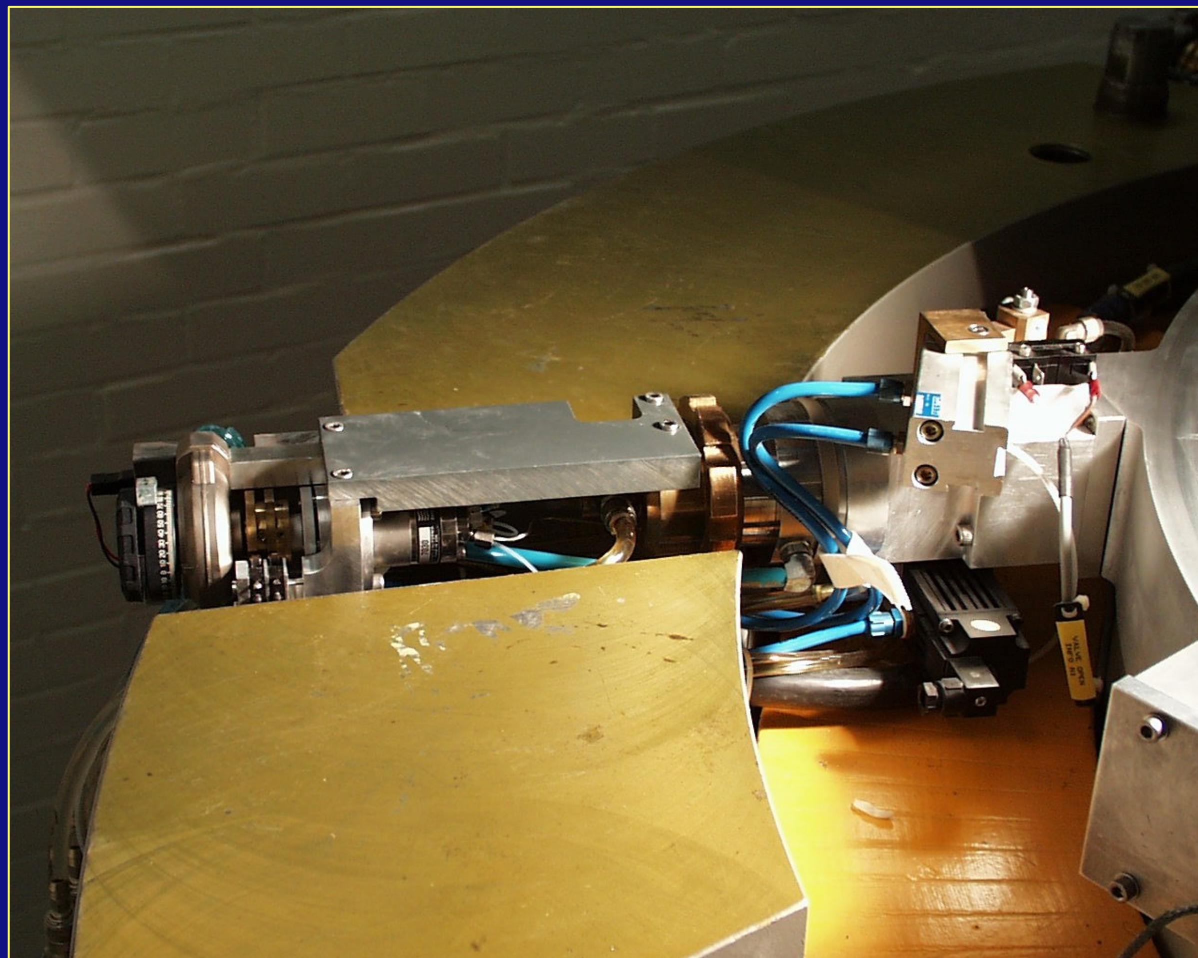
Target chamber material	Ag	Ti	Nb
Energy (MeV)	18	18	18
Beam intensity (µA)	40	30	35
Thick target yield (mCi/µA @ sat)	237	245	237
Radioactivity EOB (Ci)	5.1	3.9	4.4

Results at other centers

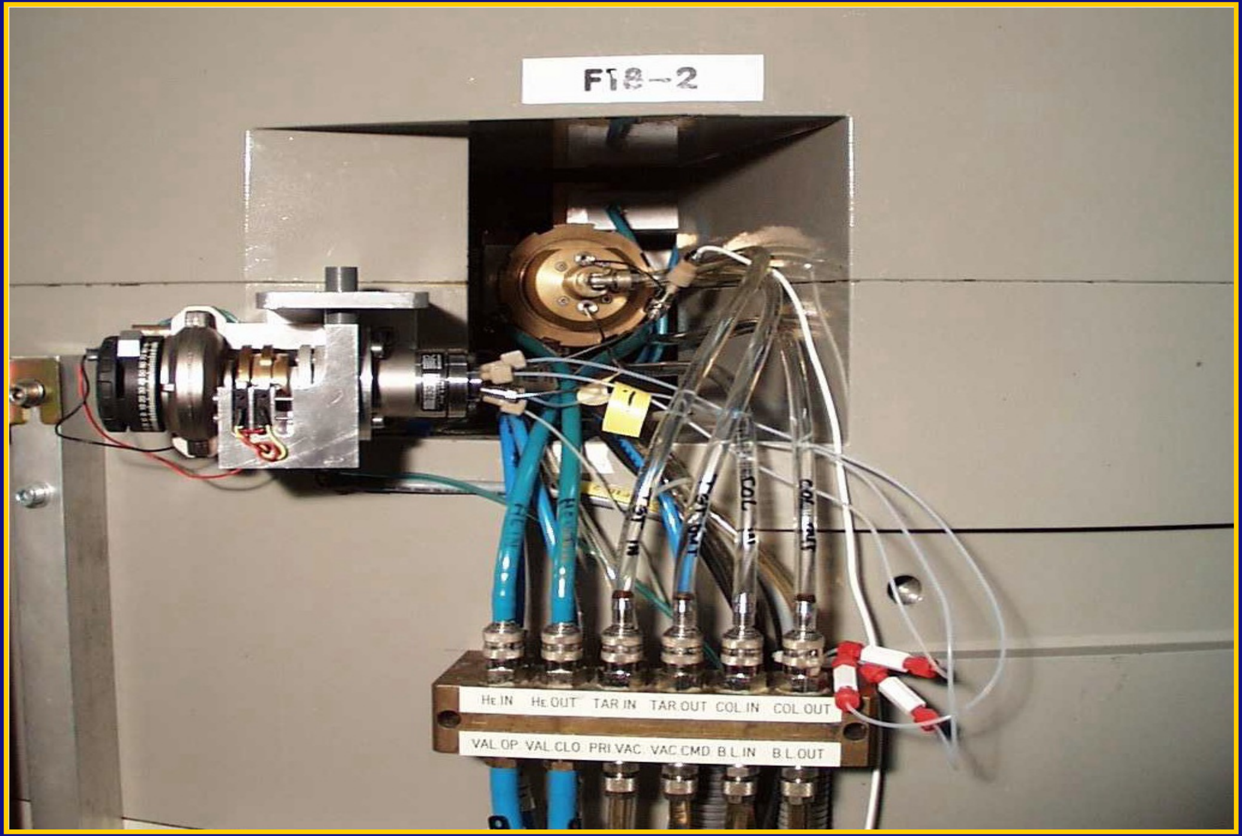
Table 3. Typical data for [^{18}F]fluorine produced at different centres from ^{18}O-enriched water targets. (Data reproduced from Guillaume *et al.*, 1991, with permission).

Centre	St. Louis	Sendai	Villigen	Turku	Jülich	Hammersmith	Liège
Material insert	SS & Ti	Ti	Ag	Ag	Ti	SS316 & Ti	Ni
Water width (mm)	3, 5, 7	3, 4, 5	5	1.5	3.5	3	3.4
Foils	Havar or Ti	Al/Ti & Ag	Ag	Ni	Ti	Al/Ti & SS316	Ti
Seal	O-ring	O-ring	Ag	Metal	Weld & Ag	Metal to metal	O-ring
Cooling (°C)	Water (10)	Coolant (0)	Water (30)	Coolant (10)	Water (10)	Water (10)	Water (10)
^{18}O-Enrichment of H_2O (%)	97	20	98	98	97	20	5
Volume (mL)	1.2, 2.0, 2.8	2.5	4.5	0.195	1.3	2.0	1.8
Pressure (atm)	1	Open or circulated (Pd)	Open	Open	15-25	2	2-3
E (MeV)	15	16	16	12	16.5	16	22.6
Irradiation (μA x min)	15-20 x 80	20 x 60	20 x 60	10 x 60	20-35 x 60	20 x 60	10 x 60
Yield (GBq/μAh at EOB)	2.22	0.33	2.07	1.11	2.41	0.407	0.11-0.12
(mCi/μAh at EOB)	*ca* 60	9	56	30	70	11	3-3.2
Sp. Act. (TBq/μmol EOB)	1.85	0.148	nca	5.18	7.4	11.1×10^{-3}	0.37
(Ci/μmol at EOB)	*ca* 50	4	nca	140	200	0.3	10
Reference	Kilbourn *et al.*, 1985	Iwata *et al.*, 1987	Huszar & Weinreich, 1985; Vogt *et al.*, 1986	Solin *et al.*, 1988	Qaim *et al.*, 1987; Nebeling *et al.*, 1990	Clark *et al.*, 1990	Guillaume *et al.*, 1990

Fluoride target



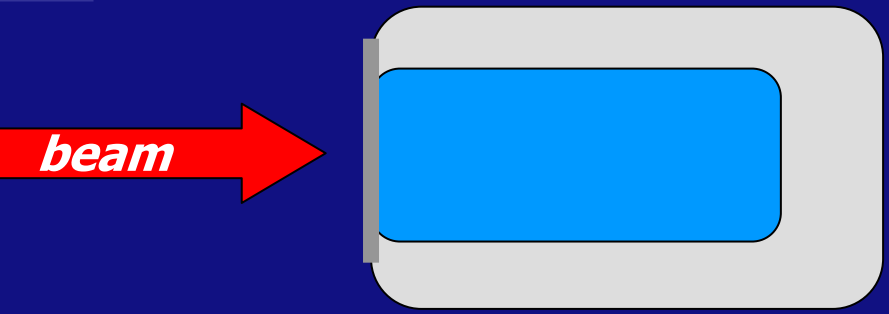
Fluoride target



Fluoride target

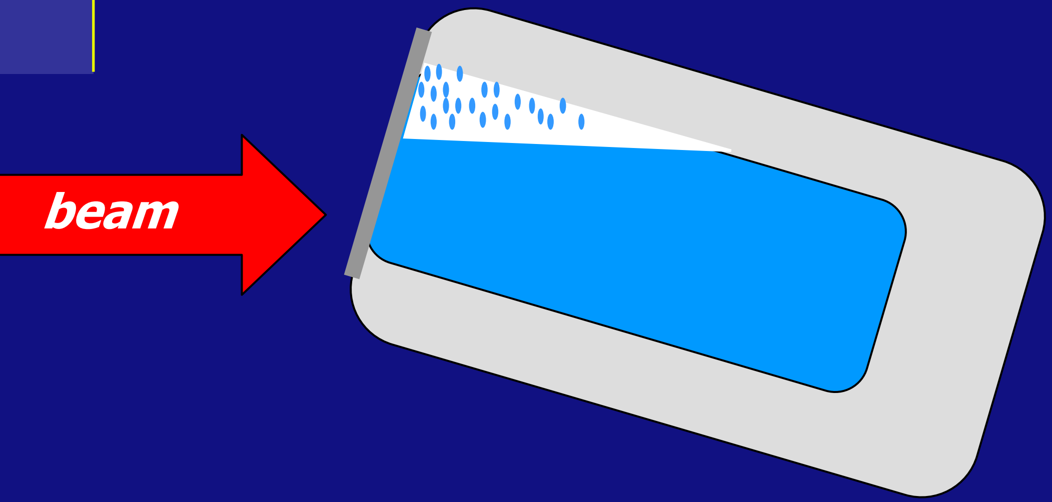
Different materials

^{18}F Fluoride targetry



Target volume ± 2.4 ml
Target filling ± 2.4 ml
max 40 μA

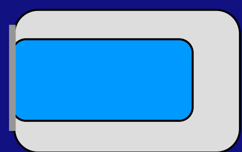
^{18}F Fluoride targetry



Target volume ± 4.5 ml
Target filling ± 3.3 ml
70 - 80 μA

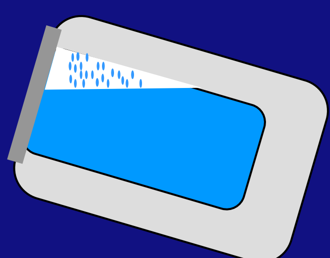
XXXL : 150 μA ?

^{18}F and [^{18}F]FDG yields 2004



3 uur 40 μA

Start synthesis 166 GBq [^{18}F]Fluoride
(End of synthesis 130 GBq [^{18}F]FDG)



3 uur 70 μA

Start synthesis 315 GBq [^{18}F]Fluoride
(End of synthesis 240 GBq [^{18}F]FDG)

^{18}F Fluorine production

Nuclear reaction

$^{20}Ne(d,\alpha)^{18}F$ or $^{18}O(p,n)^{18}F$

deuterons from 7 MeV

protons from 10 MeV

Side reaction

-

Side products

-

^{18}F Fluorine targets

Target material : Nickel or Monel

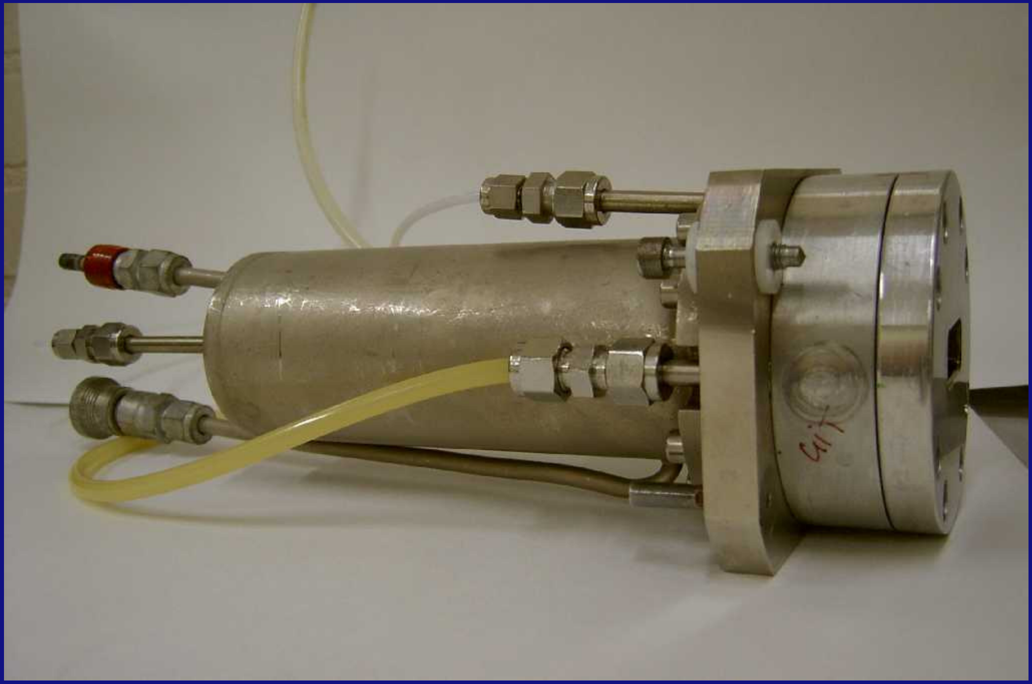
1st irradiation : ^{18}F fluorine deposit on target wall

Empty target, fill with Neon + 0.1-0.5% F_2

Irradiate

Electrophilic fluorination, or via intermediate

^{18}F Fluorine target Groningen



Installed in 1992

Design: Robert Dahl

Nickel / 153 ml

30 psi 1% F_2 / 100 psi Neon

Yield in 1992:

5 GBq / 50 μA / 1 hour

^{18}F Fluorine specific radioactivity

Addition of F_2 is essential,
but decreases specific radioactivity

Typically : less then 1 GBq/µmol

Gives problems for receptor studies,
however for F-DOPA no problem

Production results

Table 2. Typical conditions and production parameters for the cyclotron production of [^{18}F]fluorine by the ^{20}Ne(d,α) reaction at different centres. (Data from Guillaume *et al.*, 1991, with permission).

Centre		BNL	MRCCU Hammersmith	Jülich	Liège
Target body	(type; mL)	Honed Ni; 50	Polished Ni-201; 100	Ni; 38	Ni; 206
	(internal size, cm)	2.5 i.d. x 10	2.5 i.d. x 20	2.2 i.d. x 10	
Target gas	(% F_2 in Ne)[a]	0.1	0.12-0.15	0.18	0.17
	(µmol F_2)[b]	50-60	88[c]	60	220
Pressure	(beam off, atm)	25.8	13.5	18	12.3
	(beam on, atm)	32.5	23	30	15
Window	(material, µm)	Al, 810-Ni, 25	Havar, 50-Ni, 25	Nb, 25-Havar, 50	Al, 80-Ni, 20
	(seals)	Metal O-ring	Lead	Metal joints	Indium O-rings
E (Incident)	(MeV)	14-9.4	13.8	11.25	12
Irradiation	(µA x h)	15 x 2	15 x 1.67	40 x 1	10 x 1
Recovery of	(GBq)	13.6	9.25	18.5	4.4
^{18}F at EOB	(mCi)	367	250	500	120
	(% of theoretical)[d]	55	43	50	51
Yield	(MBq/µAh at EOB)	463	343-370	444	370-555
	(mCi/µAh at EOB)	12.5	9-10	12	10-15
Specific activity	(MBq/µmol at EOB)	259-370	41	130	29.6-44.4
	(mCi/µmol at EOB)	7-10	1.1	3.5	0.8-1.2
Reference		Casella *et al.*, 1980	Clark *et al.*, 1990	Blessing *et al.*, 1986	Guillaume *et al.*, 1990

[a)] Nominal value.
[b] Calculated from target volume and nominal filling parameters.
[c)] Experimentally determined as 194-242 µmol recovered, under conditions in which the fill-line contributes fluorine.
[d] Theoretical yields were calculated according to Casella *et al.* (1980).

Production results Groningen

Radionuclide production:	**1998 - 2004**	**2005**
Target	SCX nickel plated / 150 ml Havar frontfoil (25 um)	SCX nickel plated / 150 ml Havar frontfoil (25 um)
Targetgas	0,44 % F2 in Neon / 75 psi	0,44 % F2 in Neon / 75 psi
Beamcurrent	15 uA	**25 uA**
Irradiation time	60-120 minutes	120 minutes
Preparation for the production	1x conditioning target and lines 1x 3 µAh irradiation to waste	1 x conditioning target and lines 1 x 3 µAh irradiation to waste
Yield $[^{18}F]F_2$	30-50 MBq/µAh at EOB 1.2 – 2.0 GBq at BOS	**70 - 80 MBq/µAh at EOB** **3.5 – 4.0 GBq at BOS**
Specific activity	4.4 ± 1.0 GBq/mmol	**10.7 ± 3.0 GBq/mmol**

New developments

Optimization of ^{18}O gas targets : yields 40-50 GBq

Turku method : transfer [^{18}F]fluoride to [^{18}F]F_2

Higher yields and thereby increasing specific activity

Further reading

Radiopharmaceuticals for Positron Emission Tomography
Ed G. Stöcklin and W.W. Pike
Kluwer Academic publishers, Dordrecht, 1993, isbn 0-7923-2340-8

Nuclear Science series:
Fluorine-18 Labeling of Radiopharmaceuticals
M.R. Kilbourn
National Academy Press, Washington, 1990

Handbook of Radiopharmaceuticals :
Radiochemistry and applications
Ed MJ Welch, CS Redvanly
Wiley, Sussex, 2003, isbn 0-471-49560-3