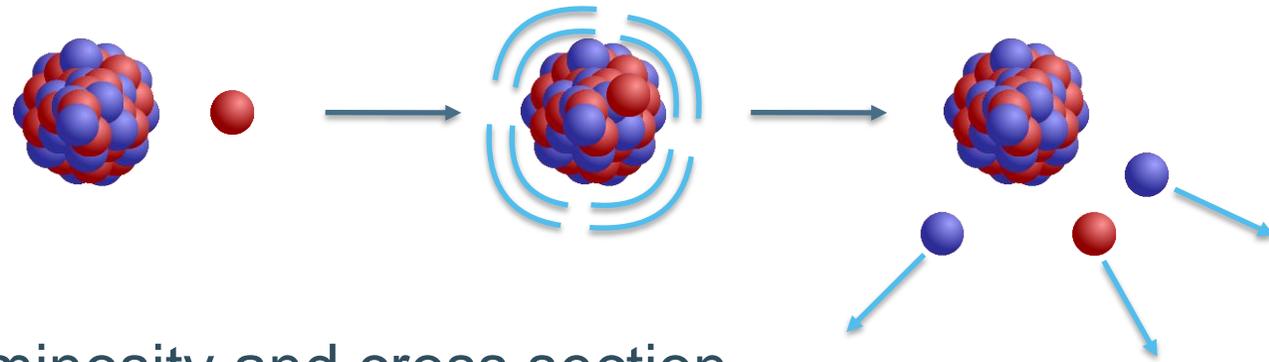


From research ...
... to patient care
—
Challenges and prospects

Chair Roger Van Geen
Lecture 5 – 29 November 2021



Quick recap 1

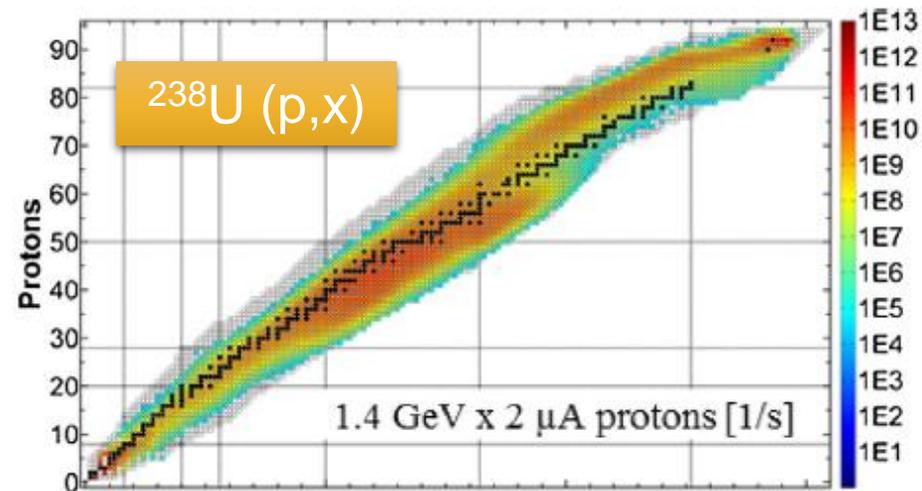


- Production is a question of luminosity and cross section

- It is thus a question of:

- Beam particle
- Beam intensity
- Beam energy
- Target material
- Target density

$$\frac{dn}{dt} = +L\sigma = +N_b \cdot d_t a_t \cdot \sigma$$

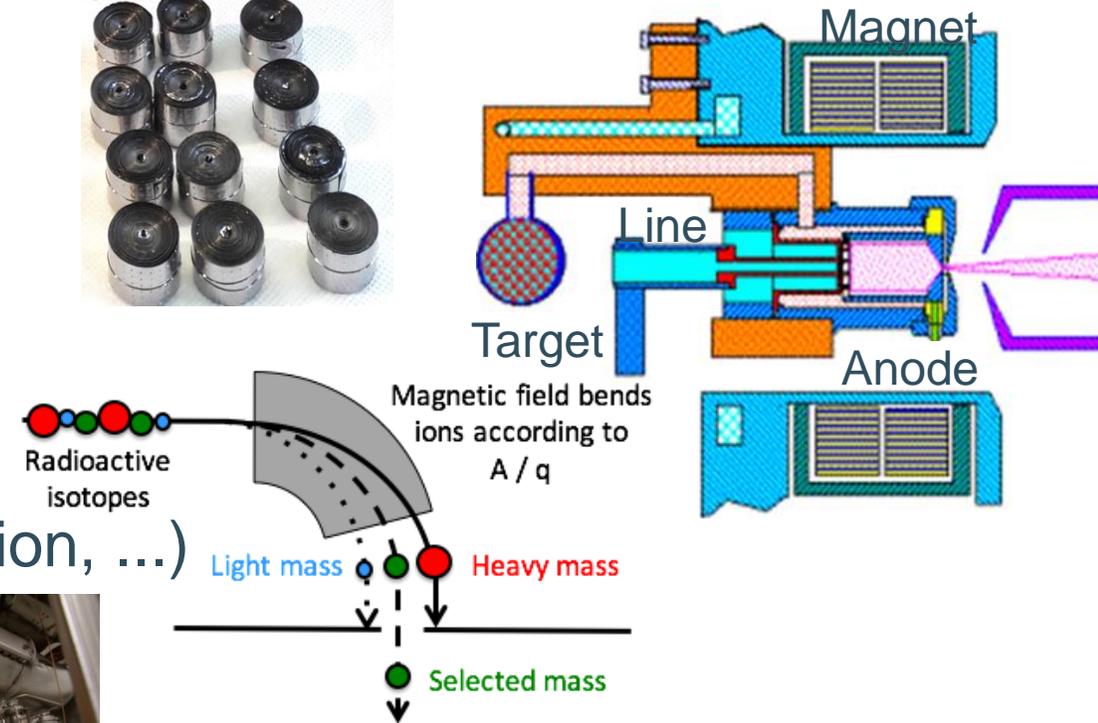


What about purity!?

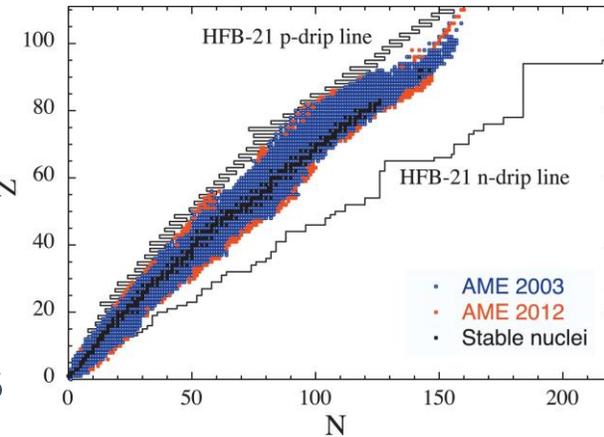
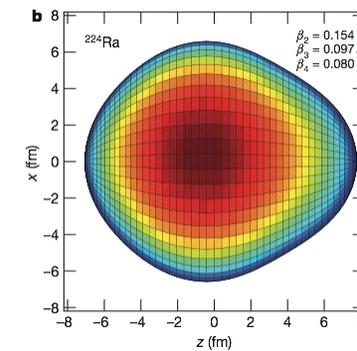
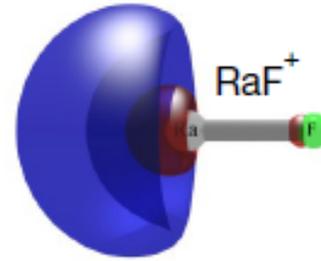


Quick recap 2: ISOL

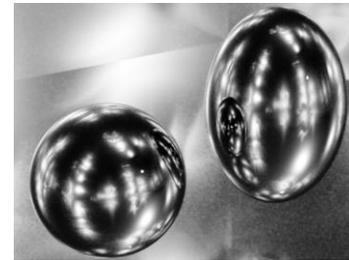
- The Isotope Separation OnLine technique is ideal to separate isotopes from each other and produce pure samples.
- The key aspects of the ISOL technique are:
 - The target material (density, porosity, ...)
 - The ion source (selectivity, efficiency, ...)
 - The separation (mass resolving power)
 - The manipulation (time structure, collection, ...)



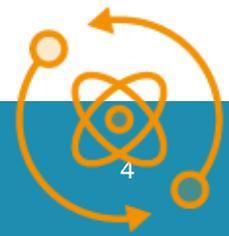
Quick recap 3



- Addressing fundamental research with radioactive ion beams
 - ❖ To answer questions of nuclear structure
 - ❖ To search for physics beyond the standard model
 - ❖ To explore the limits of existence (driplines, superheavy elements)



- Using all possible tools are our disposal
 - Ground-state properties investigated by atomic techniques
 - Looking at nuclear decays, exciting the nucleus or inducing reactions
 - Searching for symmetry violating effects



Quick recap 4

- Combining molecular imaging with targeted radiotherapy with just the swap of an isotope offers the possibility to provide personalized care to patients
- BUT most of the appropriate isotopes for this approach are not currently available on the market, yet radioactive ion beams can provide a viable option to support research and, hopefully, supply in the future
 - Tb is the most versatile element
 - There are other pairs that can be used, 2 by 2
 - There are options to use different elements with comparable chemistry, like ^{68}Ga for imaging or the pair ^{135}La - ^{225}Ac



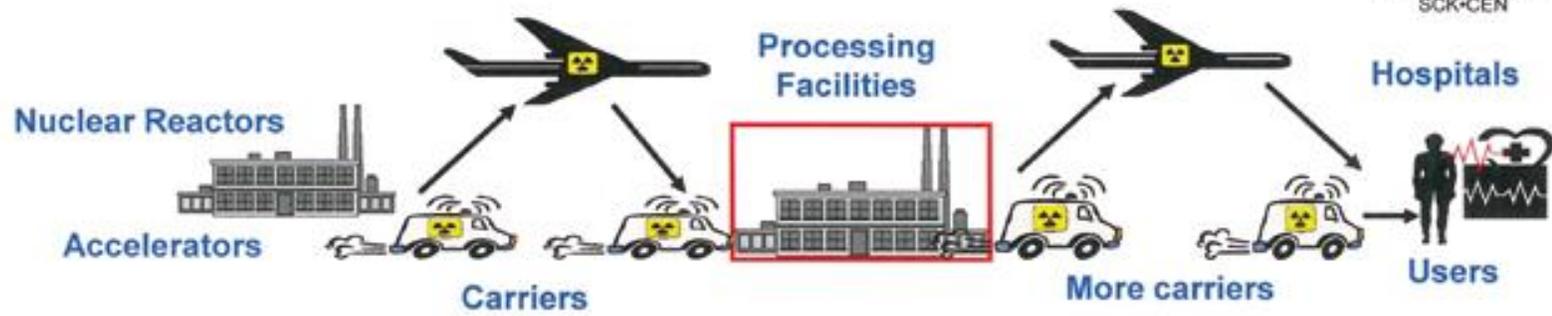
Outline for today

- Distribution of radioisotopes
 - ❖ How does that work?
 - ❖ What are the issues that we face?
- After the collection...
 - ❖ What the physicist does not much understand...
- Going clinical
 - ❖ What nuclear data are yet missing to use those isotopes

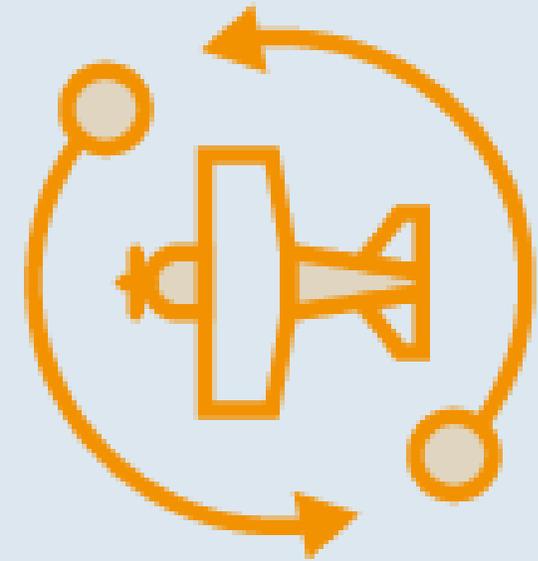


With many thanks from PRISMAP!!

From the producers to the users ... No time to lose ...



Radioisotope distribution



The best way to deliver radioisotopes is...

... by myself, in my pocket!

... by road.

... by plane.

... by boat.

... bicycle!

Delivering ^{155}Tb to UZ Leuven in 2019...



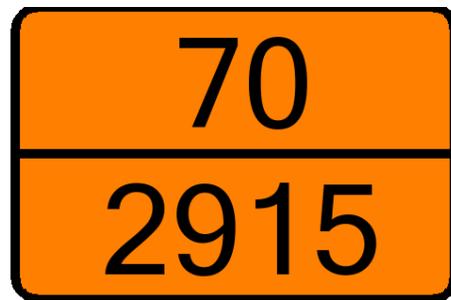
Shipping categories

How do we know which category to use?!



Dangerous good

- To transport high levels of radioactivity
- Requires a type-A container and proper signage



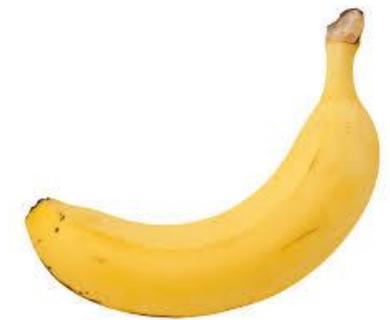
Excepted package

- For transporting small levels of radioactivity
- Requires a less remarkable sign and can be shipped more simply



Exempted

- The activity level is so small that it does not even require any sign at all – like a banana and its ^{40}K content



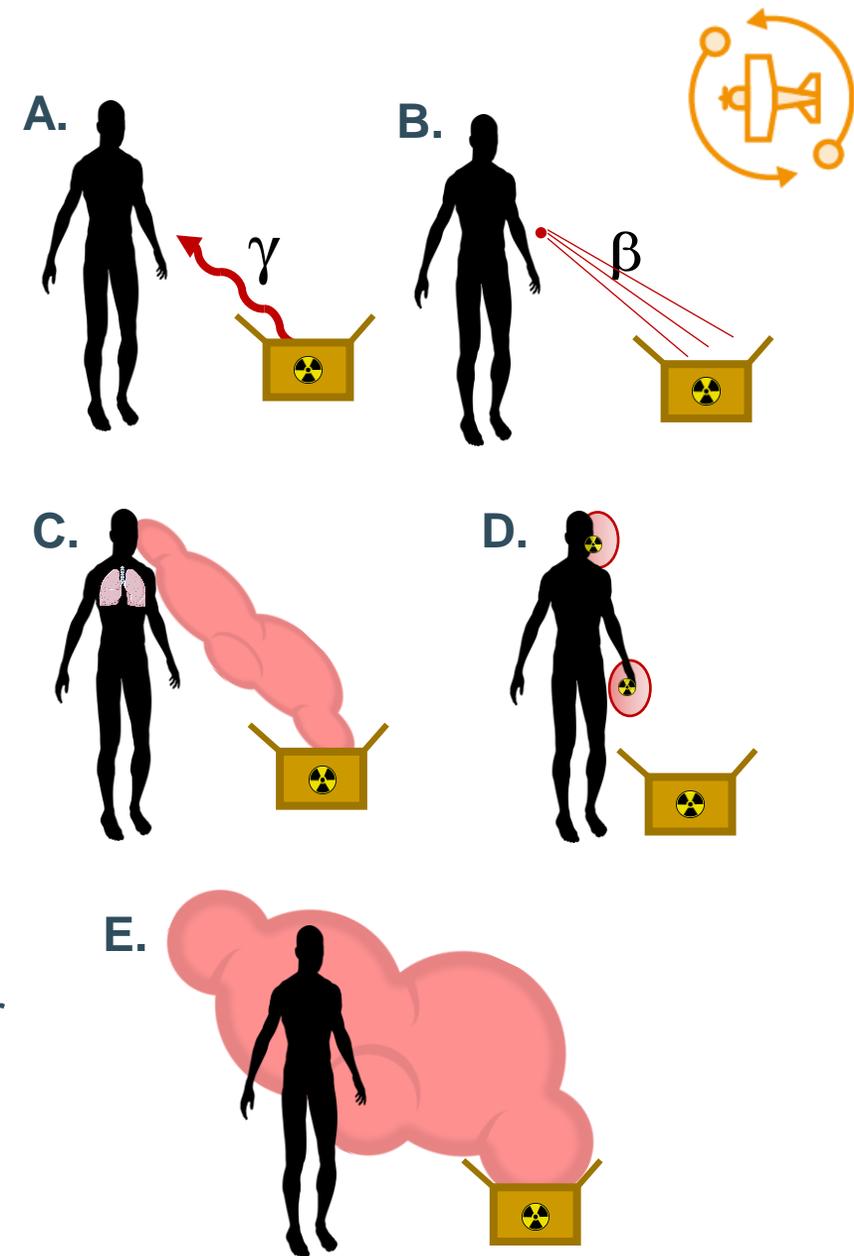
Transport regulations

- The UN Scientific Committee on the Effects of Atomic Radiations determines the scientific knowledge on the impact of radiation
- The International Commission on Radiological Protection issues recommendations based on the UNSCEAR findings
- The International Atomic Energy Agency suggests regulations based on the ICRP recommendations, which are then turned to national law
- The (European) Agreement concerning the transport of Dangerous goods by Road and the International Air Transport Associations specify those further for road and air transport



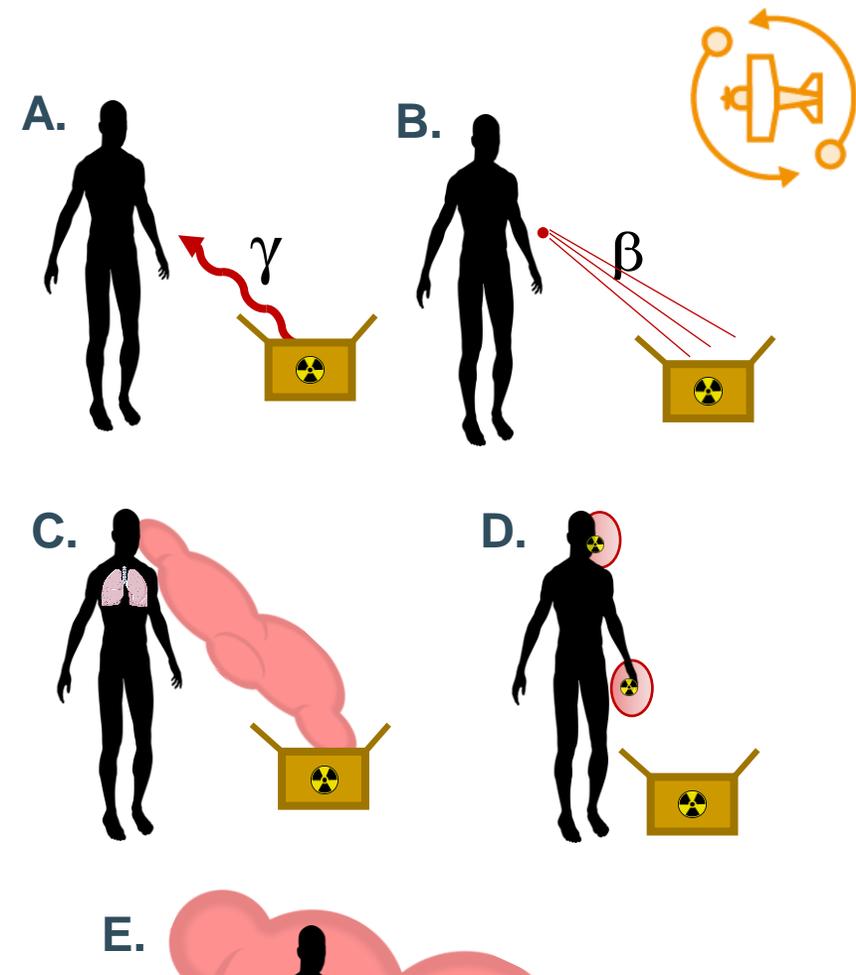
Incident scenarios

- A set of scenarios are described to determine the different risks that may occur during transport:
 - A. Exposure to γ rays that are no longer shielded
 - B. Exposure to β particles that are no longer contained
 - C. Inhalation of a volatile radioactive isotope
 - D. Skin contamination or ingestion
 - E. Submersion in a radioactive gas
- Based on those scenarios, limits are established that corresponds to an effective whole body dose rate of 100 mSv/hr under the assumption that the exposure is at most 30 minutes.
 - Those are tabulated as A_1/A_2 values



Incident scenarios

- The calculations are based on models which are full of strange assumptions and extrapolations, from a time of limited computing power in the XXth century
- Each isotope must be studied independently. In the absence of specific information from the IAEA, a blanket upper limit is placed, which is rather limiting



A_1 and A_2 values for isotopes that have not been studied yet.

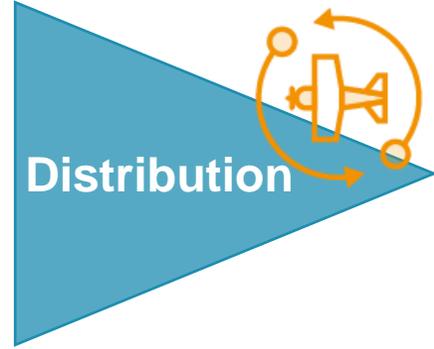
Radiation type	A_1 [TBq]	A_2 [TBq]
Gamma or beta	0.1	0.02
Alpha	0.2	9E-5
Neutron or unknown	0.001	9E-5

E.g.: ^{149}Tb is an α emitter and its default limit is **$A_2=90$ MBq**, though its α branching is not that large.

After proper estimates, the IAEA agreed to raise the value to **$A_2=800$ GBq**, nearly 10^4 times more!

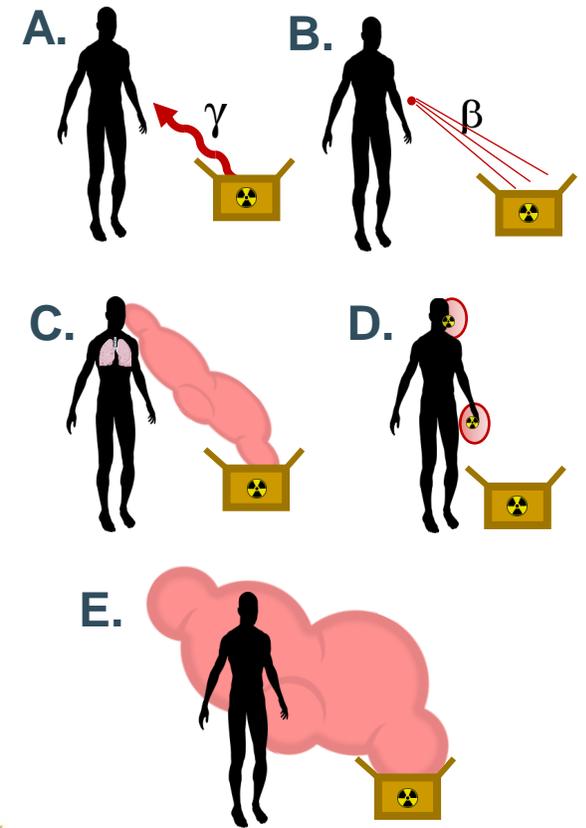
Tb-IRMA-V: Distribution

Recall from Lecture 4



- Limited international regulation on the transport of Tb radioisotopes
 - Basic regulations are very stringent and impractical for medical practice
 - New regulations from IAEA since 2019 on $^{149,161}\text{Tb}$
 - Calculations completed and to be submitted to the Federal Agency for Nuclear Control for $^{152,155}\text{Tb}$
 - All values appropriate for medical use

Isotope	IAEA	New A2
^{149}Tb	800 GBq	800 GBq
^{152}Tb	(20 GBq)	800 GBq
^{155}Tb	(20 GBq)	2 000 GBq
^{161}Tb	700 GBq	700 GBq



LEMER PAX

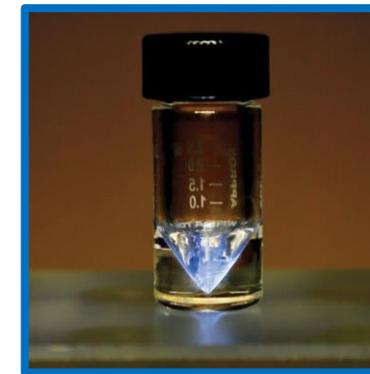
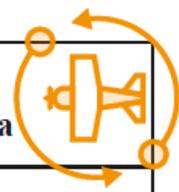
Tb-IRMA-V

We must systematically investigate whether updates are needed!

Excepted packaging

- Shipping a radioactive sample as excepted package instead of a full type-A shipping is a major advantage!
- The physical state of the sample matters a lot!
- Worthy to consider drying samples for transport, though recovery efficiencies have to be considered as part of the full process!

Physical state of contents (1)	Materials Package limits ^a (4)
<u>Solids</u> special form other form	$10^{-3} A_1$ $10^{-3} A_2$
<u>Liquids</u>	$10^{-4} A_2$
<u>Gases</u> tritium special form other forms	$2 \times 10^{-2} A_2$ $10^{-3} A_1$ $10^{-3} A_2$



When poll is active, respond at pollev.com/thomaseliasc687

Text **THOMASELIASC687** to **+32 460 20 00 56** once to join

Who decides whether a package comes on a plane?

The regulations are clear: UNSCEAR - ICRP -
IAEA - IATA

National regulations of the airport of
departure trump all other rules

National regulations from where the plane
is registered is what is most relevant.

O! Captain! My Captain! The pilot is an
almighty god on their vessel!

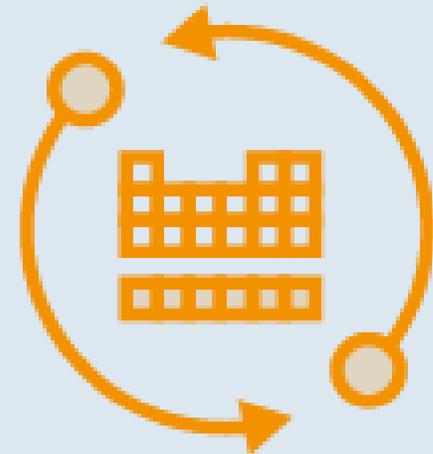
Air transport

- In Europe, air cargo carriers do not transport radioactive goods, though they do in North America.
 - Lobby is required to change this
- Many pilots do not know the nature of the risks (or lack thereof) with radioactive material and very often refuse boarding.
- Small private planes / clubs might be the easiest alternative for mid-distance air travel.



BREAK

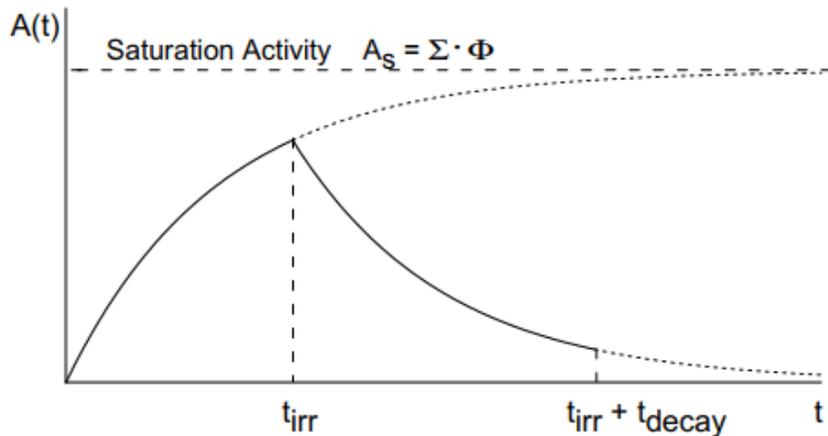
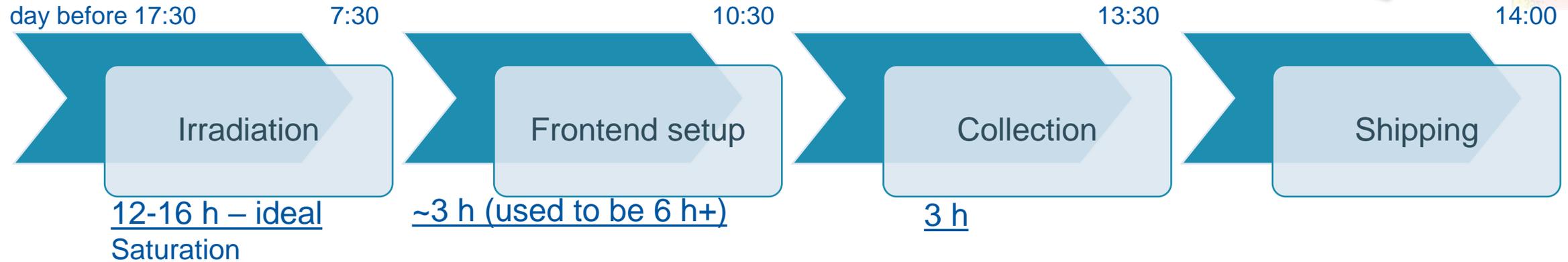
What comes after the collection



Producing ^{149}Tb : racing the half-life

Recall from
Lecture 4

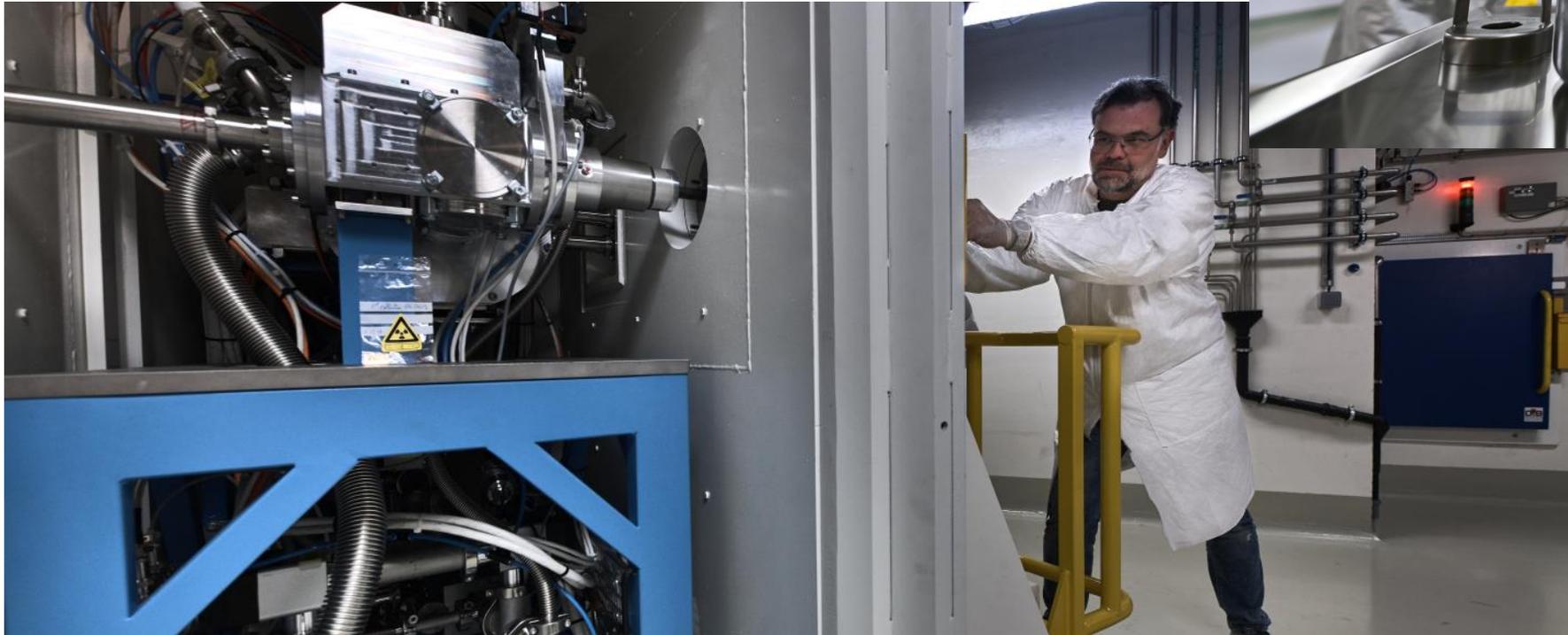
Tb 149
4.1 h
 ϵ
 α 3.97
 β^+ 1.8...
 γ 352;
165...
102



- Setup includes vacuum pumping (30 min), water cooling for HV operation (15 min), target heating (90 min) and beam optimization (before final temperature) (60 min).
- Between collection and shipping, minimum quality controls are necessary: decay spectroscopy, packaging, loading.

Retrieving the sample

Manipulation in a radiation area



Radioprotection

Qualification for shipping

CERN - Import/Export of Radioactive Goods (Class 7)

English Home Institute list Register a new Institute Importation request

Approved Institutes for Importation/Exportation of Radioactive Material

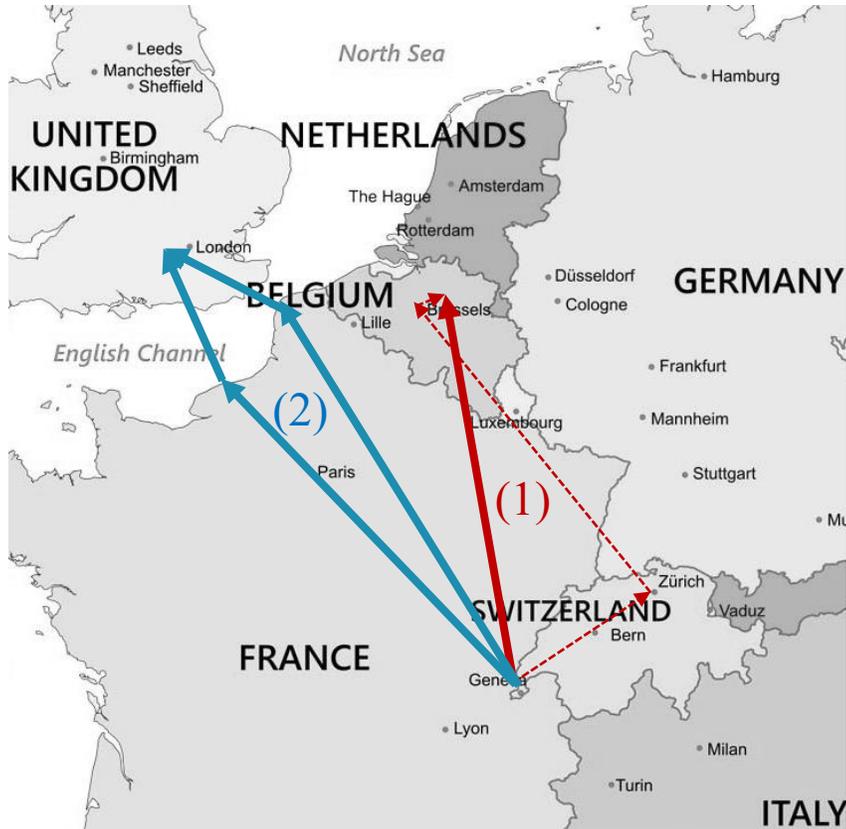
Institute list						Country
Institute ID	Country	City	Name	Institute status	Certificate status	
119	BELGIUM	Elsene	Vrije Universiteit Brussel	Inactive	Cancelled	
222	BELGIUM	Geel	IRMM	Active	To be renewed	
505	BELGIUM	Gent	Ghent University	Active	To be renewed	
200	BELGIUM	Heverlee	KU Leuven	Active	Valid	
514	BELGIUM	Leuven	KU Leuven - Radiofarmaceutisch Onderzoek	Active	Valid	
3	BELGIUM	Louvain-la-neuve	Centre de Recherches du Cyclotron	Active	To be renewed	
465	BELGIUM	Mol	SCK-CEN	Active	Valid	



Activity measurement

Necessary paperwork

Transport



(1) **Geneva to Leuven:** by road → delivery in about 12 hours

BUT transporter decided to go via plane!
GVA – Zurich; Zurich-Brussels; Brussels-Leuven.

Flight cancelled/delayed in Zurich

Delay of 2 days and a half ! More delay avoided with transporter accepting to exceptionally deliver on Saturday + 1 person at Leuven available to receive the package on Saturday

(2) **Geneva to London**

Possible by taking the boat in Ouistreham
BUT only one boat in the evening

→ If delay on the road, package delivery delayed by 24 h

Decision to go via the Tunnel *La Manche* → one train every 1h
WARNING special tunnel license needed. To be anticipated by the transporter

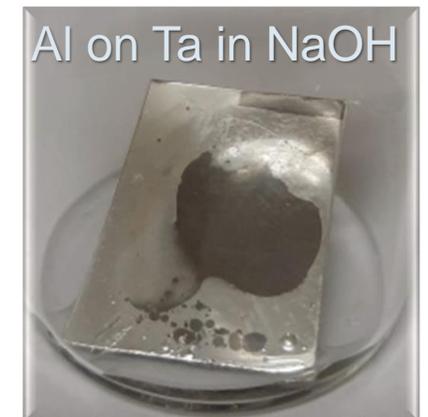
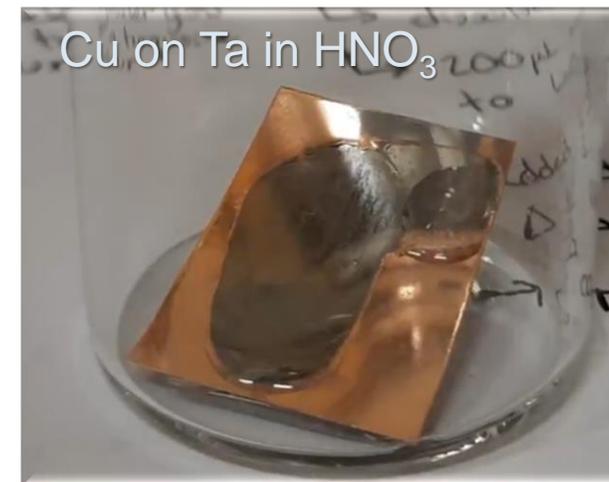
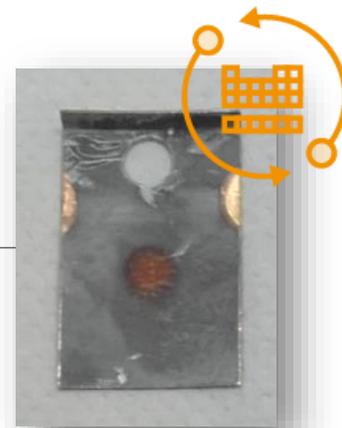
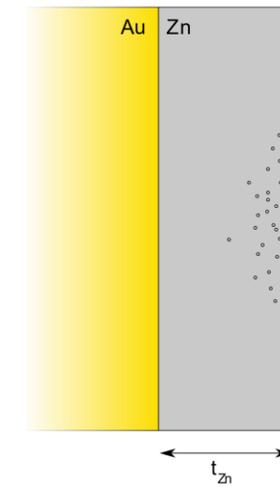
➤ **To be taken into account for Road Transports in Europe:**

Among all European transporters contacted, no transporter driving over week-ends : stop on Friday evening and re-start Sunday night + additional fee for package storage over the week-end.

European transporters can't pick up a package in CH and deliver it in CH (« *cabotage* » rule - not allowed). But can pick a package in CH and deliver in Europe (& vice-versa) with a special authorization delivered by the Swiss Authorities (OFSP).

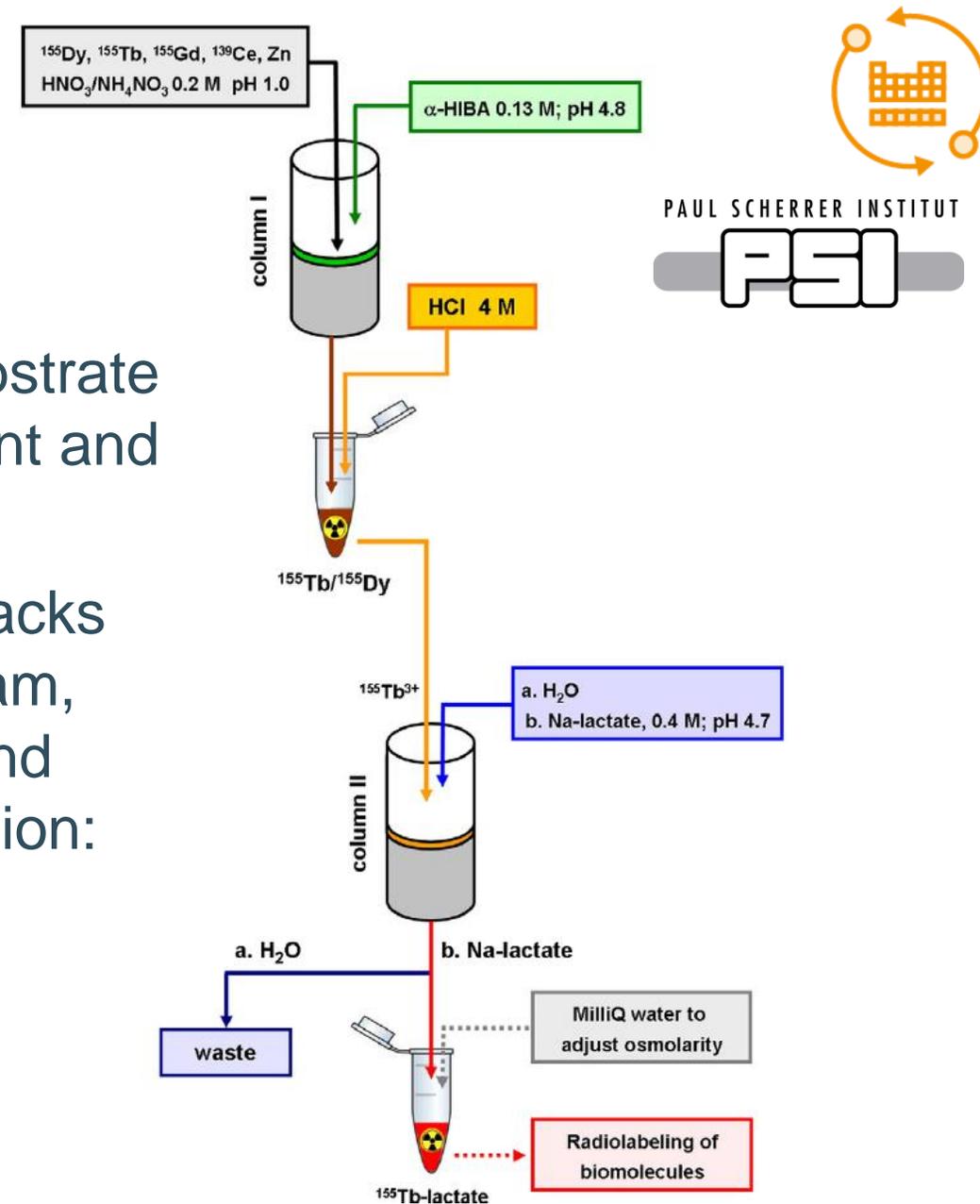
Radiochemistry

- A MEDICIS collection is made onto a soft metal coating on a gold or tantalum foil, e.g. Al, Cu, Zn, ... or on a salt sample.
- TRIUMF performs its collections on salts only.
- The sample must first be dissolved – in acid or water – to recover the radioisotopes.
- However, the excess material has to be removed prior to processing.



More radiochemistry

- Separating the collected isotopes from the substrate can be foreseen in the design of the experiment and should thus be well under control.
- HOWEVER the ISOL technique has its drawbacks and though we would hope to have a pure beam, compromises must be made between purity and efficiency that may lead to isobaric contamination:
 - ^{155}Tb is mixed with ^{155}Dy and $^{139}\text{Ce}^{16}\text{O}$
 - ^{225}Ac is mixed with ^{225}Fr and ^{225}Ra
- Some separations are easier than others!

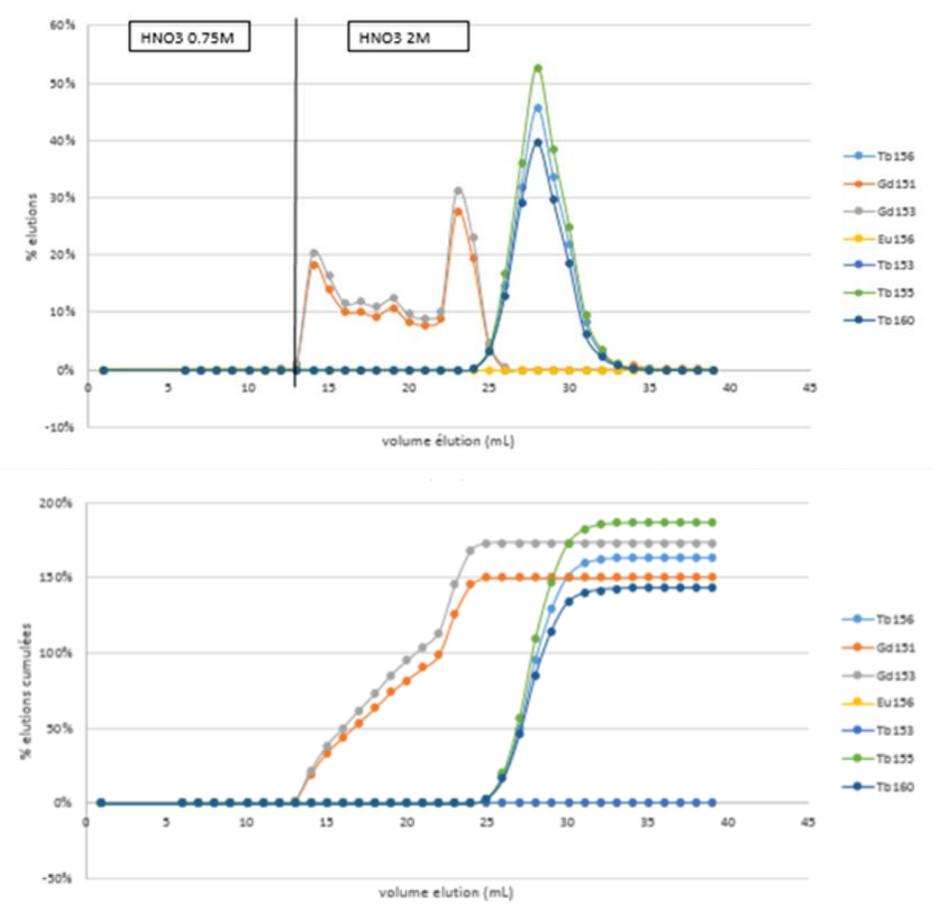


PRE-radiochemistry

90% suppression
of Gd per pass



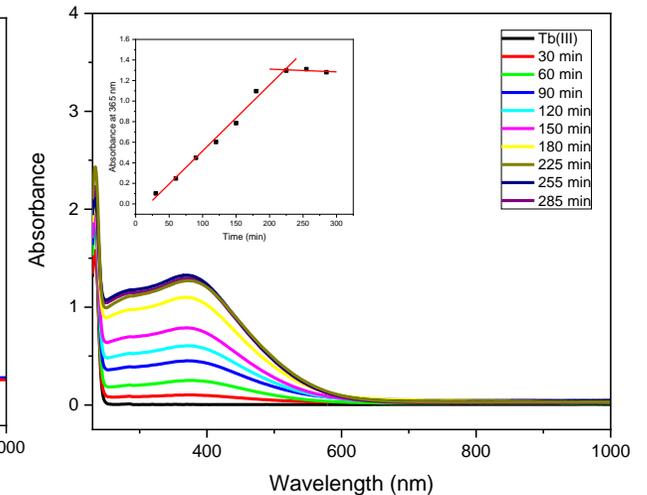
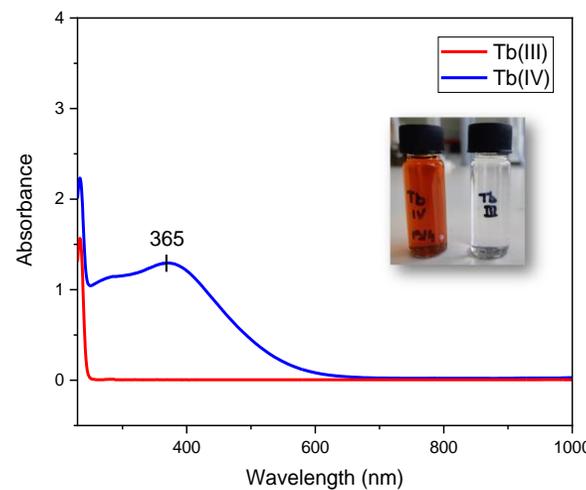
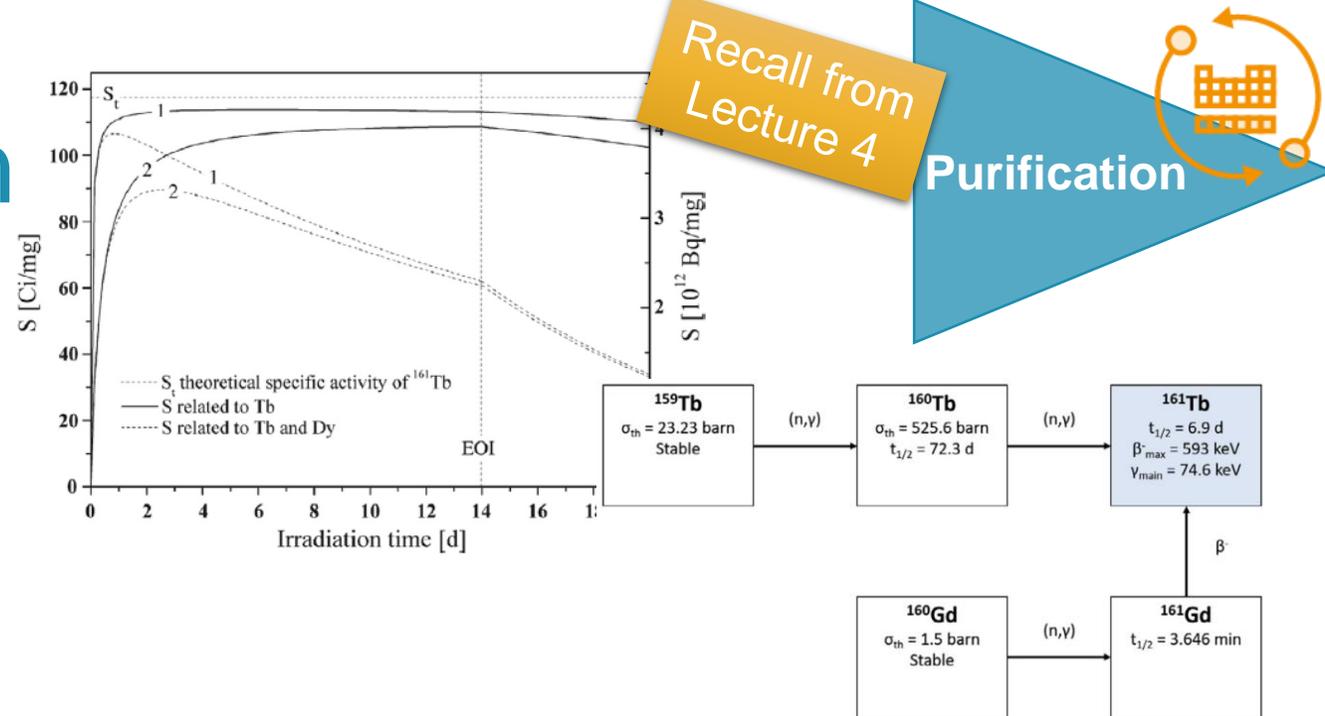
- During LS2, MEDICIS maintained the production of ^{155}Tb thanks to imported samples
 - $^{\text{nat}}\text{Gd}(d,nx)^{155}\text{Tb}$ irradiations were performed at the ARRONAX cyclotron in Nantes.
 - The produced samples contained all possible Tb isotopes, thus requiring the mass separation.
 - The Tb:Gd ratio was $1:10^6$ and completely choked the ion source!
 - The original ionization scheme was actually enhancing the Gd as well as the Tb!!
- A 4-pass column radiochemistry had to be employed to reach Tb:Gd ratios of 1:100 that were useable for MEDICIS.



It is a very wasteful process resulting in substantial chemical/radiological waste!

Tb-IRMA-V: Purification

- Concentrating on the Tb/Gd separation
 - ▶ ^{161}Tb production in the BR2 reactor at SCK, already delivering radioisotopes
 - ▶ Working on oxidizing Tb(III) to Tb(IV) to go beyond the existing state-of-the-art with α -HIBA

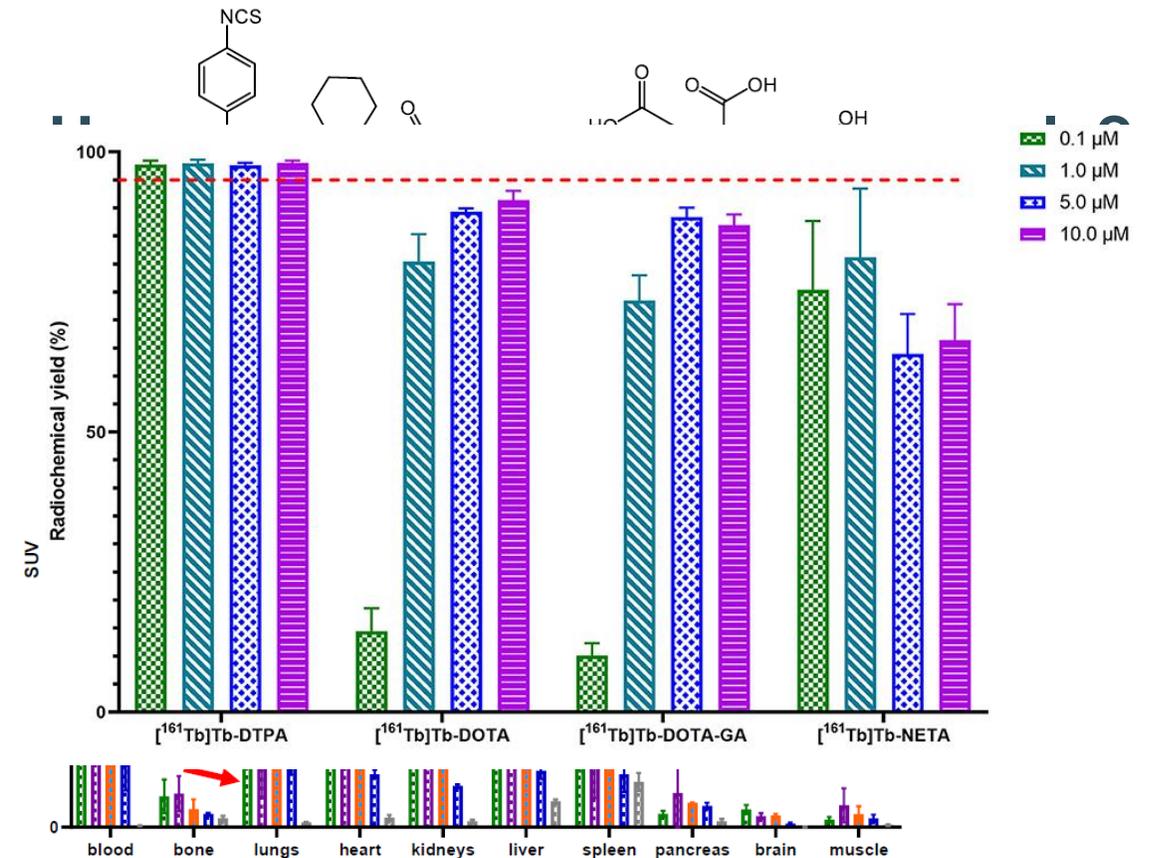
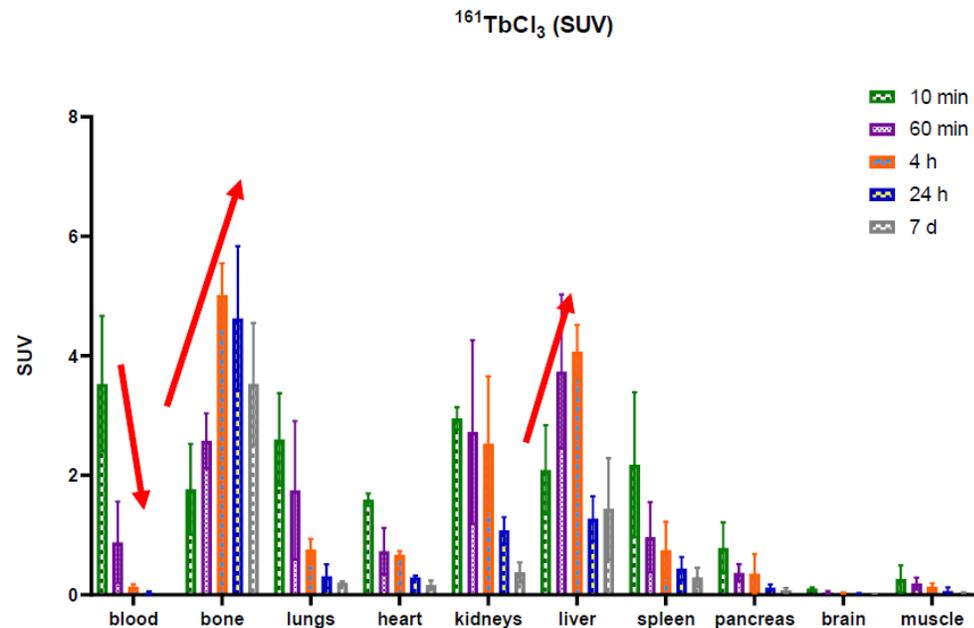


Tb-IRMA-V



From a free radionuclide to a radiopharmaceutical

Where does a free radionuclide go?



Tb-IRMA-V

Licensing



- Working with a new radioisotope is not as trivial as receiving it happily from CERN...
- Each new isotope has to be licensed by the appointed authority – in Belgium, the Federal Agency for Nuclear Control, FANC, is in charge of such licensing.
- Some research institutes have broad licenses that allow them to work with anything, anytime, within limited activities – like IKS.
- Others require specific licenses, especially for large activities, such as the Laboratory for Radiopharmaceuticals Research in Gasthuisberg.
- Each country has different requirements for licensing!



Requirements for adding novel isotopes to handling permits

Radionuclide	Dose rates [Otto2016; doi: 10.1093/rpd/ncu316]				Frosio 2019		ICRP 119 (JAERI 2002-013)		CH	CH	Airborne	
	$H_p(10), 100\text{cm}$ (γ dose rate) $\mu\text{Sv h}^{-1} \text{GBq}^{-1}$	$H_p(3)_{\text{slab}}, 100\text{cm}$ (γ dose rate) $\mu\text{Sv h}^{-1} \text{GBq}^{-1}$	$H_p(0.07)_{\text{slab}}, 10\text{cm}$ (γ dose rate) $\text{mSv h}^{-1} \text{GBq}^{-1}$	$H_p(0.07)_{\text{slab}}, 10\text{cm}$ ($\beta+\gamma$ dose rate unshielded) $\text{mSv h}^{-1} \text{GBq}^{-1}$	$h_c(0.07)$ skin contamination $\text{mSv h}^{-1} / (\text{kBq cm}^{-2})$	inhalation $e_{\text{inh}} (5 \mu\text{m})$ Sv/Bq	ingestion e_{ing} Sv/Bq	LL Bq	LA Bq	Bq m^{-3}		
Sc-44	336	330	7.8	1237	1.7	3.0E-10	3.5E-10	10	2E+7	3E+4	1E+5	
Sc-47	20	19	1.9	1356	1.3	7.3E-10	5.4E-10	100	7E+6	1E+4		
Cu-64	31	31	1.1	876	0.8	1.5E-10	1.2E-10	100	3E+7	6E+4		
Cu-67	21	21	2.0	1194	1.4	5.8E-10	3.4E-10	100	9E+6	1E+4	1E+6	
Ag-111	5	5	0.3	1443	1.6	1.6E-9	1.3E-9	100	3E+6	5E+3	1E+6	
La-135	19	20	2.4	1.8	<0.1	2.5E-11	2.0E-11	1000	2E+8	3E+5	1E+7	
Sm-153	19	19	2.4	1.8	<0.1	2.5E-11	2.0E-11	1000	2E+8	3E+5	1E+6	
Tb-149	213	213	2.4	1.8	<0.1	2.5E-11	2.0E-11	1000	2E+8	3E+3	1E+6	
Tb-152	229	229	2.4	1.8	<0.1	2.5E-11	2.0E-11	1000	2E+8	3E+3	1E+6	
Tb-155	44	43	4.0	114	0.2	2.5E-10	2.1E-10	100	2E+7	3E+4	1E+7	
Tb-161	15	16	1.6	1270	1.3	1.2E-9	7.2E-10	1000	4E+6	7E+3	1E+6	
Er-165	13	12	1.2	1.2	<0.1	1.4E-11	1.9E-11	1000	4E+8	6E+5	1E+7	
Er-169	0	0	0.0	844	1	9.2E-10	3.7E-10	1000	5E+6	9E+3	1E+7	
Yb-175	7	7	0.4	1073	1.1	7.0E-10	4.4E-10	100	7E+6	1E+4	1E+7	
At-211	11	19	3.1	3.5	<0.1	1.1E-7	1.1E-8	1000	5E+4	8E+1	1E+7	
Ac-225 or Bi-213 gen.	41	51	4.4	2952	0.1	6.5E-6	2.4E-8	10	8E+2	1E+0	1E+4	
F-18	169	169	5.8	1676	1.7	9.3E-11	4.9E-11	10	7E+7	7E+4	1E+6	
Ga-68	161	161	5.4	1031	1.5	8.1E-11	1.0E-10	10	6E+7	1E+5	1E+5	
I-131	67	68	3.4	1383	1.4	1.1E-8	2.2E-8	10	5E+5	8E+2	1E+6	
Lu-177	7	7	0.6	1099	1.3	1.1E-9	5.3E-10	100	5E+6	8E+3	1E+7	

And what about other countries

??

Going clinical!

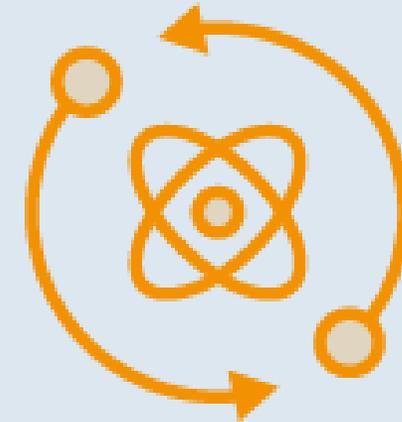
- Say you can produce the radioisotope you want...
- Say you can purify it to your degree of satisfaction...
- Say you can deliver it and receive it...
- Say you can radiolabel your favorite molecule with it...
- Say it works well in vitro and in vivo in mice models...
- NOW you wish to go clinical with it. The fun can finally start...
- But you need first the approval of the Federal Agency for Medicine & Medical Products – FAGG
- This approval is evaluated in the form of an Investigative Medicinal Product Dossier...

BREAK

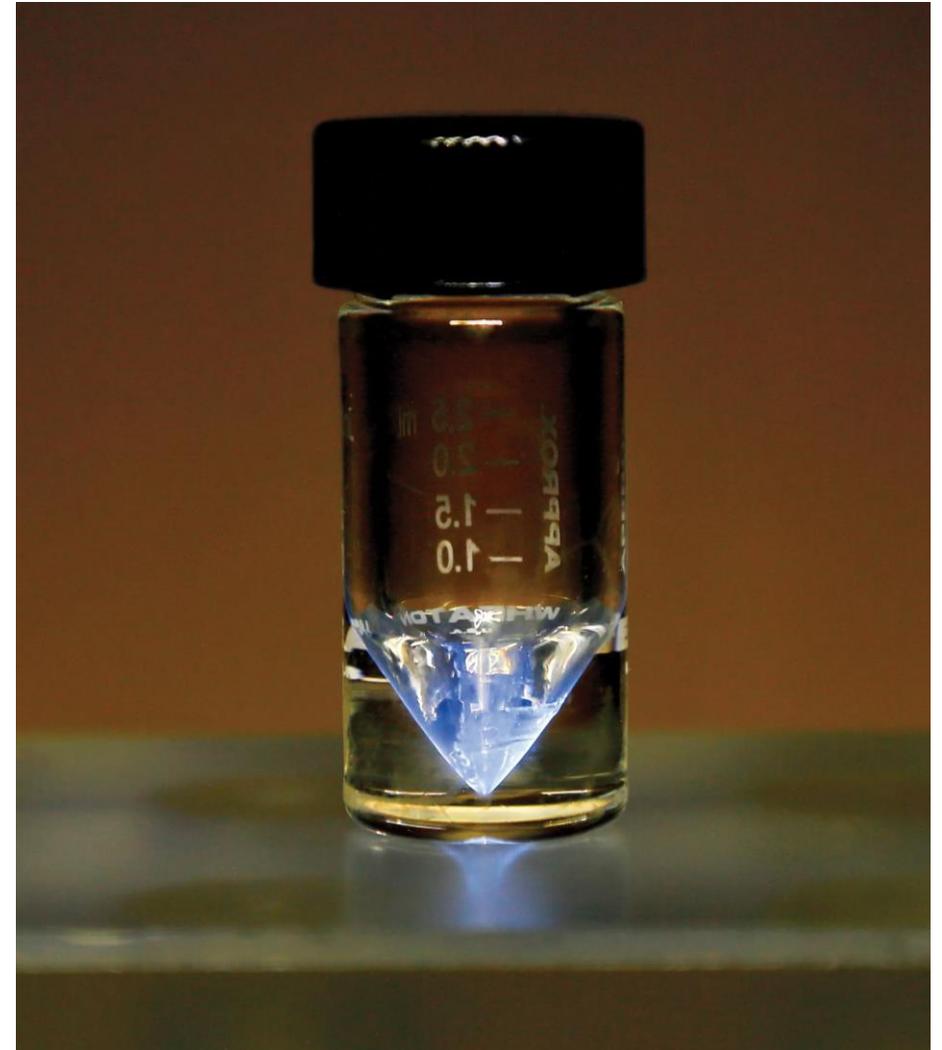
Nuclear data for nuclear medicine

Taking ^{225}Ac as example:

- *Production (cross sections, ionization, ...)*
- *Half-life*
- *Radiation & branching ratios*



^{225}Ac production

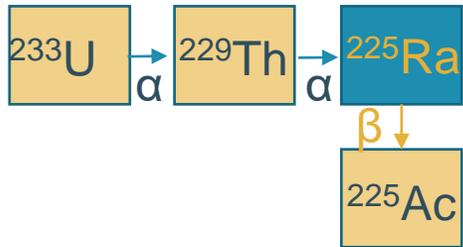




Where does ^{225}Ac come from?



 ^{229}Th Generator
-70Gbpq/a as of 2020



10 MBq per patient-dose
→ 700 doses per year

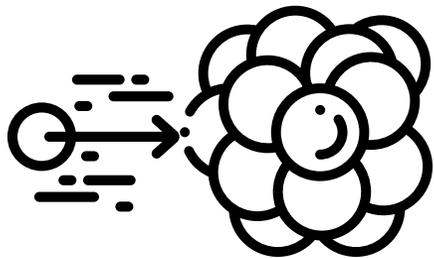
! Potential demand for
100 000 patients...



Alternative sustainable routes to produce ^{225}Ac

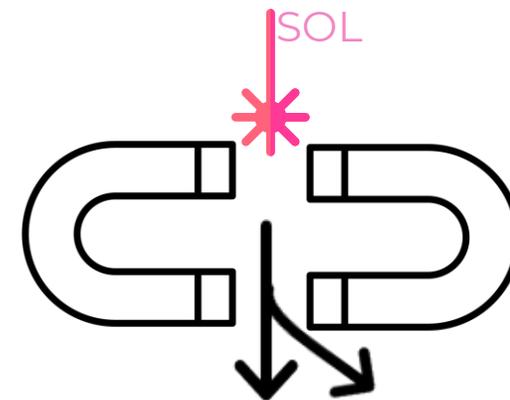
From ^{226}Ra

- $^{226}\text{Ra}(p,2n)^{225}\text{Ac}$
- $^{226}\text{Ra}(\gamma,n)^{225}\text{Ra} \rightarrow ^{225}\text{Ac}$
- Challenge with radioactive target
- Waste management issues: ^{222}Rn



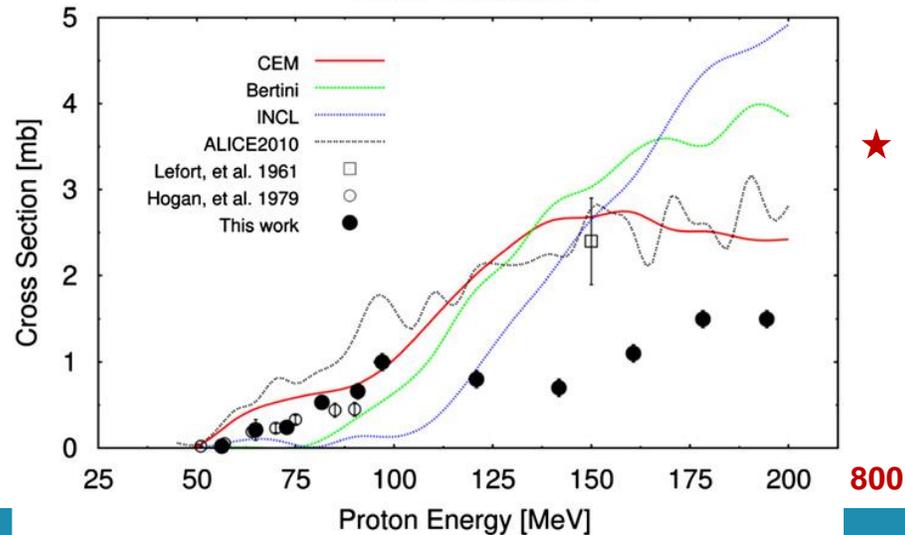
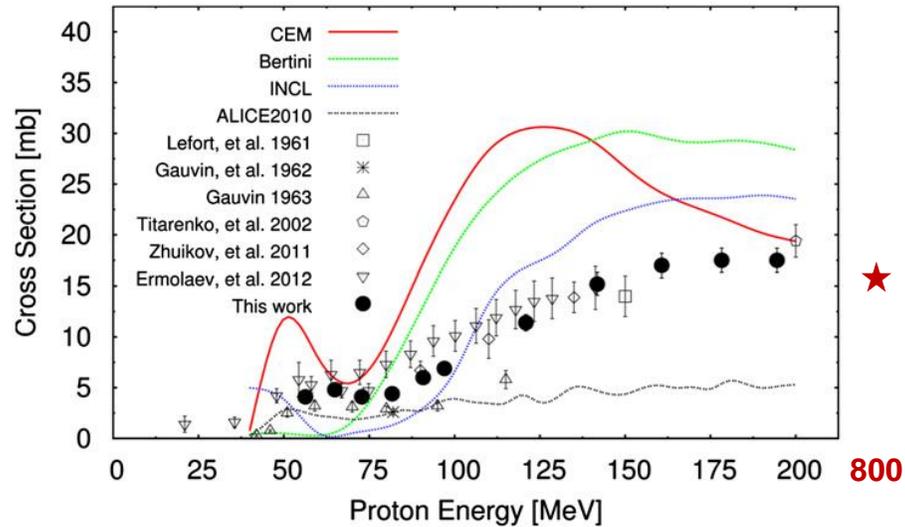
From ^{232}Th

- $^{232}\text{Th}(p,xpyn)^{225}\text{Ra}/\text{Ac}$
- Requires high-energy driver
- Co-production of many impurities and in particular ^{227}Ac





$^{232}\text{Th}(p, xpyn)$ The same applies to the ^{226}Ra -based production routes!



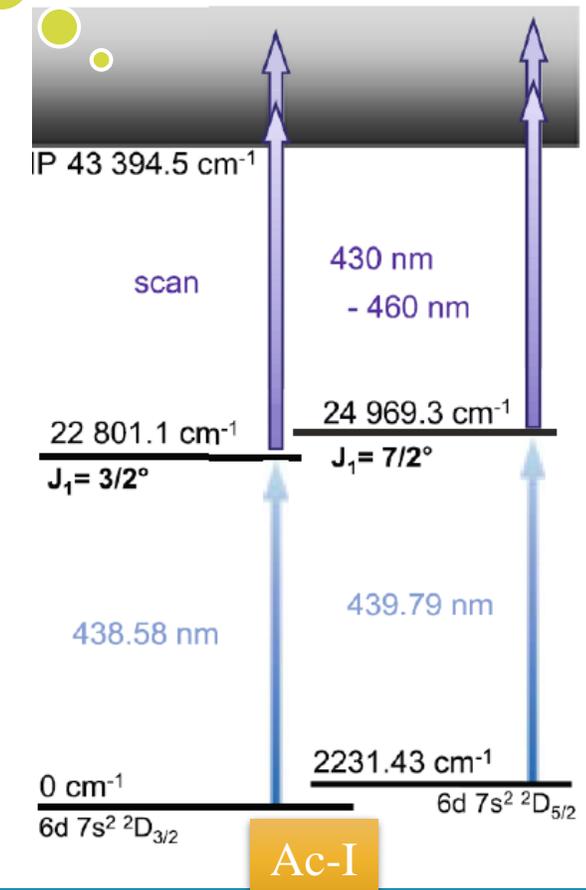
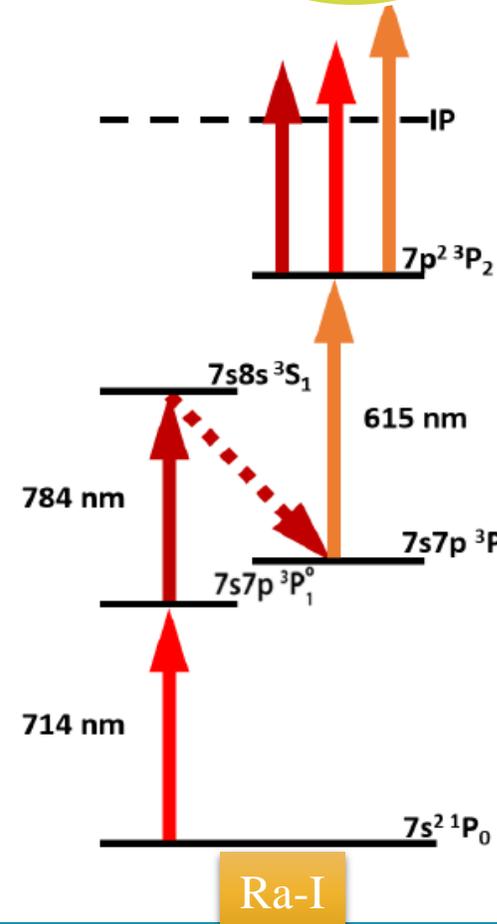
- Thorium is very abundant and could be a very practical starting material to produce ^{225}Ac .
- The production of $A=225$ isotopes requires the emission of 8 particles
 - Coulomb + 8 particles emitted ~ 85 MeV threshold
 - Mixture of $^{225}\text{Ac}/^{225}\text{Ra}$
 - Guaranteed co-production of ^{227}Ac and ^{226}Ra
- Cross section data are sparse and require further investigations

ISOLDE-produced ^{225}Ac

We have demonstrated 1% Ac extraction efficiency from UC_x , with no measurable trace of ^{227}Ac .



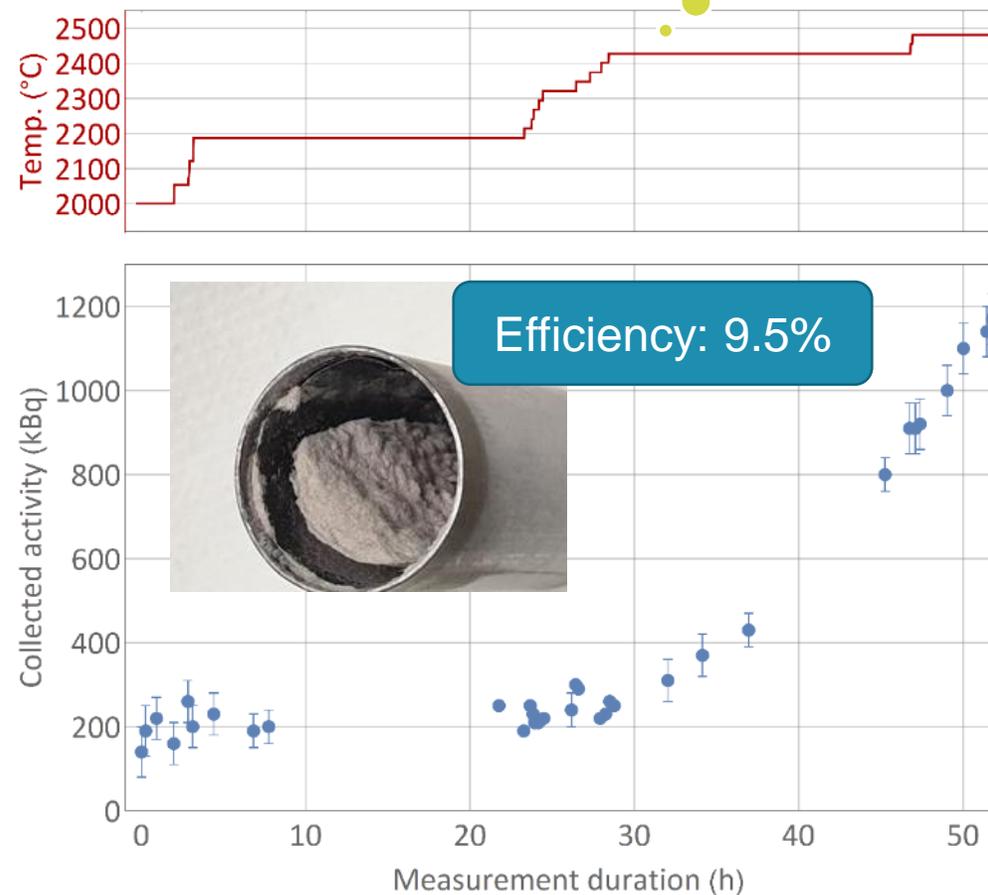
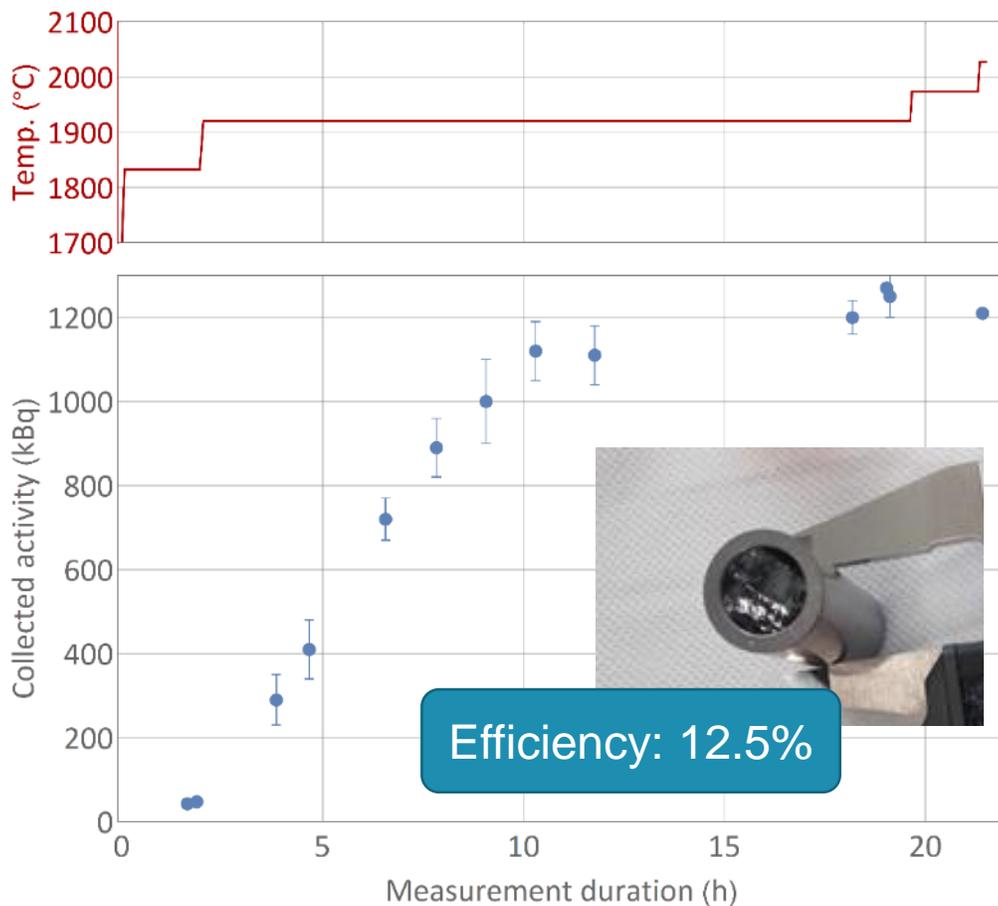
- At ISOLDE, the typical target material is $^{238}\text{UC}_x$ with 1.4 GeV protons.
- ^{225}Fr (alkali metal) is very easily extracted online and ionized.
- ^{225}Ra (alkali earth) is also well extracted and its ionization can be enhanced with lasers (x4).
- ^{225}Ac (actinide) is harder to separate from the target matrix but has the highest production cross section.



MED024: ^{225}Ac extraction at MEDICIS

Required 500° more from ThO_2 than it did from Re!

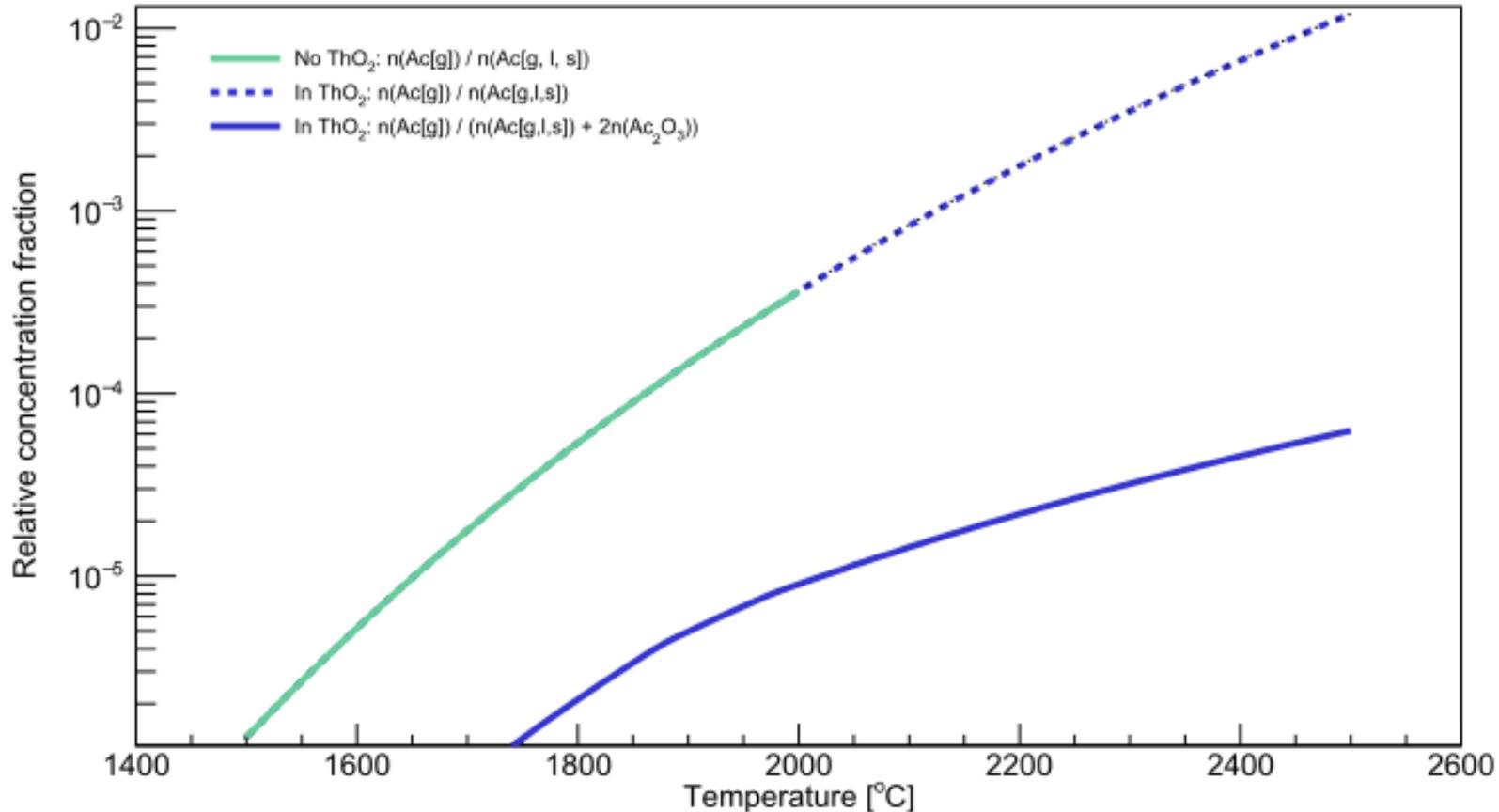
$$\epsilon = \epsilon_{diff} \epsilon_{eff} \epsilon_{ion} \epsilon_{sep} \epsilon_{trans}$$





MED024 run 2: Heat to Replete

So Why did we need that high T in run 2?

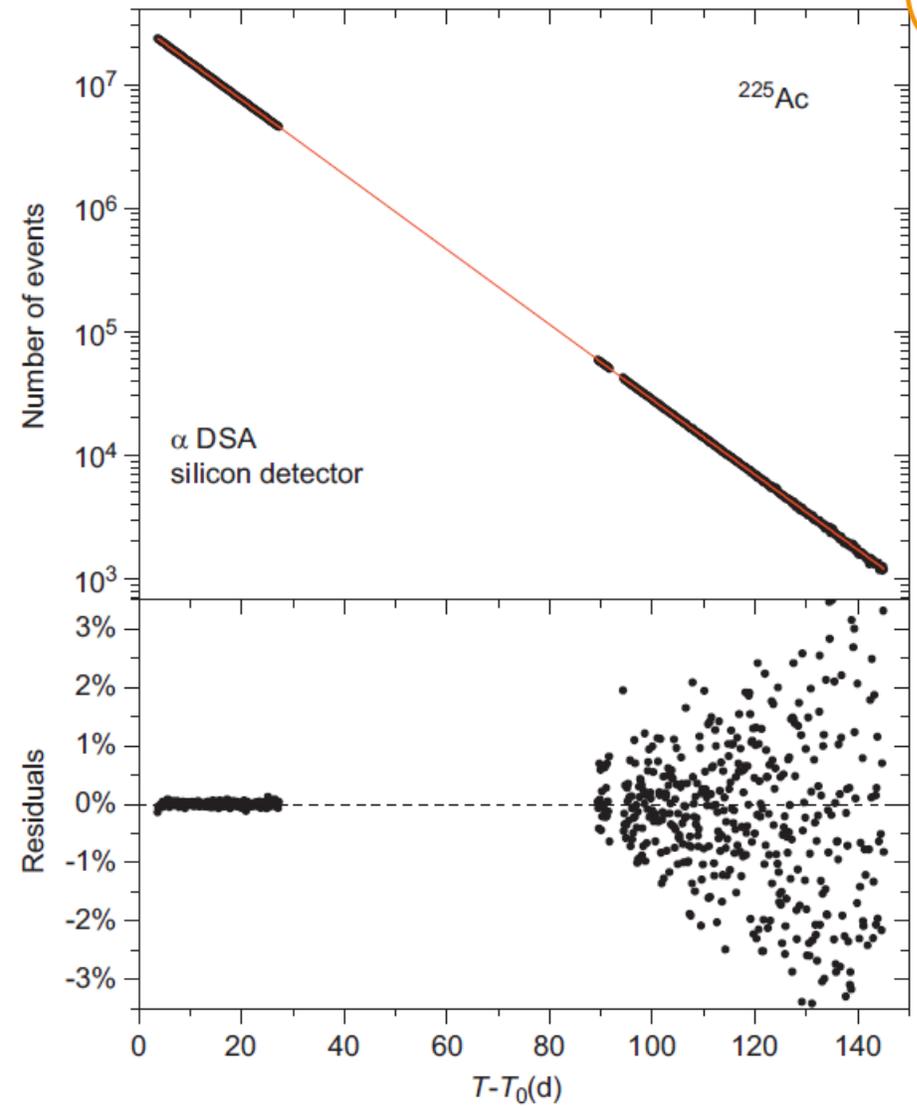


HSC chemical equilibrium simulation

- Almost all Ac is 'locked-up' in Ac_2O_3 .
- The relative concentration of $\text{Ac}(\text{g})$ to $\text{Ac}(\text{g}, \text{l}, \text{s})$ remains the same
- A much higher temperature for equivalent Ac concentration in run 2 compared to run 1

^{225}Ac half-life

10 days, sort of...





What we thought we knew

- Until recently, the best value for the half-life of ^{225}Ac came from a 1950 investigation of the decay chain of ^{233}U .
- This half-life was not assigned any uncertainty and was not revisited by any facility since then.
- The half-life enters into consideration for transport loss estimates, biodistribution and dosimetry...

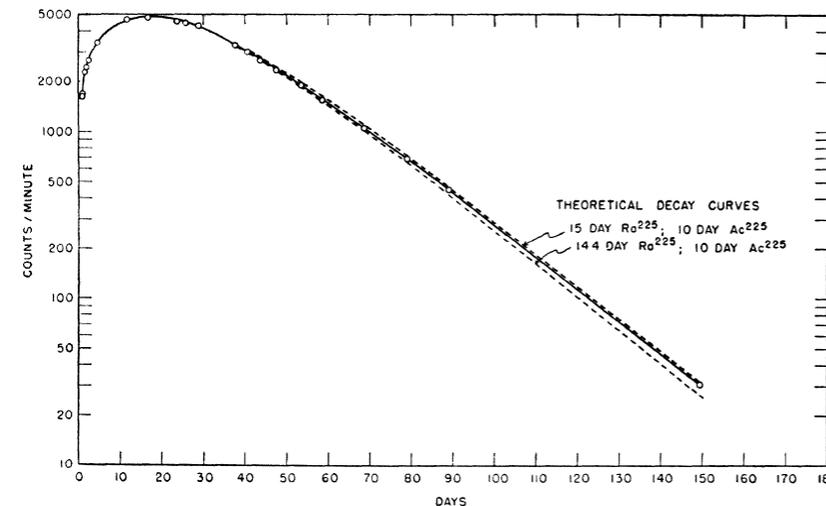
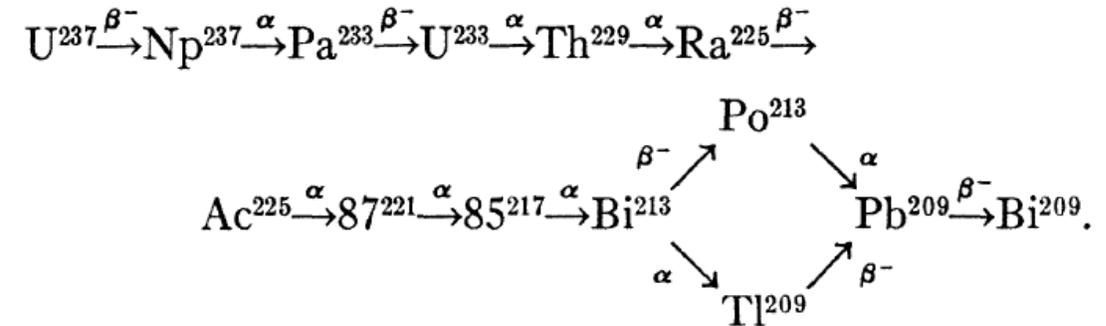


FIG. 3. Growth and decay of alpha-activity from Ra^{225} preparation. Theoretical decay curves calculated on the basis of 10-day Ac^{225} and 15-day and 14.8-day Ra^{225} are shown by the broken lines.

^{225}Ac revisited

- It took >60 years to investigate this again, starting with a ^{225}Ac sample
- Multiple techniques were used, making use of both α particles and γ rays
- Consistency was found between the techniques and high-accuracy metrology approaches were used to determine the final half-life

$$T_{1/2} = 9.920(3) \text{ days}$$

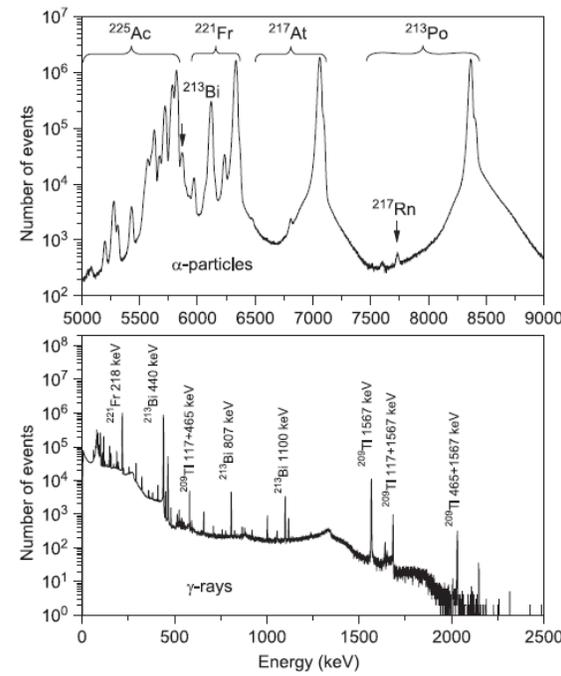
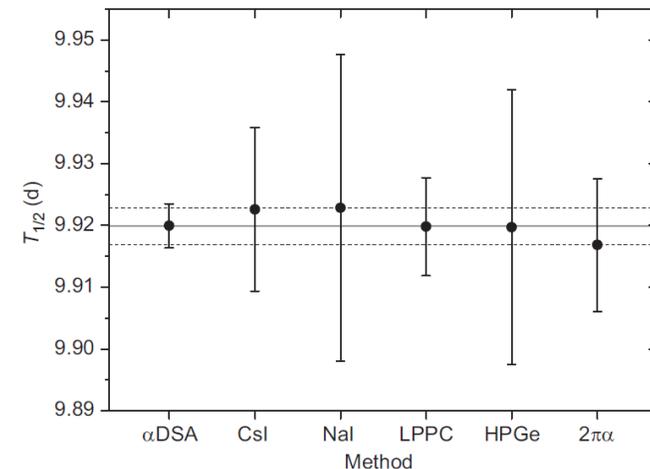
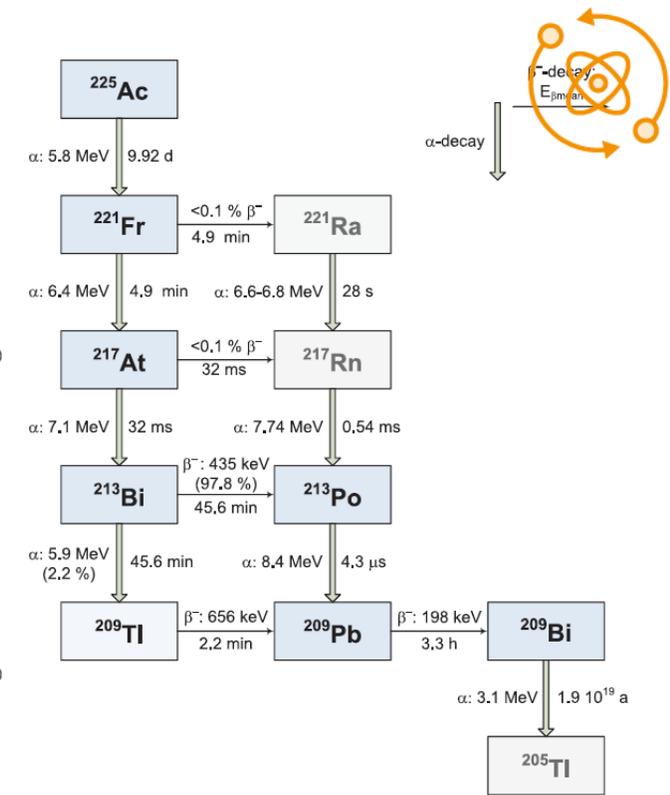


Fig. 2. Alpha-particle (top) and γ -ray spectrum (bottom) of the ^{225}Ac material.



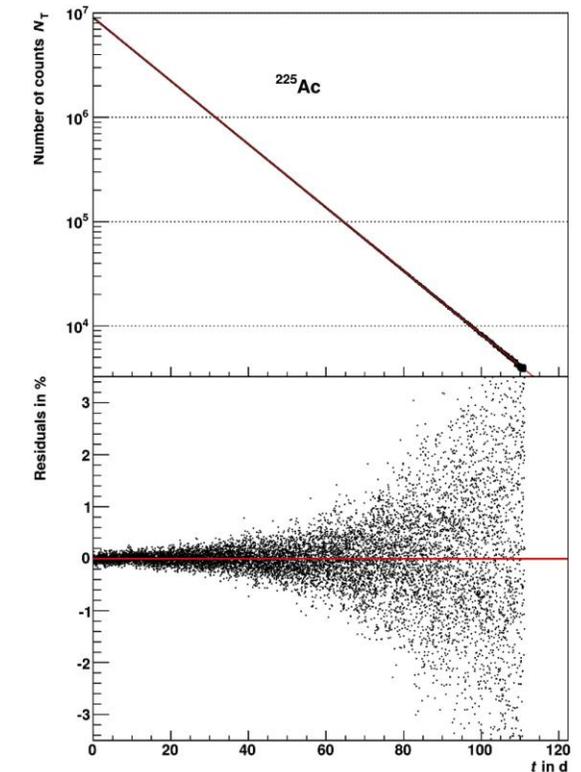
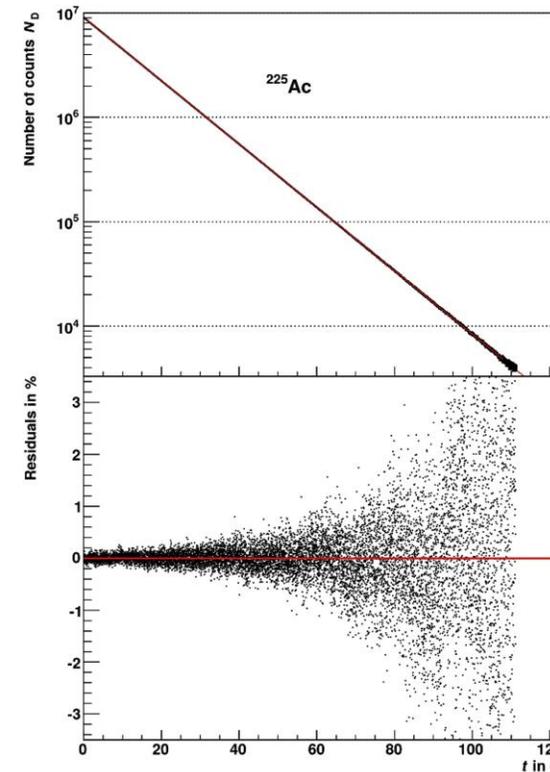


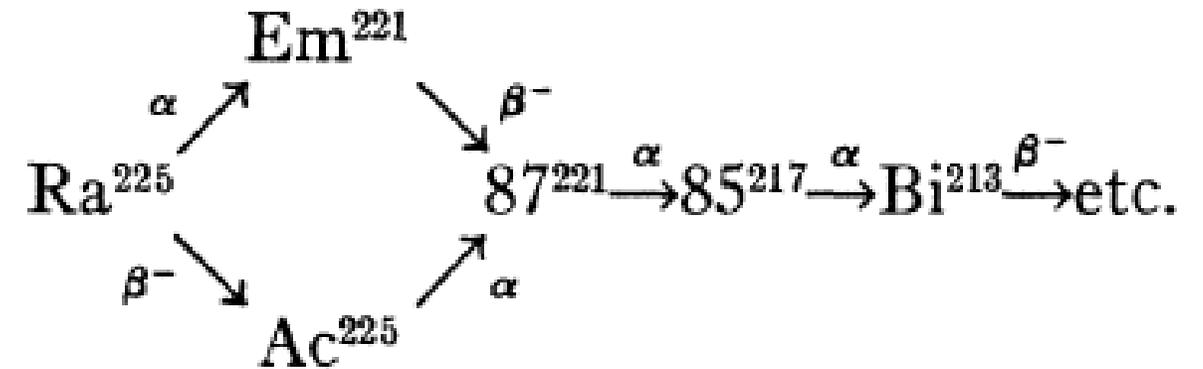
More on the ^{225}Ac half-life!

The entire chain was investigated as well!

- The Joint Research Center could NOT have the last word!
- If a standard is being challenged, the challenge must be countered and the new result confirmed.
- PTB – The German institute for standards – took it upon themselves to answer the call.

$$T_{1/2} = 9.9179(30) \text{ days}$$



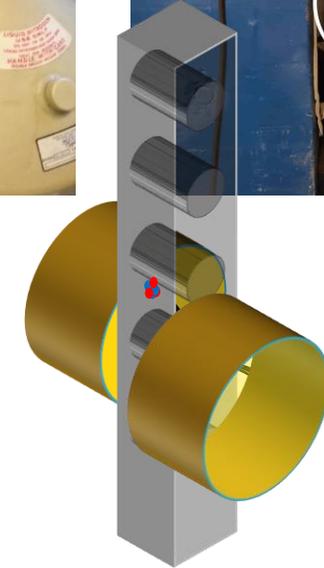
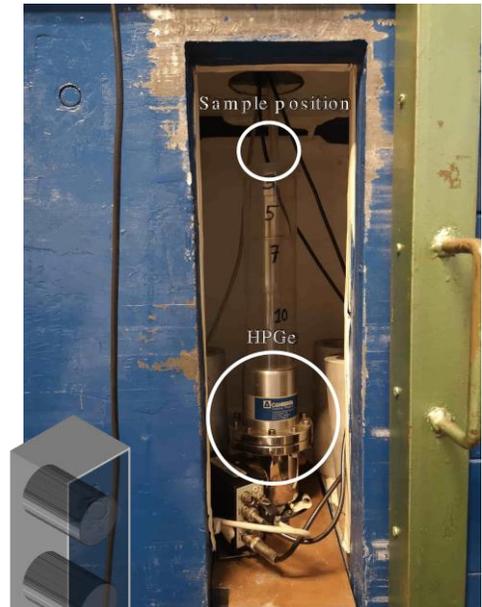


Radiation and branching ratios

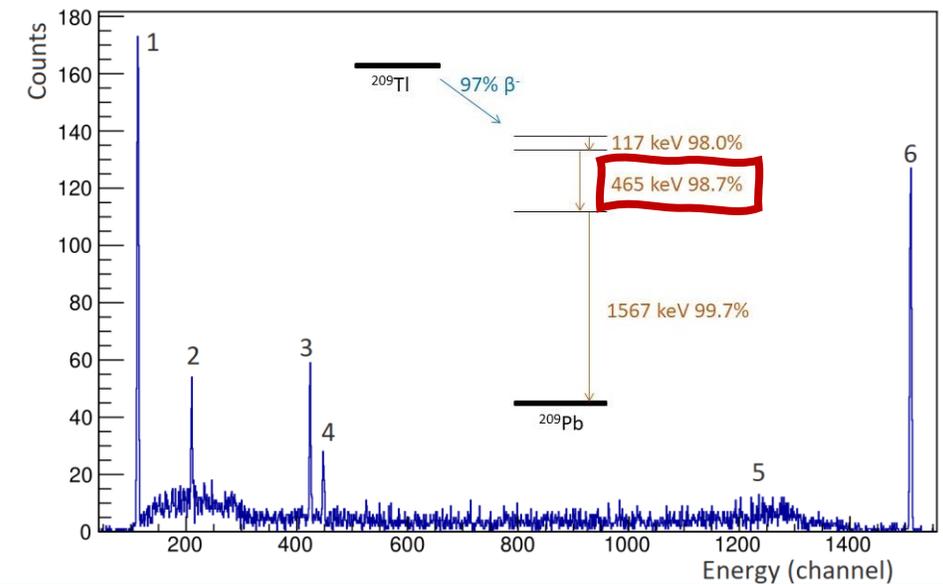
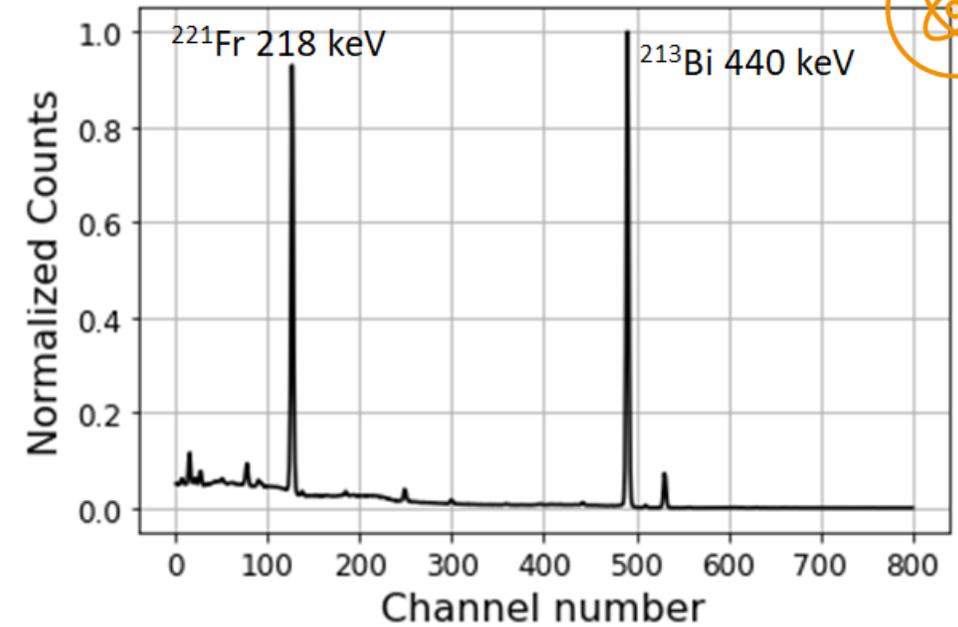
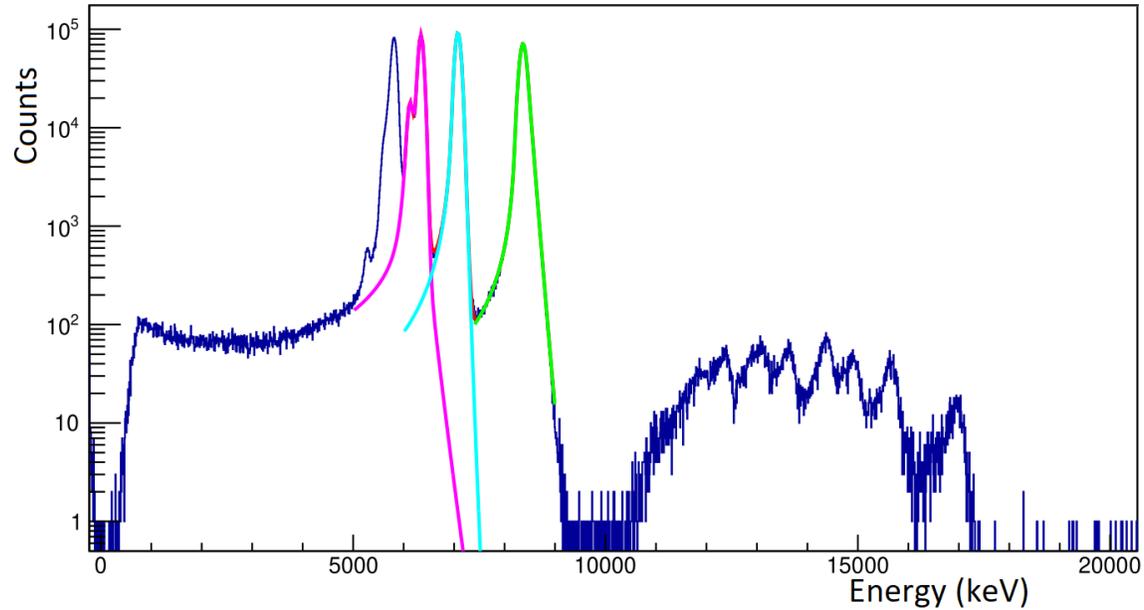


Looking at the decay chain from different angles

- Combined analyses can be made with α spectroscopy, γ -single spectroscopy and $\gamma\gamma$ -coincidence spectroscopy,
- As part of MED024, we wished to extract the original activity by different means for consistency check.
- The numbers did not add up...

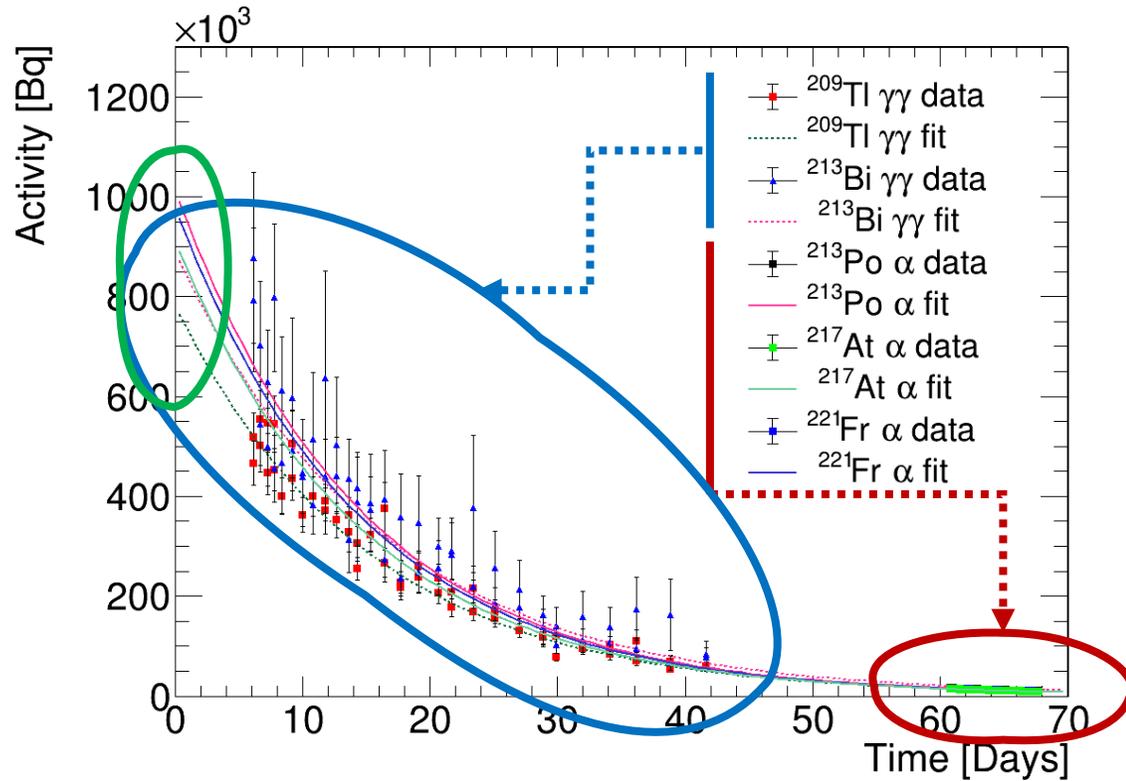


The data came in great!





... but



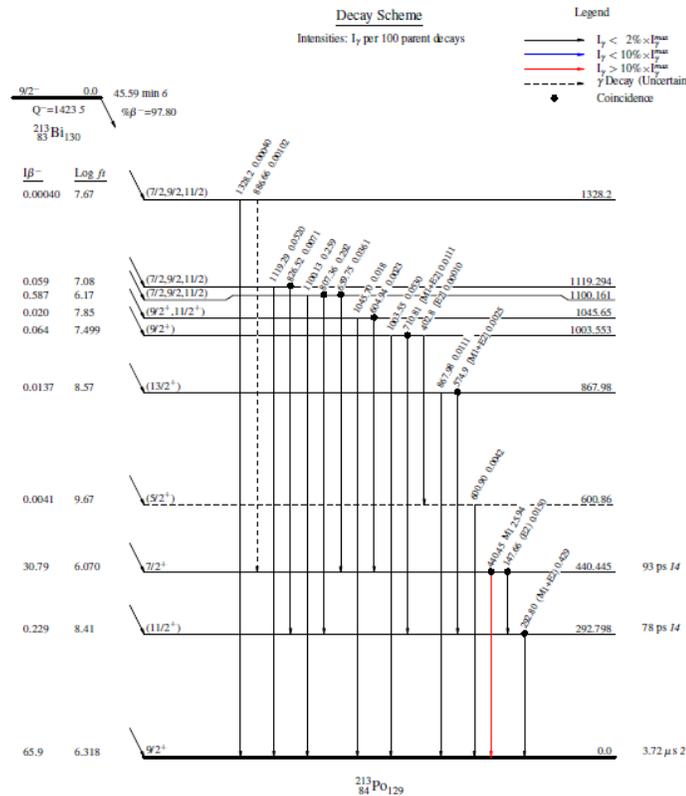
- The sample was used at the setups in sequence and the data lack therefore overlap.
- The projected activity at time 0 = End Of Collection are very discrepant and cannot agree within uncertainty.
- The largest discrepancies are found between different isotopes using the $\gamma\gamma$ -coincidence technique, which should be most accurate!



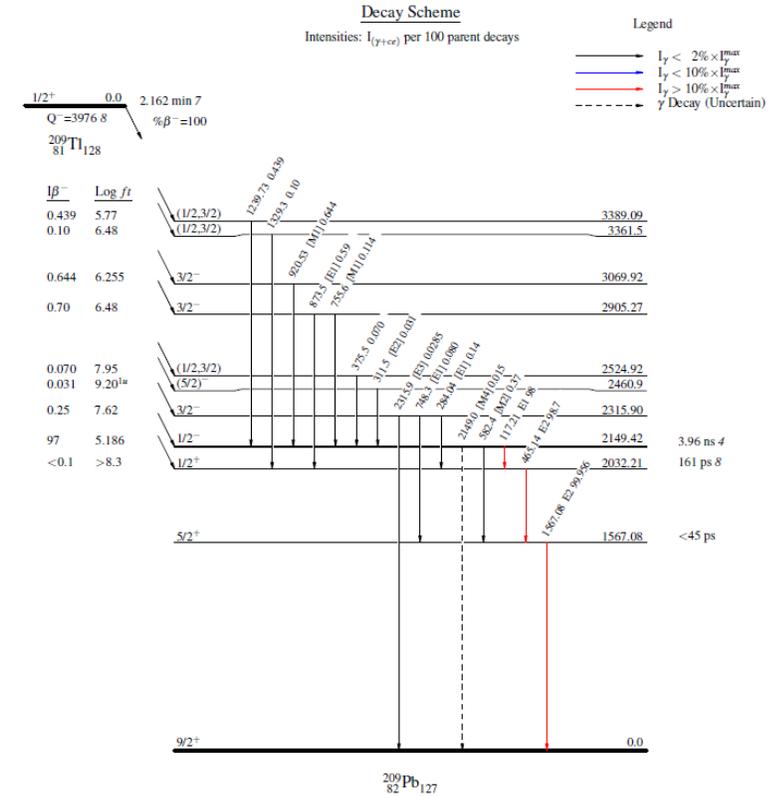
Looking more closely at the $\gamma\gamma$ cases

$$A = \frac{N_1(E_1)N_2(E_2)}{N_{12}(E_1, E_2)} \frac{I_{12}}{I_1 I_2}$$

^{213}Bi decay



^{209}Tl decay

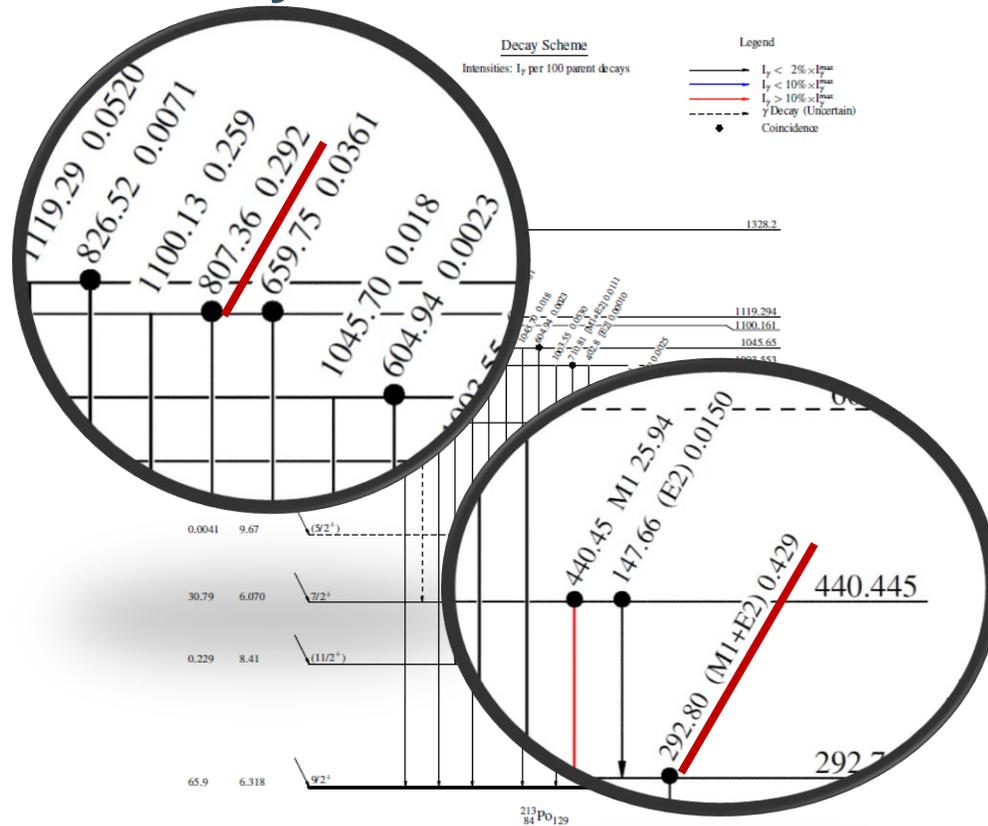




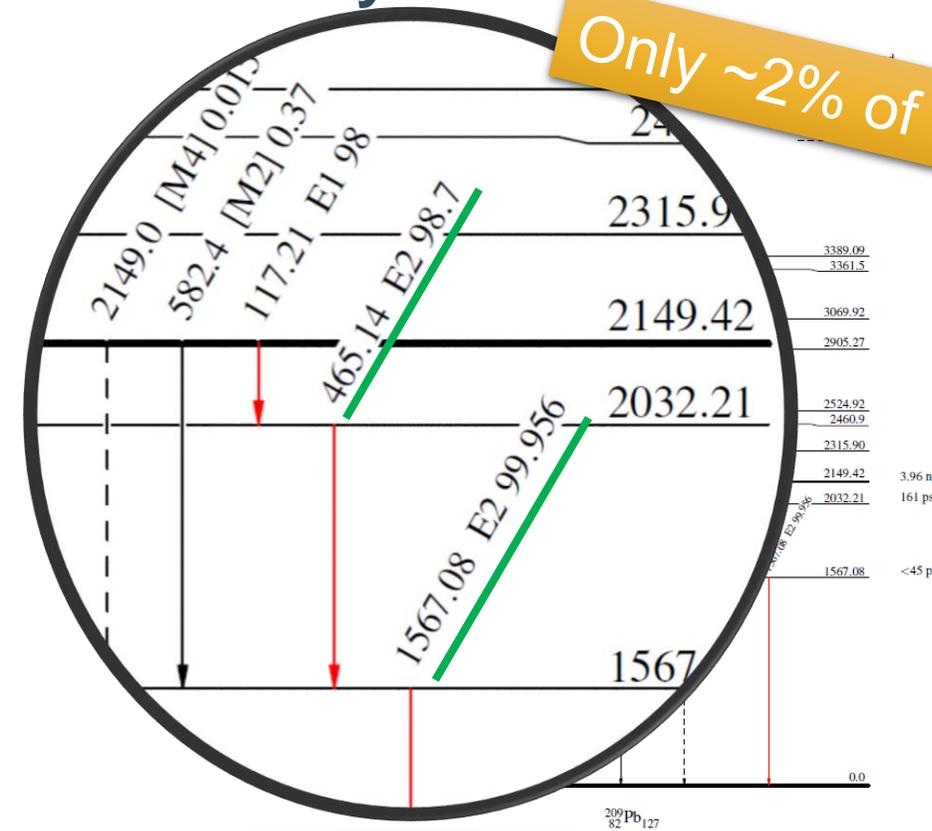
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^{213}Bi decay



^{209}Tl decay

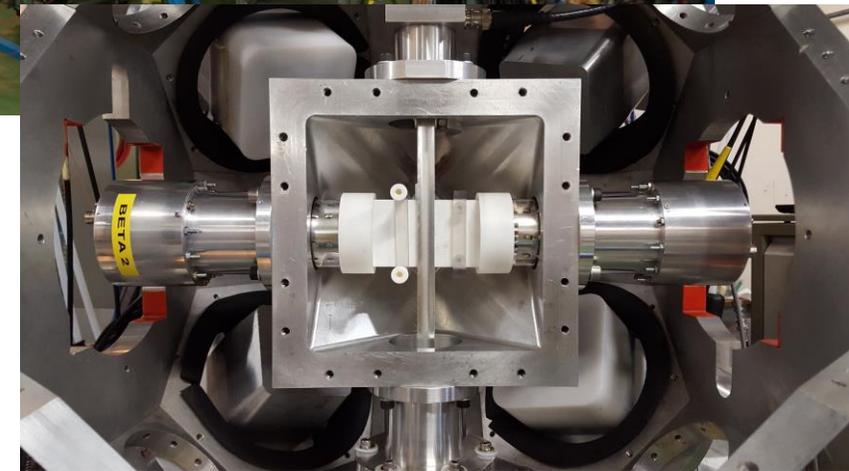
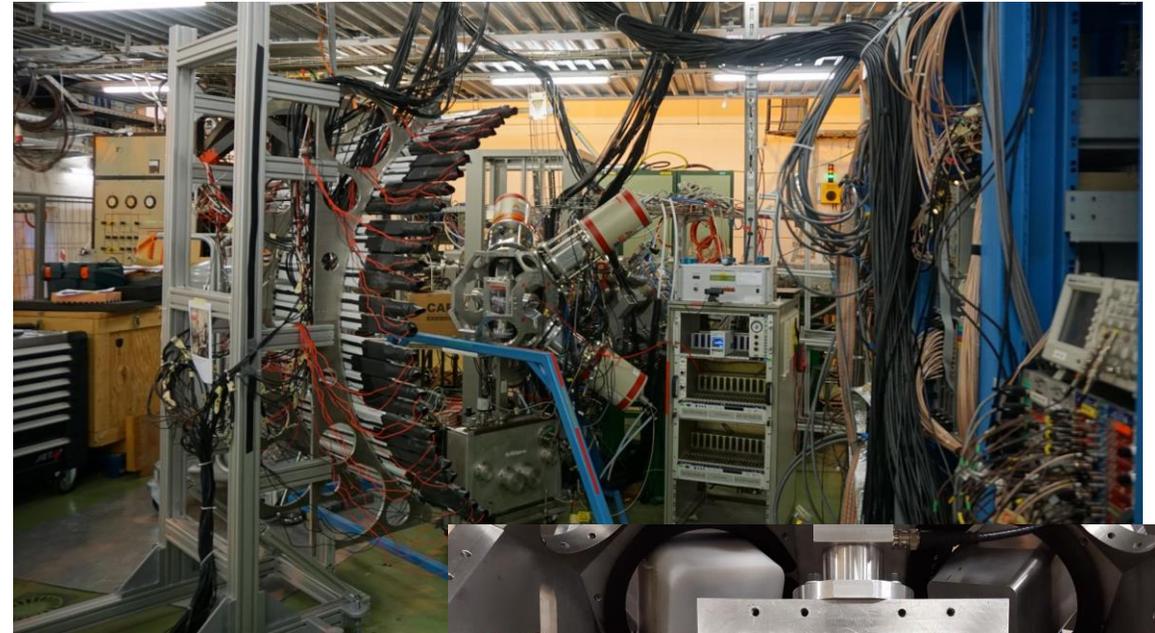


Only ~2% of the chain!



Measuring the decay branching and multipolarities

- ISOLDE can deliver intense beams of ^{225}Ac , ^{221}Fr , ^{213}Bi and ^{209}Tl to study them each independently.
- The ISOLDE Decay Station IDS allows the study of their decay with high efficiency and the possibility to observe the angular distribution of the γ rays to extract multipolarities.
- Charged particles coincidences are also available and build up is removed by using a tape roll.



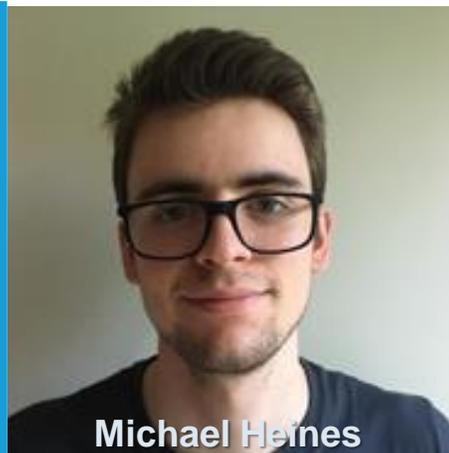


- ❖ While the prospect of giving access to novel radioisotopes with the ISOL technique is great, we see that there are many challenges remaining
 - Distributing radioisotopes around Europe is not trivial and requires dedicated efforts, one isotope at a time!
 - Producing those isotopes is great, but then they still have to be conditioned and prepared prior to be used for radiopharmaceutical products! And that is without asking about GMP yet...
 - Basic knowledge is sometimes still lacking on those isotopes, challenging their use in clinical settings where reliable data is a premise to any clinical application

Bedankt! Thank you! Danke! Merci!



Dr Charlotte Duchemin



Michael Heines



Wiktoria Wojtaczka



Sophie Hurier



Dr Cyril Bernerd



Jake Johnson



Silvia Bara



Benji Leenders



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