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Production of Lu-177 Using JRR-3 and PWR

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- Objectives
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  - Unnecessity of Lu-177m
- Experiments and calculation of JRR-3
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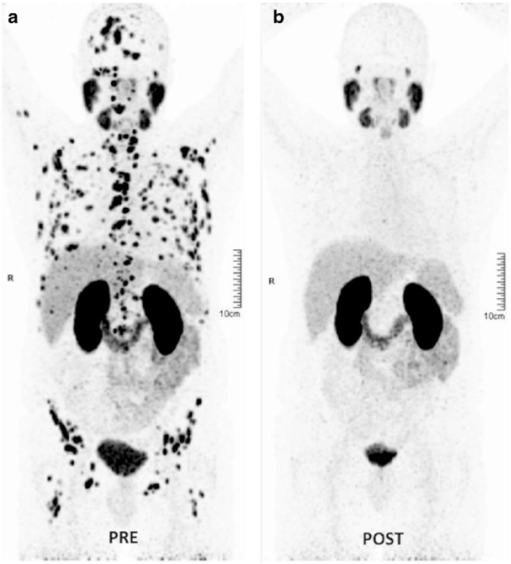
- Conclusions

Background

- Lu-177(half-life : 6.7day) is a medical radio isotopes used to treat Castration-Resistant Prostate Cancer(CRPC) and neuroendocrine tumors.

- Japan currently relies entirely on imports for Lu-177, some concerns regarding this are the aging of overseas reactors and supplies could be disrupted during transportation.

- Achieving domestic supply is a future challenge.



Objectives

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- Comparison with experiments and calculation of Lu-177 production at JRR-3
- Investigate the Lu-177 production using PWR to achieve Japan's demand
  - CRPC　Annual patients : 10,000~15,000
    Dosage : 7.4GBq × 6 times/person

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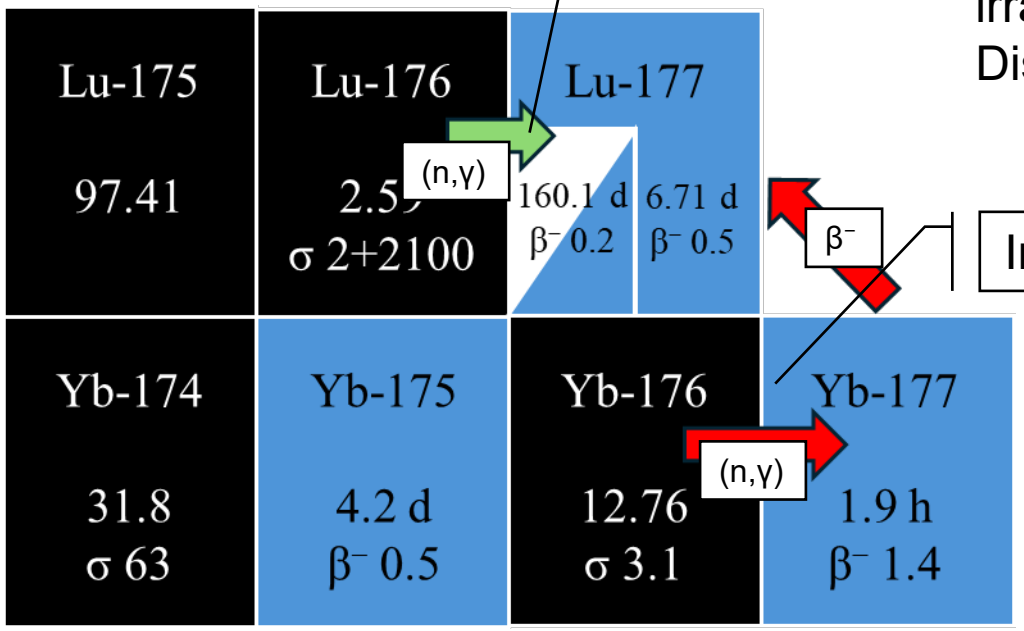
Medical Isotope Lu-177

Lu-177 production route in reactor



Direct route

Target : Lu-176
Advantages: Large amount produced, no need for chemical separation after irradiation
Disadvantages: produces Lu-177m

Indirect route

Target : Yb-176
Advantages: Does not produce Lu-177m
Disadvantages: Yb/Lu separation required after irradiation

Contamination of Lu-177m

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- Half-life : 160.1 day
- A byproduct produced by the direct route
- Concerns : accumulation of radioactivity in the human body, radioactive waste management, and radiation protection measures.

Specific activity : >740GBq/mg-Lu
Purity(Lu-177m/Lu-177) : <0.05 %

- NCA (no carrier added) without Lu-177m is preferred.

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Experiments and Calculation of JRR-3

Core specifications of JRR-3

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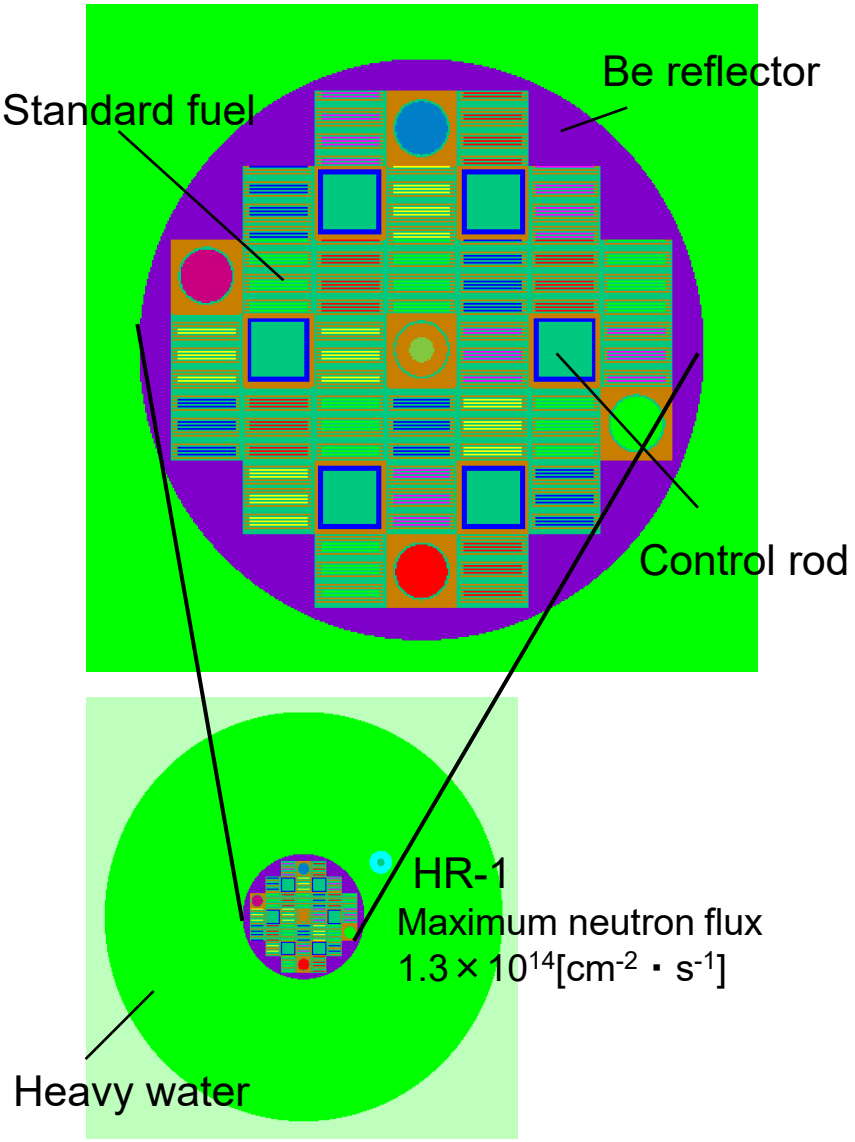

Fig. JRR-3 reactor core configuration

Table. Core Specifications of JRR-3

Thermal power	20 MWt
Maximum thermal neutron flux	3.0×10^{14} n/cm^2・s
Core average temperature	325 K
Core size	Diameter : 60 cm Height : 77 cm
Core materials	Standard fuel: 26 bottles Follower type fuel: 6 bottles Irradiation tube: 5 Be reflector: Peripheral
Reflector	Heavy water tank

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Lu-177 production experiments at JRR-3

- Experiments and calculation of Lu-177 production were conducted in JRR-3 reactor.
- Experiments were performed under the following conditions and calculated under the same conditions.

Target	Lu-176(64.3 % enriched)
Mass	0.094 mg
Irradiation position	Hydraulic rabbit(HR-1)
Irradiation days	14days

Calculation specifications

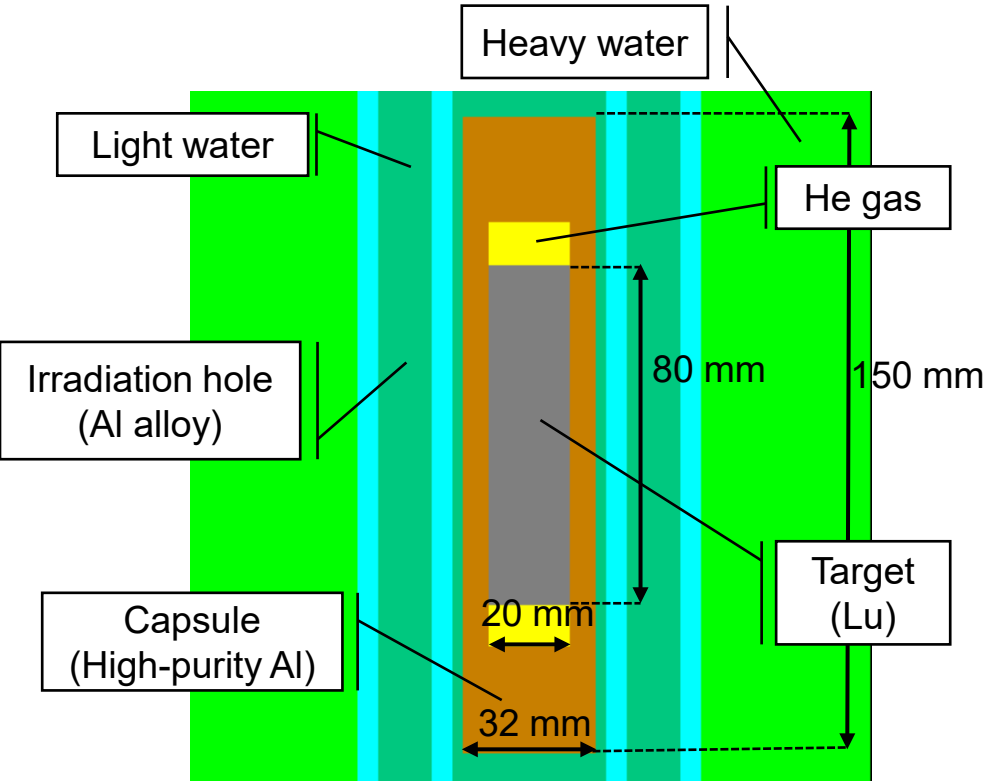


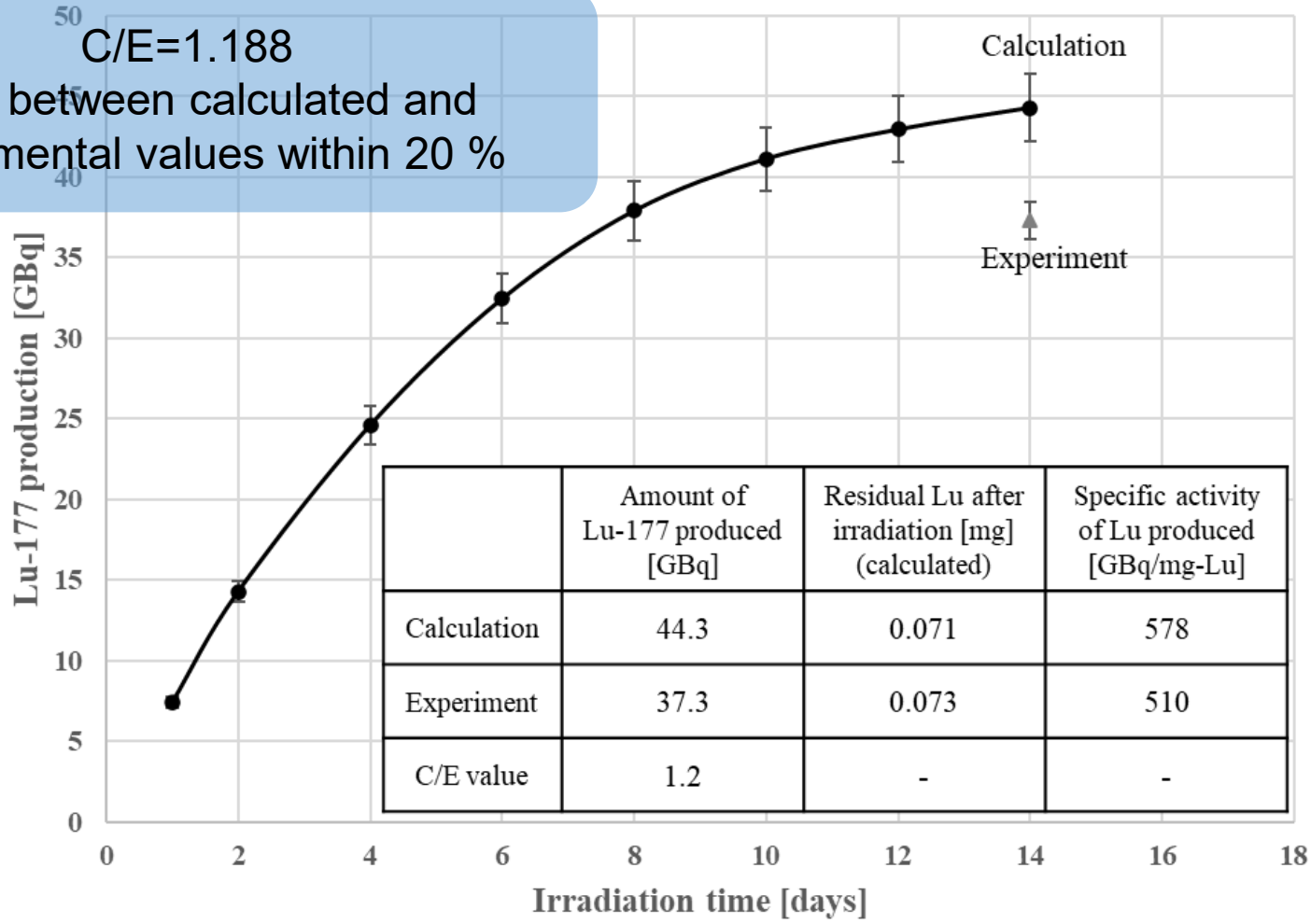
Fig. Target configuration loaded in hydraulic irradiation hole (HR-1)

Table. Calculation specifications

Target isotope	Lu-176 (64.3 % enriched)
Target Mass	0.094 mg
Irradiation position	Hydraulic rabbit(HR-1)
Irradiation days	14days
Calculation code	MVP-BURN
Nuclear date library	JENDL-5.0
Total number of histories	1,000,000

C/E value evaluation of Lu-177 production

C/E=1.188
Error between calculated and experimental values within 20 %



	Amount of Lu-177 produced [GBq]	Residual Lu after irradiation [mg] (calculated)	Specific activity of Lu produced [GBq/mg-Lu]
Calculation	44.3	0.071	578
Experiment	37.3	0.073	510
C/E value	1.2	-	-

Fig. Lu-177 production at HR-1 irradiation position

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Lu-177 Production Calculation at PWR

Calculation specification of Lu target in PWR

➢ Evaluation of Lu-177 production at PWR

Thermal power	17.7 MWt
Fuel specification	PWR 1 assembly (Fuel assembly type:17 × 17)
Target isotopes	Natural Lu, Natural Yb Lu-176 (70% enriched) Yb-176 (70% enriched)
Target mass	0.1 mg
Loading area	Instrumentation tube located at the center of the fuel assembly （Axial center position）
Irradiation time	14 days
Calculation code	MVP-BURN
Nuclear date library	JENDL-5.0
Boundary condition	Infinite
Total number of histories	1,000,000

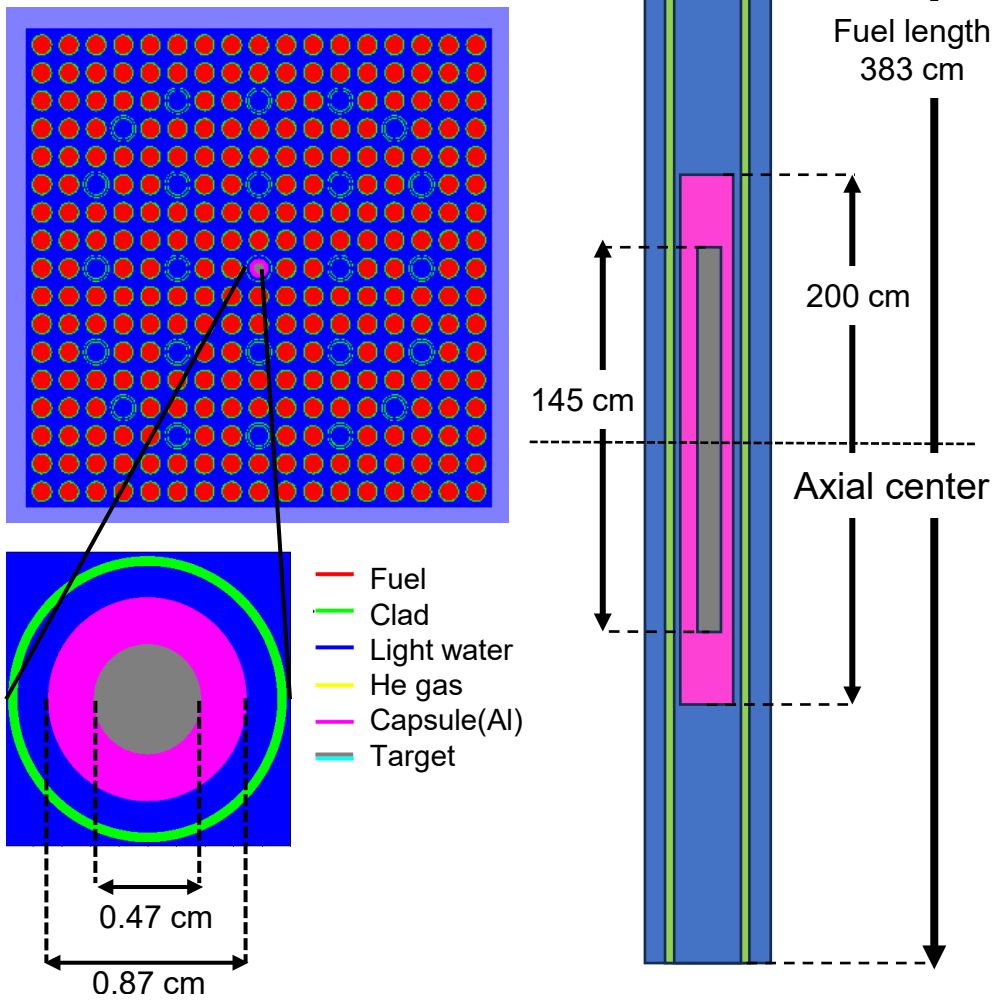

Fig. 17×17 fuel assembly and target configurations

Lu-177 production amount

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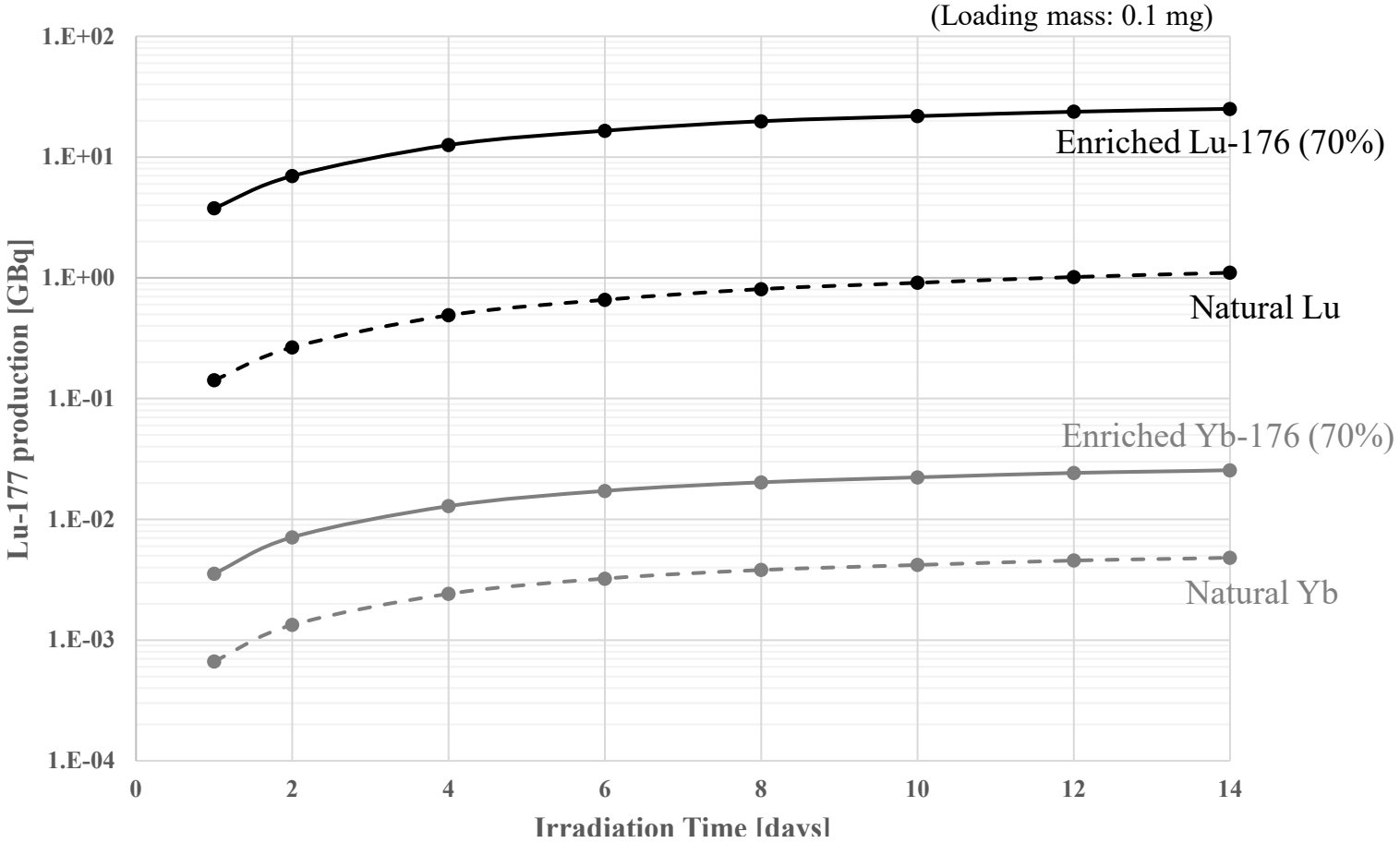
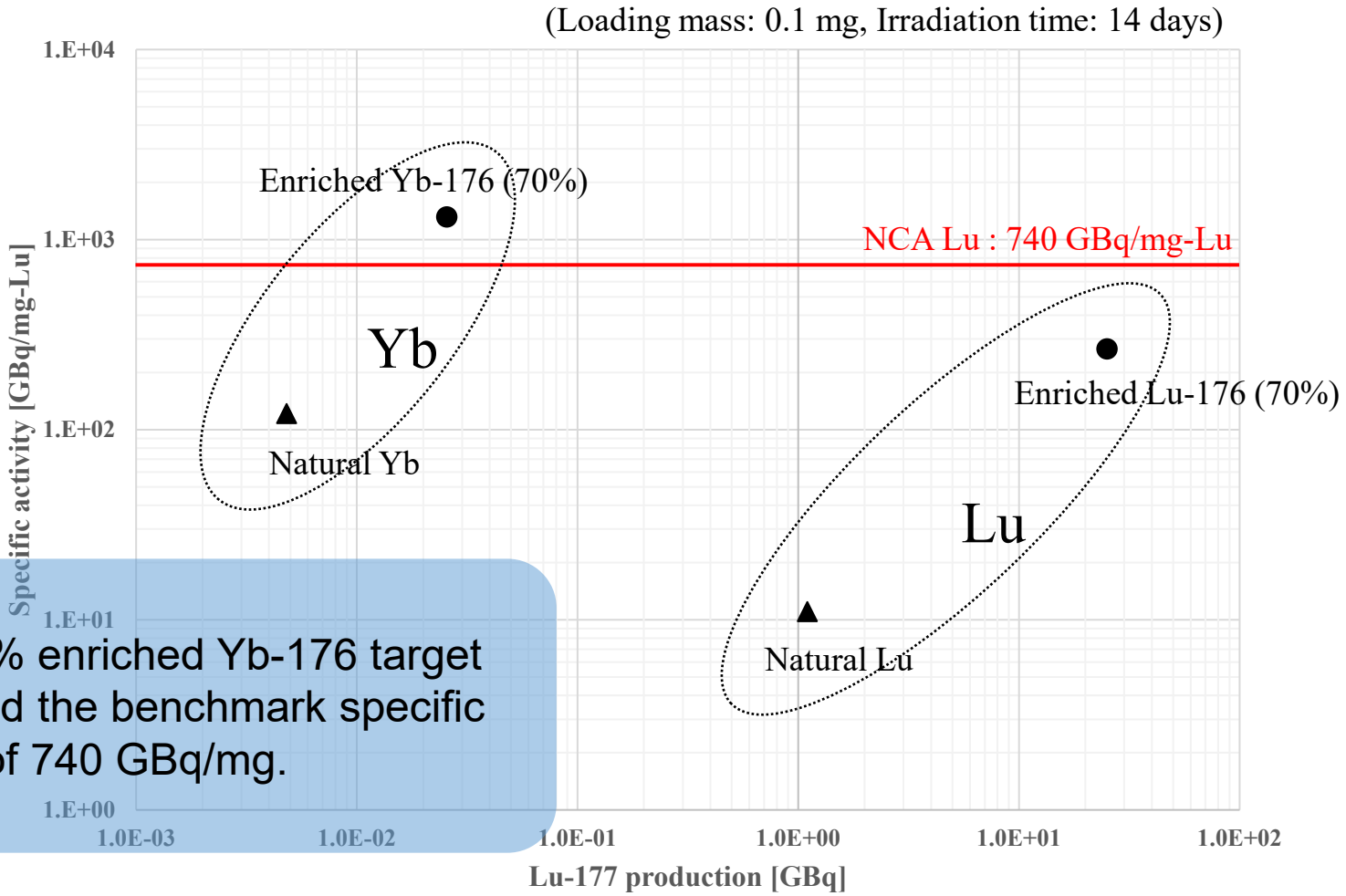


Fig. Lu-177 production in PWR with different targets

- Increased production is similar for the four nuclides.
- The production is approximately 200 times higher in the Lu than in the Yb.
- 70% isotope enrichment in the Lu results in an additional increase of 10^3 times.

Specific activity of Lu-177 produced



Only 70% enriched Yb-176 target exceeded the benchmark specific activity of 740 GBq/mg.

Fig. Lu-177 production amount versus specific activity after 14 days of irradiation

Performance comparison of Lu-177 produced

Table. Mass and quality of Lu-177 produced in PWR

	Amount of Lu produced [GBq]	Specific activity of Lu-177 produced [GBq/mg-Lu]	Purity (Lu-177m/Lu-177) [%]
Natural Lu	1.1	11	0.01
Enriched Lu-176	25.1	266	0.01
Natural Yb	0.005	121	0.000026
Enriched Yb-176	0.026	1316	0.000002

1/1000

×5

1/5000

While Yb targets yield less Lu-177 than Lu targets, their specific activity was considerably higher and approximately one five-thousandth of purity.
→The production method using enriched Yb-176 is considered the most suitable.

Yb-176 requirement for annual Lu-177 production

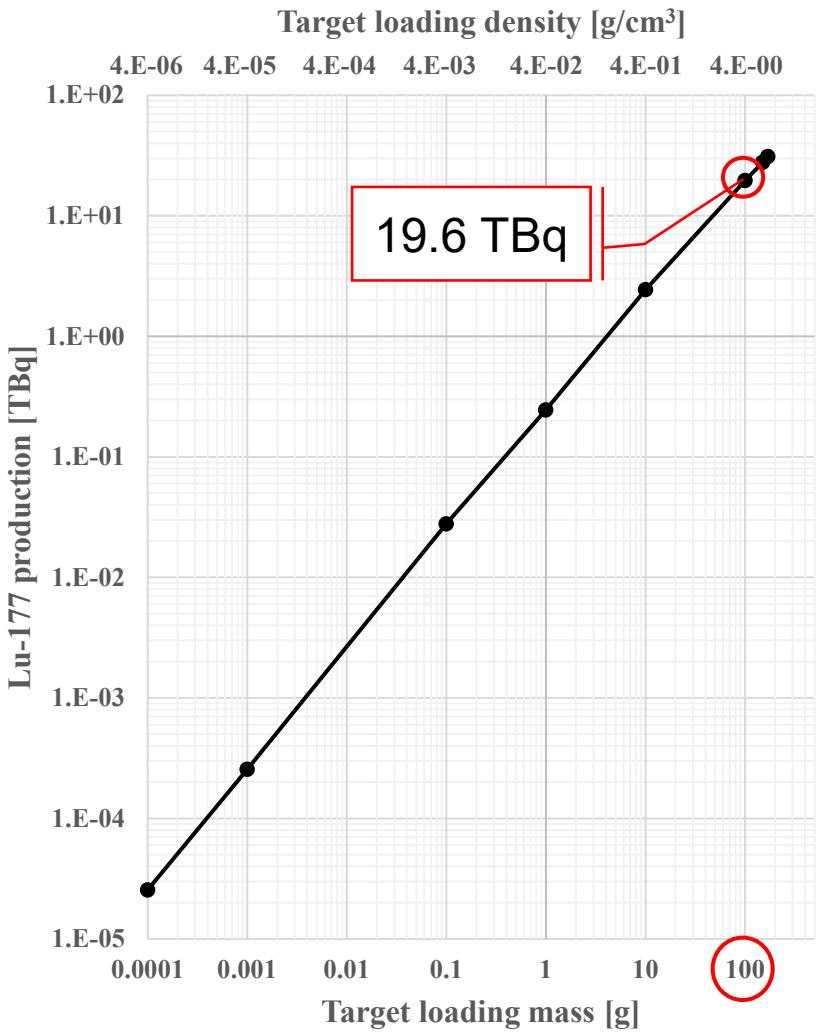


Fig. Target mass versus Lu-177 production amount

Yb-176 loading weight : 100 g/assembly

Irradiation + Unloading/Separation
(2 weeks) (1 week)
= 3 weeks/batch
→Assuming 17 irradiations per year

Amount of Lu-177 produced
= 19.6 TBq × 17 irradiation = 333 TBq/year
→**7500 person**

Yb-176(200g) irradiation
with 2 assemblies/reactor

Capable of supplying 15,000 patients
(number of CRPC patients per year)

Conclusions

- Lu-177 production experiments were conducted at the research reactor JRR-3 of the Japan Atomic Energy Agency.
  - 1 Ci of Lu-177 was produced from 0.1 mg of enriched Lu-176 (63.4%) for 14 days irradiation.
  - The calculated results agreed with the experimental values within 20% error.

- Investigation of Lu-177 production method by pressurized water reactor (PWR)
  - The irradiation of 200 g of enriched Yb-176 suggests a feasible approach for supplying Lu-177, which is carrier-free and has high specific activity to all CRPC patients in Japan (approximately 15,000 patients per year).

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Lu-177 medical utilized

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- Lu-177-PSMA(Not yet approved in Japan)

→CRPC (Castration-Resistant Prostate Cancer)

  - PSA (prostate-specific antigen) levels are used as a diagnostic indicator for prostate cancer
  - Higher PSA = higher likelihood of prostate cancer
  - German Lu-177-PSMA trial (mCRPC patients):
    - 21 of 30 patients showed PSA reduction
    - 13 of them had >50% reduction in PSA

- Lu-DOTATATE(Approved in Japan)

→NET(neuroendocrine tumors)

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Radiation Safety and Waste Management Issues

- Lu-177m/Lu-177 ratio doubles after a 1-week delay in use.
- All radioactive waste must be stored in dedicated decay facilities (may take years).
- ~80% of dose (1.45 MBq) is excreted in urine → requires holding tank storage.
- Regulatory limit for Lu-177m disposal: 10 Bq/g.
- Significant dilution is needed before discharge.

MVP-BURN burnup chain

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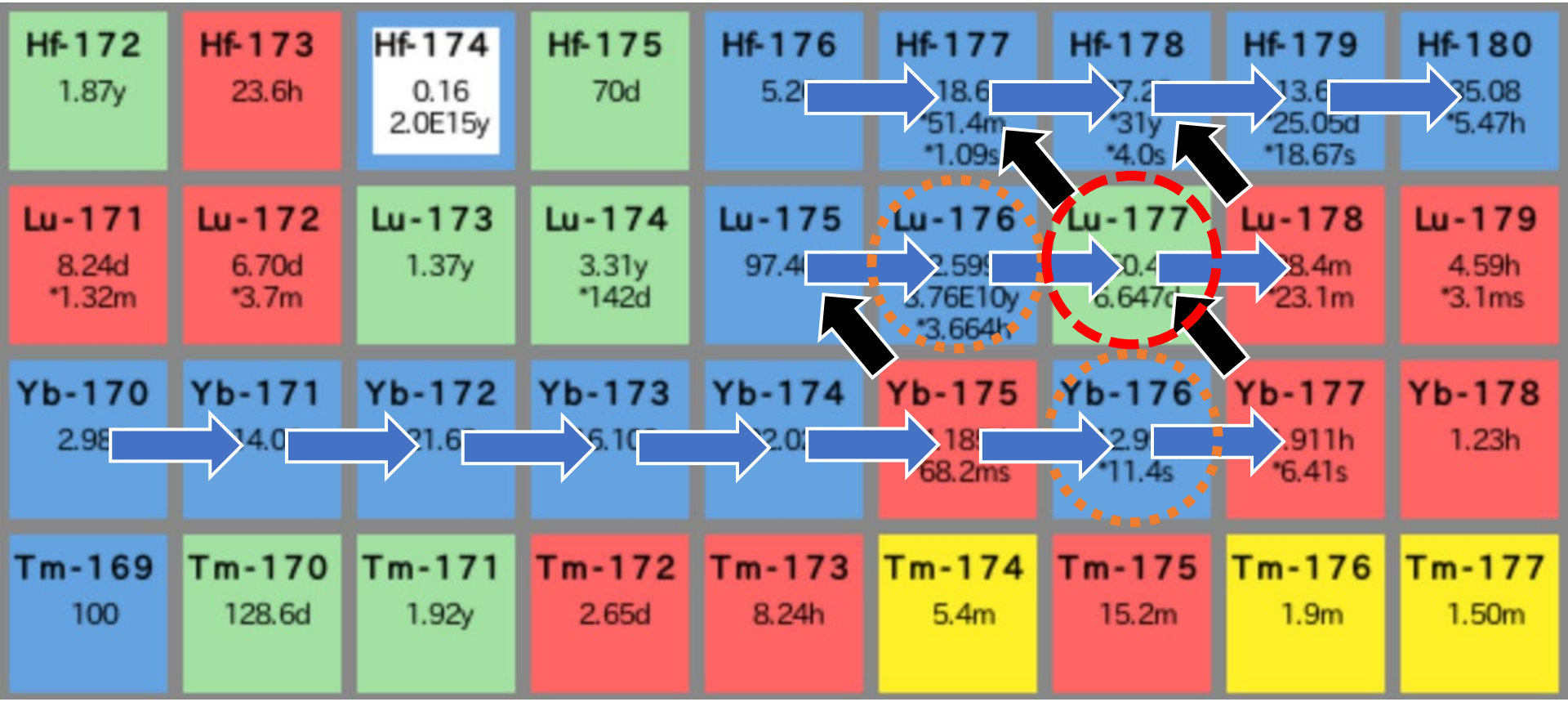
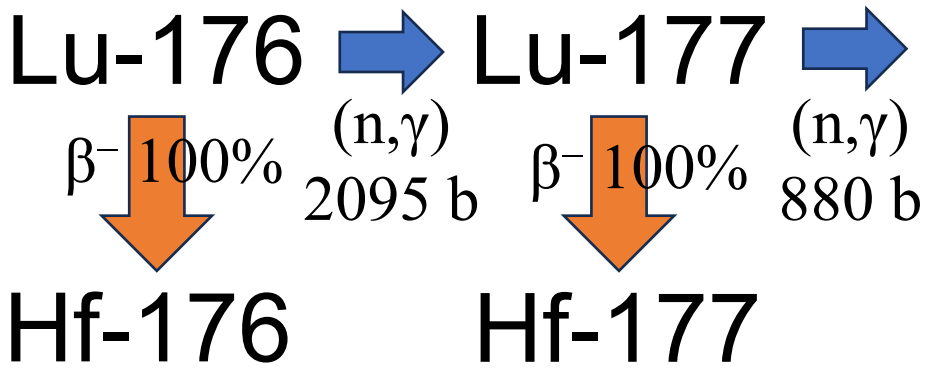
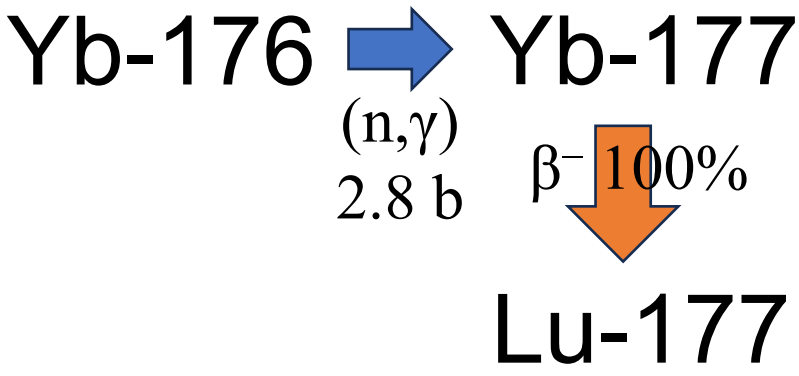


Neutron capture cross section

- Direct route



- Indirect route



Calculation of specific activity

- **In the JRR-3 experiments, using the Westcott formalism, Lu-177 burnup was considered to calculate the amount of Lu remaining after irradiation.**

- Westcott formalism

  The Westcott formalism is a method used to accurately evaluate the reaction rate with thermal neutrons for nuclides whose neutron cross section (σ) does not follow the 1/v law.

Neutron flux in reactor

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- JRR-3 HR-1 irradiation hole

Reference value(maximum): 1.3×10^{14}[cm-2・s-1]

Analysis value: 1.33×10^{14}[cm-2・s-1]

- PWR instrument guide tube position

Analysis value: 1.33×10^{13}[cm-2・s-1]

Reference value(core average): 3.0×10^{14}[cm-2・s-1]

Instrument guide tube

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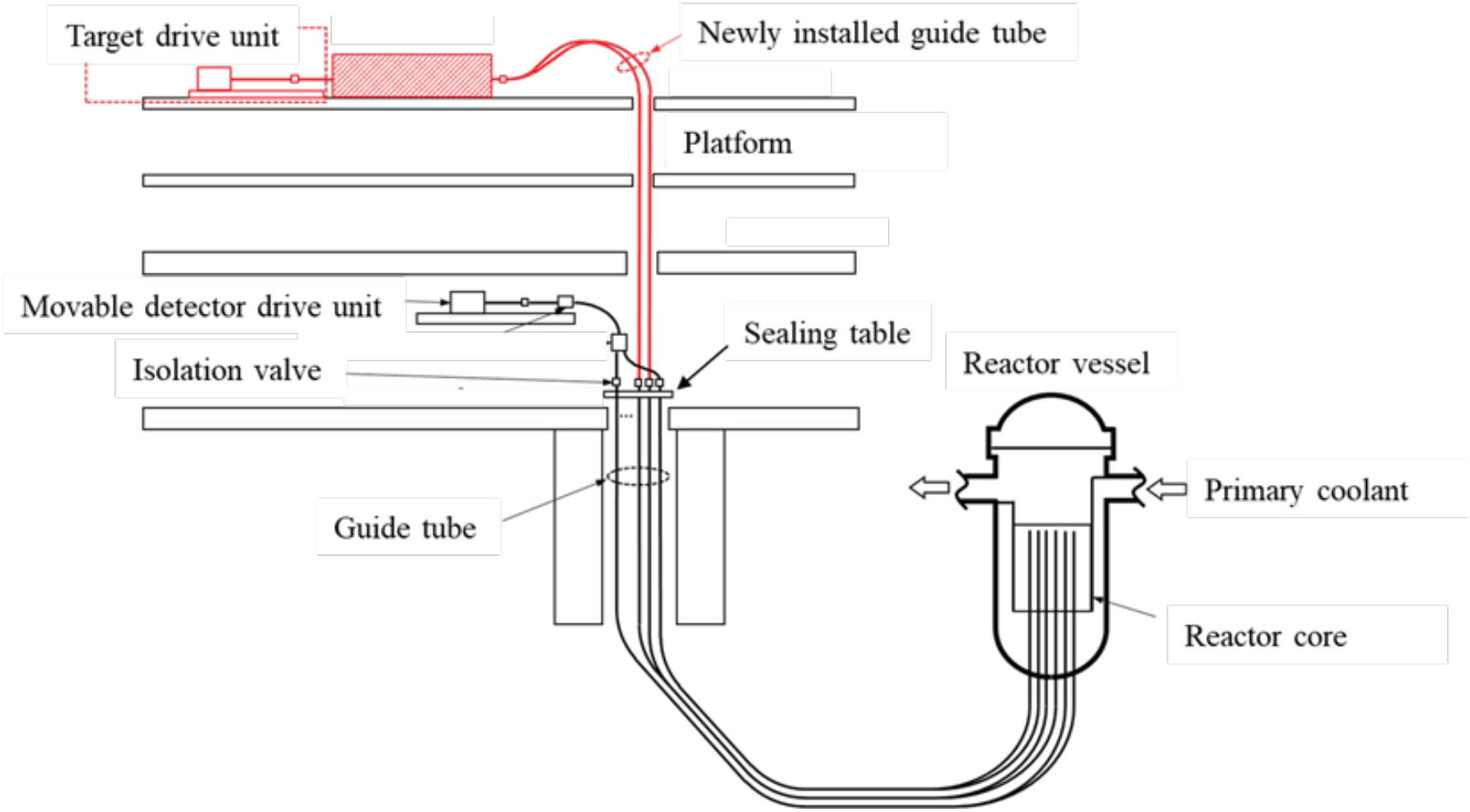
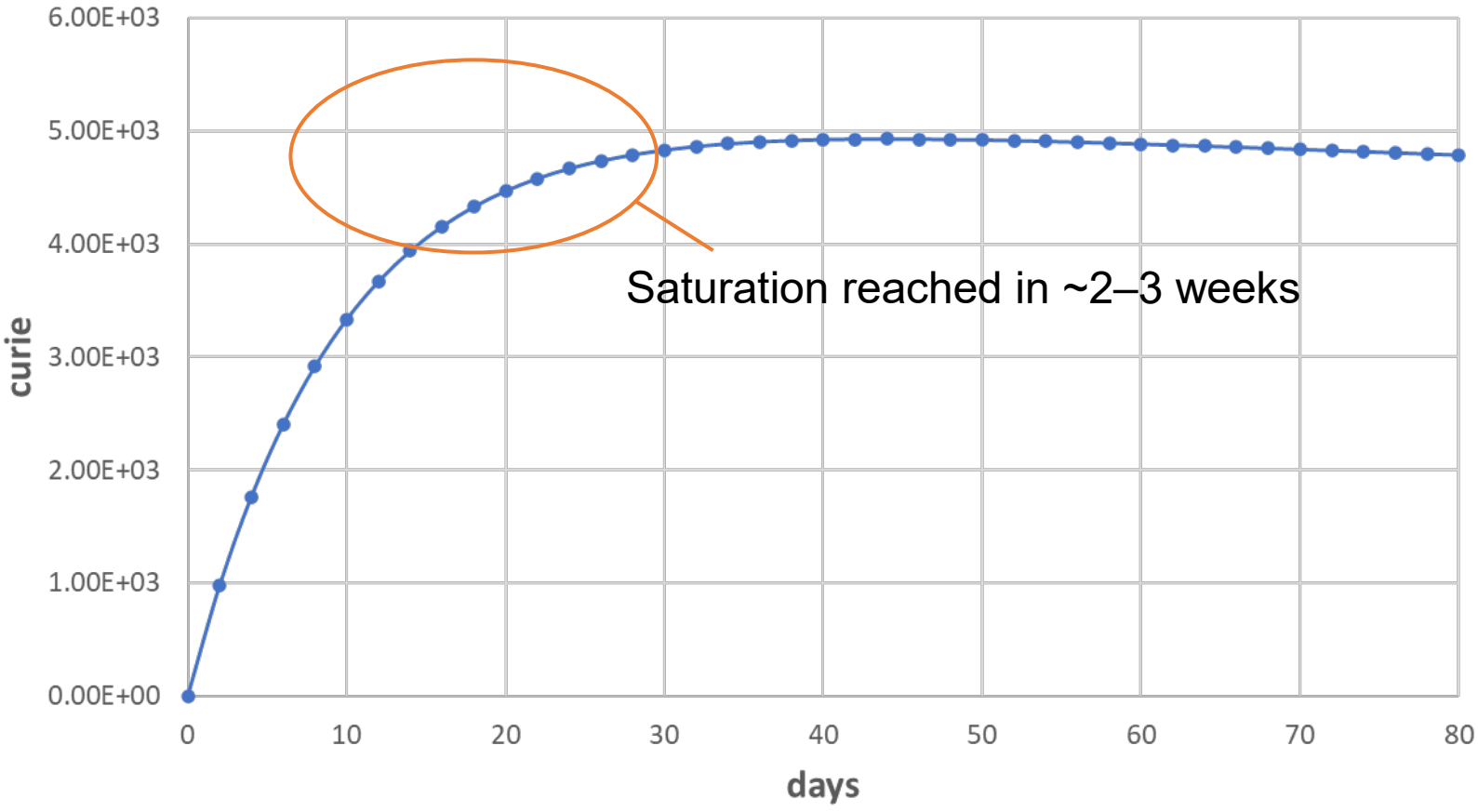


Irradiation time



Lu-177 annual production from Lu-176 target

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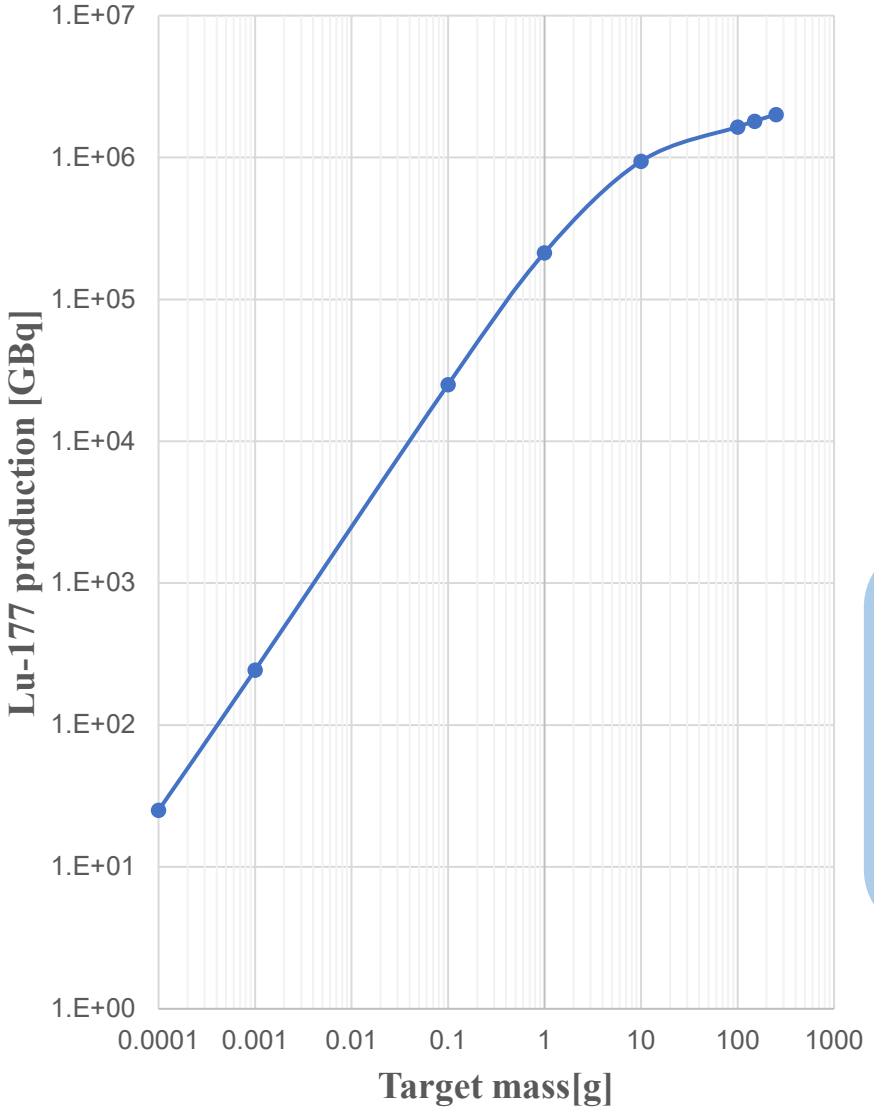

- Target loading: **0.1 g**/assembly
- Yield: **25** TBq/3-week batch
- Annual output: 425 TBq/year
- Equivalent to: **~9,572 patients/year** (based on 44.4 GBq/patient)

- Enriched Lu-176 requires only 1/1000 the mass
- Produces similar Lu-177 yield as enriched Yb-176

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Price Range of Lu and Yb Isotopes

- Lu-176(72% enrichment): 205,50EURO/mg

33,574 yen/mg → 3,357,400 yen/0.1g

- Yb-176(97.79% enrichment): 16,95EURO/mg

2,769 yen/mg → 276,900,000 yen/100g

1 EUR=163.38 yen

Stable Isotope Prices | Institute for Rare Earths and Metals (institut-seltene-erden.de)