Nuclear Physics applied to the production of Innovative Radio-Pharmaceuticals

Part II: tutorial on the ^{52}Mn case

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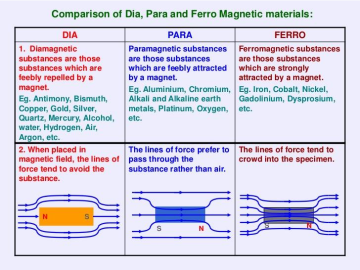
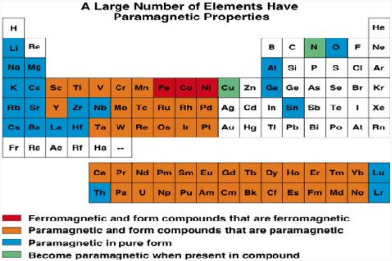
Why ^{52}Mn?

It is always very challenging to find out a chemical compound that can behave at the same time as:

- a **contrast agent** showing **paramagnetic** properties;
- having some **radioactive** isotopes with useful nuclear properties for PET imaging like ^{18}F.


Comparison of Dia, Para and Ferro Magnetic materials:

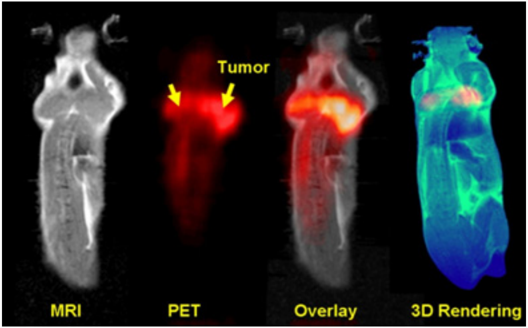
DIA	PARA	FERRO
1. Diamagnetic substances are those substances which are feebly repelled by a magnet. Eg. Antimony, Bismuth, Copper, Gold, Silver, Quartz, Mercury, Alcohol, water, Hydrogen, Air, Argon, etc.	Paramagnetic substances are those substances which are feebly attracted by a magnet. Eg. Aluminium, Chromium, Alkali and Alkaline earth metals, Platinum, Oxygen, etc.	Ferromagnetic substances are those substances which are strongly attracted by a magnet. Eg. Iron, Cobalt, Nickel, Gadolinium, Dysprosium, etc.
2. When placed in magnetic field, the lines of force tend to avoid the substance.	The lines of force prefer to pass through the substance rather than air.	The lines of force tend to crowd into the specimen.



The **only radionuclide** with $1 < Z < 92$ having main positron emitting nuclear properties basically mimic ^{18}F (i.e. average energy β^+ 250 keV and similar β^+ spectrum energy range) is ^{52}Mn only, that could be employed as PET tracer. ^{51}Mn is an alternative radionuclide PET candidate, although with a higher energy β^+ spectrum.

PET and MRI fusion

A breakthrough in **Multi-Modal Imaging** (MMI) diagnostic procedures may be achieved with a genuine fusion between PET/SPECT and MRI analyses. However that could be obtained only by using both a radioactive and contrast agent based upon the same chemical compound.



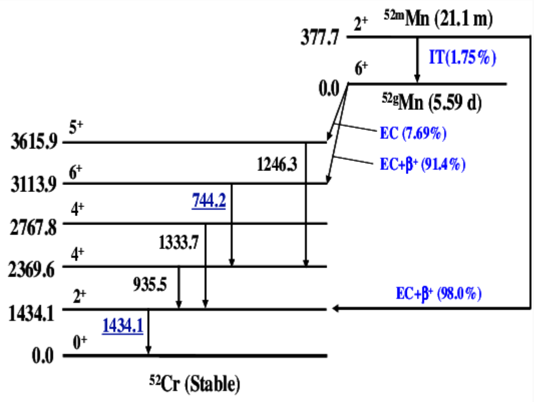
With the recent achievements in PET/MRI scanner technology, the use of radio-manganese, a manganese compound (i.e. a mixture of ^{52g}Mn and ^{51}Mn), may enable future dual modal imaging techniques, having both properties for MRI and PET.

Feasibility study: INFN project **METRICS** (CSN5).

^{52}Mn decay scheme

^{52}Mn has a metastable state:

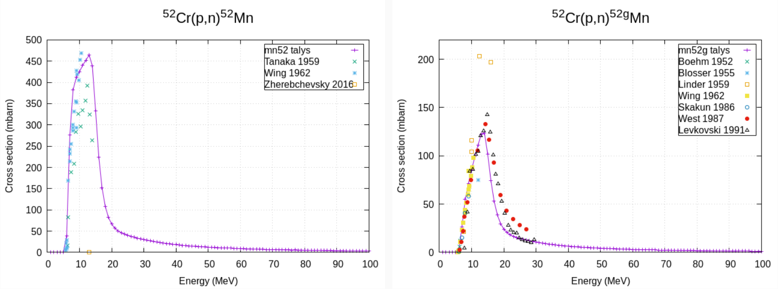
(IT=Isomeric Transition; EC=Electronic Capture)



It is possible to produce ^{52}Mn from Chromium with the reaction ^{52}Cr(p,n)^{52}Mn.

Cross section for the reaction ^{52}Cr(p,n)^{52}Mn

^{52}Mn is produced mainly at low energy via the **compound nucleus** mechanism:



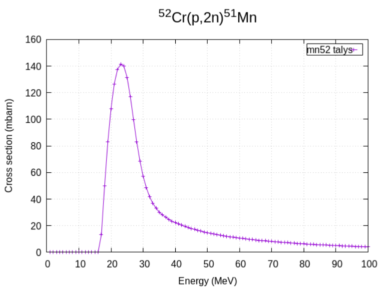
In the following we only focus on the ground state.

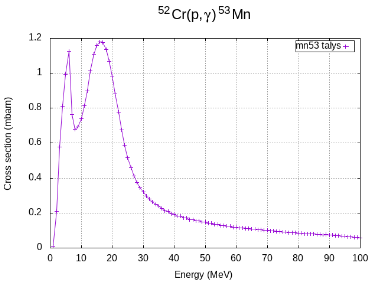
^{52}Mn contaminants

All the Mn isotopes: **contaminants** are also produced by the same reaction.

Isotope	half-life
^{48}Mn	158 ms
^{49}Mn	382 ms
^{50g}Mn	283 ms
^{50m}Mn	1.75 min
^{51}Mn	46 min
^{52g}Mn	5.6 d
^{52m}Mn	21.1 min
^{53}Mn	3.7x10^{6} y
^{54}Mn	312 d
^{55}Mn	stable

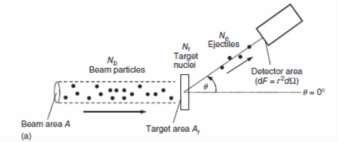
Looking at half-lives, the most dangerous is ^{53}Mn... but with a little cross section.





Reaction rate

Let us consider a production experiment for a given radio-isotope as ^{52}Mn:



We want to evaluate the number of secondary nuclei generated in the target under specific irradiation conditions (beam current, irradiation time, target thickness...)., i.e. in our case the amount of ^{52}Mn that is produced.

It is calculated starting from the **reaction rate**, i.e. to the number of nuclei produced per second:

$$R = \frac{I_0}{z_{proj}|e|} \frac{N_a}{A} \int_{E_{out}}^{E_{in}} \sigma(E) \left(\frac{1}{\rho_t} \frac{dE}{dx} \right)^{-1} dE \qquad \text{[nuclei/s]}$$

where I_0 is the charge beam current (measured in ampere), z_{proj} the atomic number of the incident particle, e the electron charge, N_a the Avogadro number, A the target atomic mass, E_{in} and E_{out} the energy of the projectile impinging on the target and after exiting from the target respectively, $\sigma(E)$ the production cross section of the nuclide analysed, ρ_t the target density and $\frac{dE}{dx}$ the stopping power of the projectile in the target.

Stopping power

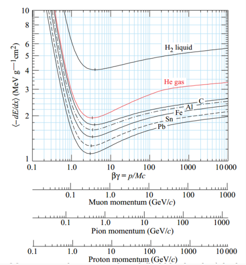
The incident proton loses energy and slows down inside the target: the energy loss is given by the so called **stopping power**:

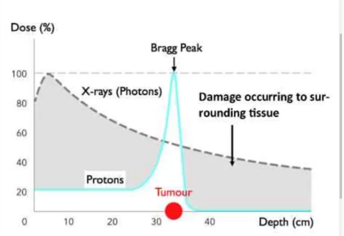
$$S(E) = -\frac{1}{\rho_t}\frac{dE}{dx} \qquad [\text{MeV cm}^2/\text{g}]$$

Bethe-Bloch formula:

$$\frac{1}{\rho_t}\frac{dE}{dx} = 2\pi N_a r_e^2 m_e c^2 \frac{Z}{A}\frac{z^2}{\beta^2}\left[\log\left(\frac{2m_e\gamma^2 v^2 W_{max}}{I^2}\right) - 2\beta^2\right]$$

$$W_{max} \simeq 2m_e c^2\beta^2\gamma^2$$



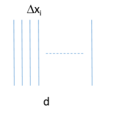


Thick Target yield

The **yield** is defined as the **number of produced nuclei per incoming charged particle** and is measured in [nuclei/C] or in [MBq/μA]. Typically:

$$Y(E) = n \frac{\int_0^E \sigma(E) dE}{\frac{dE}{dx}}$$

with n=target density.



Two cases:

- **thin target yield**: very little energy loss, with $\sigma_i \sim$ const and $S_i(E) \sim$ const in each layer Δx_i

$$Y_i \approx n \sigma \Delta x_i$$

- **thick target yield (TTY)**: we integrate over many layers, by taking into account the stopping power...

$$Y \approx n \sum_i \sigma_i \frac{\Delta x_i}{\Delta E_i} \Delta E_i$$

Care is required since many different definitions of yield are present in the literature.

In this exercise we are interested in the **final activity of** ^{52}Mn produced, which is obtained by evaluating the number of nuclei $N(t)$ produced during a given irradiation. If the product is stable:

$$N(t) = Rt$$

Time evolution

If the product is radioactive with decay constant λ (for ^{52}Mn:$\lambda = 1.435 \times 10^{-6} s^{-1}$), the number of the produced nuclei present in the sample $N(t)$ satisfies

$$\frac{dN(t)}{dt} = R - \lambda N(t)$$

with $t = 0$ as time of beginning of the irradiation. The solution is:

$$N(t) = R\frac{1 - e^{-\lambda t}}{\lambda}$$

The activity is given by:

$$A(t) = \lambda N(t) = R(1 - e^{-\lambda t})$$

We can define:

- **End Of Bombardment** (EOB) activity immediately after the irradiation;
- **Saturation** activity for $\lambda t >> 1$: $A(t) \to R$.

How to optimize yield?

This is true for all the produced isotopes, both ^{52}Mn all all the other Mn.

Aim: to maximize the yield of the desired isotope and to minimize the contaminants.

- increase the current
- increase the irradiation time
- increase the target quantity (thickness, enrichment)
- carefully select the nuclear reaction and the projectile energy

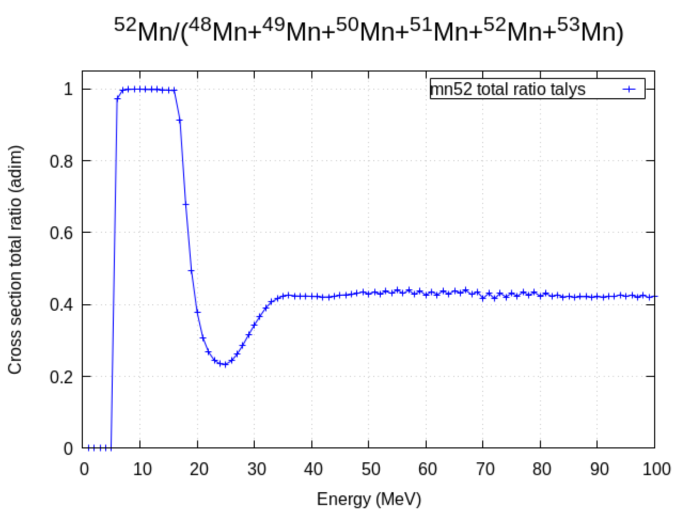
Not an easy task!

Important parameters to look at:

- reactions thresholds
- cross sections ratio
- **Isotopic Purity**: $IP = \frac{N_{^{52}\text{Mn}}}{N_{\text{all Mn}}}$
- **Radionuclidic Purity**: $RNP = \frac{A_{^{52}\text{Mn}}}{A_{\text{all Mn}}}$

Cross section ratio

In our case, we can identify a **low energy window** where only ^{52}Mn is produced without any contaminant.



The Excel exercise

The problem

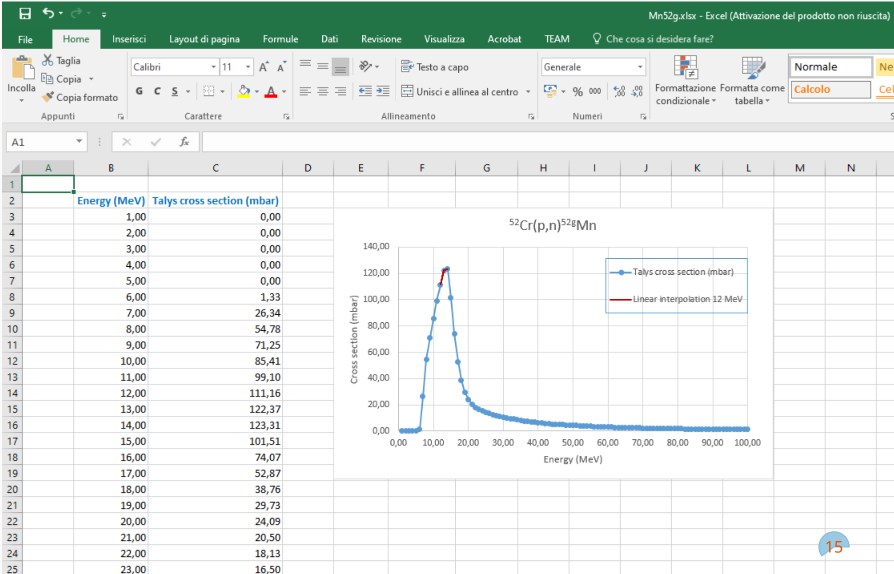
Evaluate the ^{52}Mn EOB activity produced with the following irradiation profile:

- current: 300 μA
- irradiation time: 1 h
- E_{in}: 14 Mev, E_{out}: 12 MeV
- target thickness: $\sim$ 100 μm

Four steps:

- cross-section readout and plot;
- stopping power evaluation
- yield integral evaluation: rate and EOB activity
- saturation activity

Step 1: cross section



Energy (MeV)	Talys cross section (mbar)
1,00	0,00
2,00	0,00
3,00	0,00
4,00	0,00
5,00	0,00
6,00	1,33
7,00	26,34
8,00	54,78
9,00	71,25
10,00	85,41
11,00	99,10
12,00	111,16
13,00	122,37
14,00	123,31
15,00	101,51
16,00	74,07
17,00	52,87
18,00	38,76
19,00	29,73
20,00	24,09
21,00	20,50
22,00	18,13
23,00	16,50

Step 2: stopping power

Mn52g.xlsx - Excel (Attivazione del prodotto non riuscita)

Formula

$$\frac{dE}{\rho_t dx} = 2\pi N_a r_e^2 m_e c^2 \frac{Z}{A}\frac{z^2}{\beta^2}\left[\log\left(\frac{2m_e\gamma^2 v^2 W_{max}}{I^2}\right) - 2\beta^2\right]$$

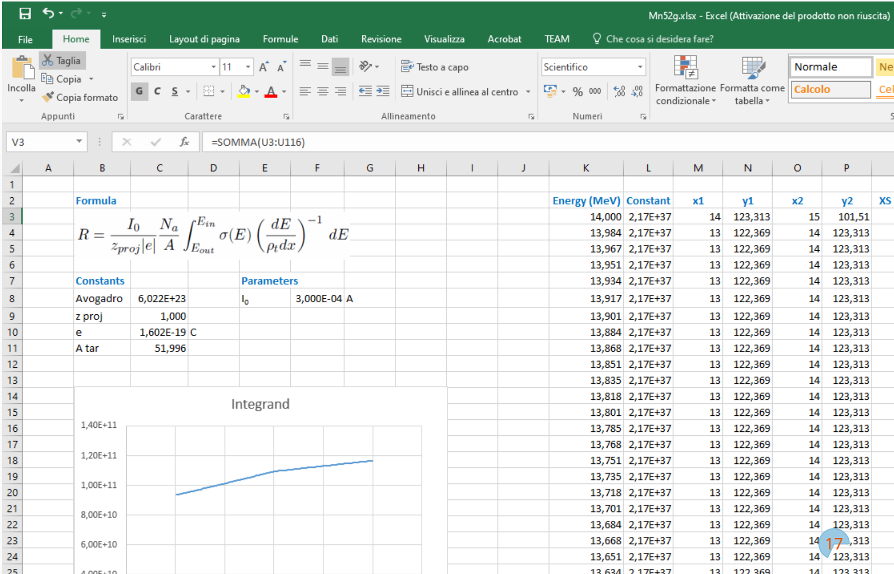
$$W_{max} \simeq 2 m_e c^2 \beta^2 \gamma^2$$

Constants			Parameters		
Avogadro	6,022E+23		increment dx	0,0001	cm
r e	2,818E-13	cm	density Cr52	7,19	g/mL
m e	0,511	MeV			
m proj	938,272	MeV			
z proj	1,000				
Z_1	24	A_1	51,9961	Z tar	24,000
Z_2	0	A_2	0	A tar	51,996
a_1	1				
a_2	0				
I_1	266,38676	eV		I tar	266,387
I_2	1	eV			

2,50E+02

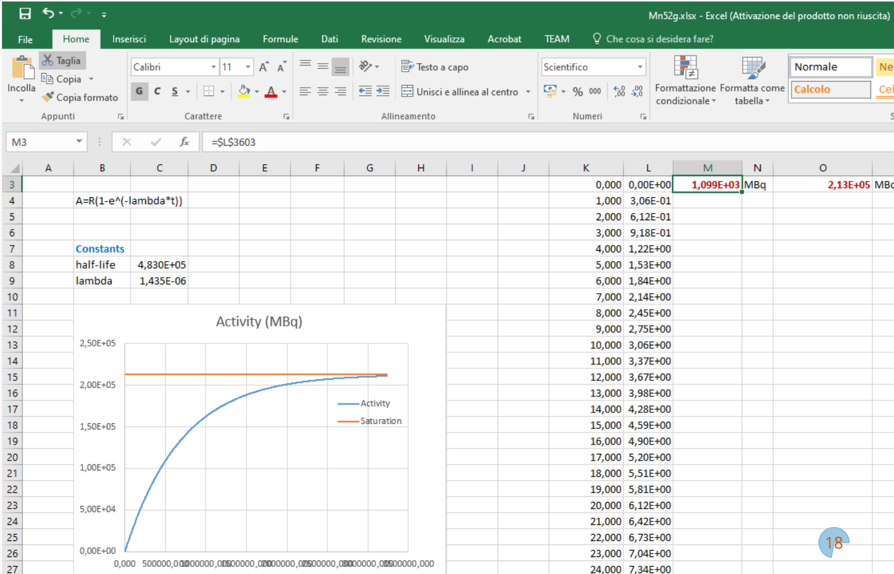
Energy (MeV)	gamma	beta^2	constant/beta^2	W_{max}
14,000	1,015	0,029	2,428E+00	3,073
13,984	1,015	0,029	2,431E+00	3,069
13,967	1,015	0,029	2,434E+00	3,065
13,951	1,015	0,029	2,436E+00	3,062
13,934	1,015	0,029	2,439E+00	3,058
13,917	1,015	0,029	2,442E+00	3,054
13,901	1,015	0,029	2,445E+00	3,051
13,884	1,015	0,029	2,448E+00	3,047
13,868	1,015	0,029	2,451E+00	3,043
13,851	1,015	0,029	2,454E+00	3,040
13,835	1,015	0,029	2,456E+00	3,036
13,818	1,015	0,029	2,459E+00	3,032
13,801	1,015	0,029	2,462E+00	3,029
13,785	1,015	0,029	2,465E+00	3,025
13,768	1,015	0,029	2,468E+00	3,021
13,751	1,015	0,029	2,471E+00	3,018
13,735	1,015	0,029	2,474E+00	3,014
13,718	1,015	0,029	2,477E+00	3,010
13,701	1,015	0,029	2,480E+00	3,007
13,684	1,015	0,029	2,483E+	3,003
13,668	1,015	0,029	2,486E+00	2,999

Step 3: rate and EOB activity



Energy (MeV)	Constant	x1	y1	x2	y2
14,000	2,17E+37	14	123,313	15	101,51
13,984	2,17E+37	13	122,369	14	123,313
13,967	2,17E+37	13	122,369	14	123,313
13,951	2,17E+37	13	122,369	14	123,313
13,934	2,17E+37	13	122,369	14	123,313
13,917	2,17E+37	13	122,369	14	123,313
13,901	2,17E+37	13	122,369	14	123,313
13,884	2,17E+37	13	122,369	14	123,313
13,868	2,17E+37	13	122,369	14	123,313
13,851	2,17E+37	13	122,369	14	123,313
13,835	2,17E+37	13	122,369	14	123,313
13,818	2,17E+37	13	122,369	14	123,313
13,801	2,17E+37	13	122,369	14	123,313
13,785	2,17E+37	13	122,369	14	123,313
13,768	2,17E+37	13	122,369	14	123,313
13,751	2,17E+37	13	122,369	14	123,313
13,735	2,17E+37	13	122,369	14	123,313
13,718	2,17E+37	13	122,369	14	123,313
13,701	2,17E+37	13	122,369	14	123,313
13,684	2,17E+37	13	122,369	14	123,313
13,668	2,17E+37	13	122,369	14	[illegible],313
13,651	2,17E+37	13	122,369	14	123,313
13,634	2,17E+37	13	122,369	14	123,313

Step 4: saturation activity



Calculation details

- mean ionization potential for Bethe-Bloch formula:

$$\frac{I}{Z} = 9.76 + 58.8\,Z^{-1.19}\text{eV for Z} \geq 13$$

- linear interpolation formula:

$$y = y_0 + (x - x_0)\frac{y_1 - y_0}{x_1 - x_0}$$

- trapezoidal rule integration:

$$\int_a^b f(x)dx \approx \frac{\Delta x}{2}\sum_{i=1}^{N}(f(x_{k-1}) + f(x_k))$$

Discussion of the result

The calculation shows that at EOB we produce about **1.1 GBq of ^{52g}Mn**.

For comparison, a typical injected dose of ^{18}*FDG* for a PET diagnosis corresponds to ~ 370 MBq.

Calculation with Talys

Talys can evaluate the cross section (left), but also perform irradiation calculations (right):

```
projectile p
element Cr
mass 52
energy 1 100 1
```

```
projectile p
element Cr
mass 52
energy 1 100 1
production y
Ebeam 14.
Eback 12.
Ibeam 0.3
Area 1.
rho 7.19
Tirrad 1 h
Tcool 0. s
```

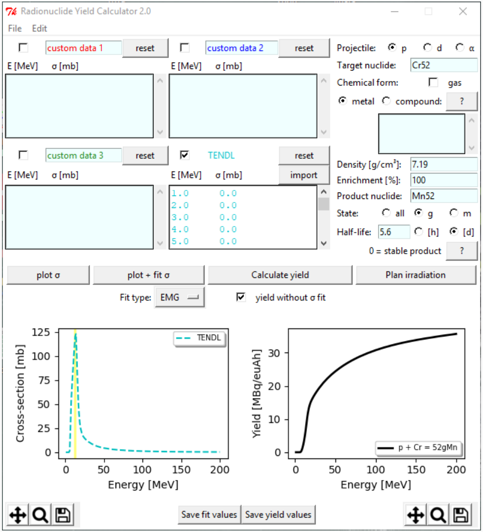
Talys results

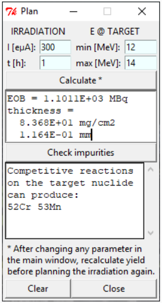
Talys irradiation results:

```
# Reaction: p +  52Cr Production of  52Mn Ground state
# Beam current:      0.30000 mA Energy range:   14.000 -->   12.000 MeV
# Irradiation time     :      0 years   0 days  1 hours  0 minutes  0 seconds
# Cooling time         :      0 years   0 days  0 hours  0 minutes  0 seconds
# Half life            :      0 years   5 days 14 hours 16 minutes 48 seconds
# Maximum production at:      0 years  59 days  6 hours 16 minutes 25 seconds
# Initial production rate:  2.24547E-10 [s^-1] Decay rate:  1.43388E-06 [s^-1]
# # time points =100
# Time [h] Activity [GBq] #isotopes [   ]  Yield [GBq/mAh]  Isotopic frac.
     0.1    1.10656E-01    7.71728E+13    3.68854E+00        0.26301
     0.2    2.21255E-01    1.54306E+14    3.68663E+00        0.26301
     0.3    3.31797E-01    2.31399E+14    3.68473E+00        0.26301
     0.4    4.42282E-01    3.08452E+14    3.68283E+00        0.26301
     0.5    5.52710E-01    3.85465E+14    3.68092E+00        0.26301
     0.6    6.63081E-01    4.62439E+14    3.67903E+00        0.26301
     0.7    7.73394E-01    5.39373E+14    3.67713E+00        0.26301
     0.8    8.83651E-01    6.16267E+14    3.67523E+00        0.26301
     0.9    9.93851E-01    6.93122E+14    3.67333E+00        0.26301
     1.0    1.10399E+00    7.69937E+14    3.67143E+00        0.26301
     1.1    1.10342E+00    7.69539E+14    0.00000E+00        0.26301
```

Other tools

Radioisotope Yield Calculator (RYC) (developed at ARRONAX)
https://www.arronax-nantes.fr/outil-telechargement/outils-radionuclide-yield-calculator/





Grazie per l' attenzione!

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