FUTURE POSSIBILITIES FOR MEDICAL RADIOISOTOPE PRODUCTION IN RESEARCH REACTORS

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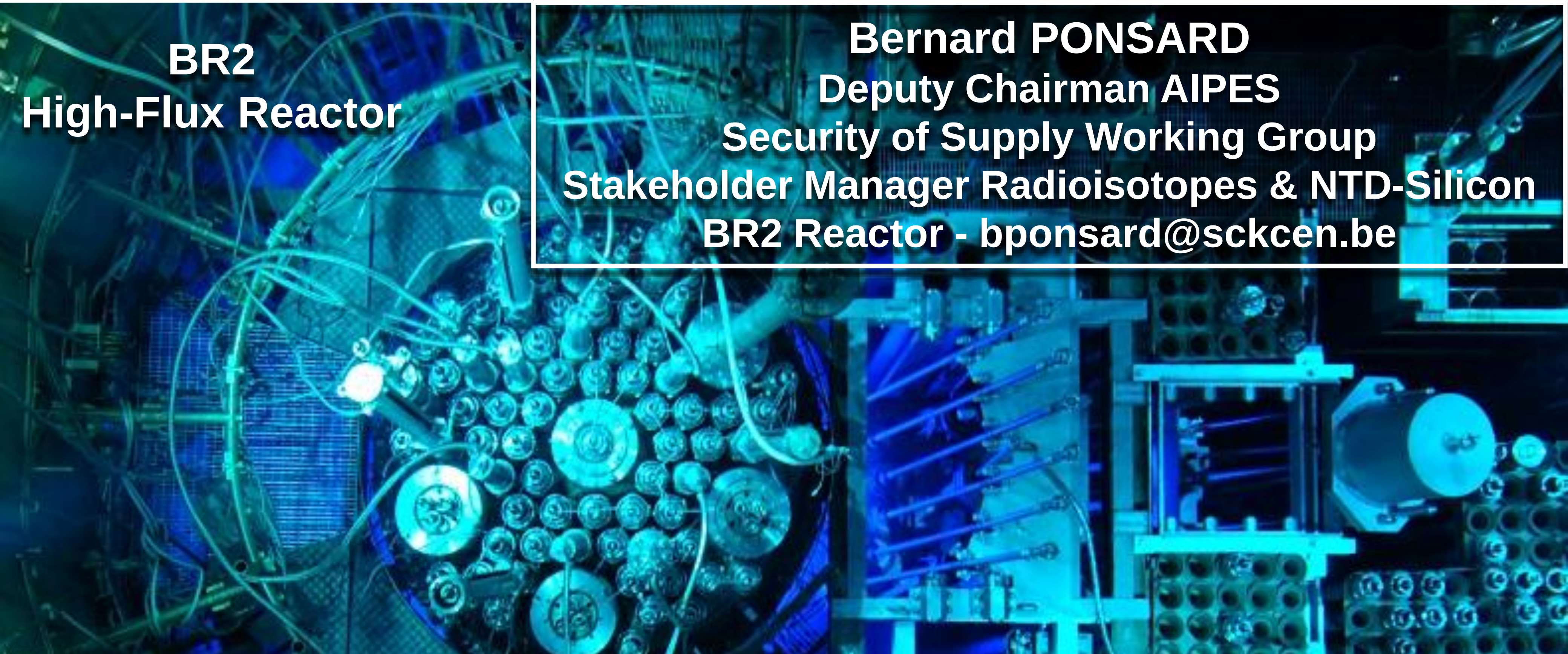
AIPES



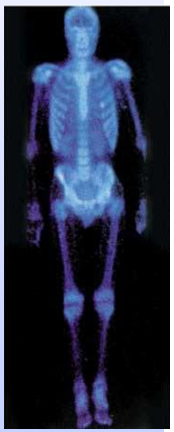
BR2
High-Flux Reactor

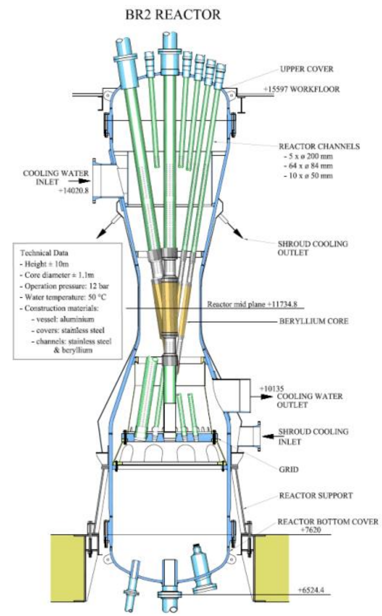
Bernard PONSARD
Deputy Chairman AIPES
Security of Supply Working Group
Stakeholder Manager Radioisotopes & NTD-Silicon
BR2 Reactor - bponsard@sckcen.be

SAMIRA WORKSHOP
Medical Radioisotopes in the Future: European Perspective
Brussels, 07/02/2019

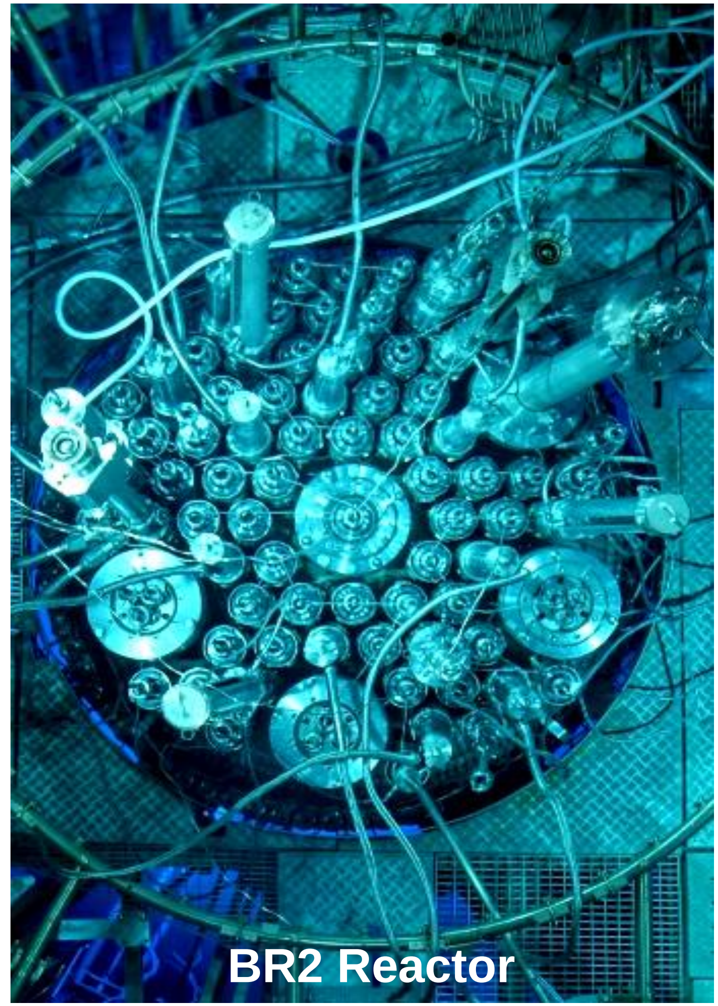
Future Possibilities For Medical Radioisotope Production in Research Reactors

- **1. Introduction**
- **2. Production of radioisotopes for diagnostic**
- **3. Production of radioisotopes for therapy**
- **4. Perspectives**
- **5. Conclusions**

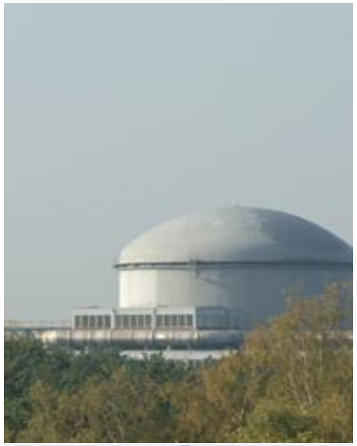




Mo-99/Tc-99m



1. Introduction



- **Research reactors** are playing a key role in the production of radioisotopes for various applications in **nuclear medicine**, i.e. **diagnostic** (Tc-99m, Xe-133, …), **therapy** (I-131, Lu-177, Ir-192, Y-90, P-32, Ho-166, Ra-223, …) and **palliation** of metastatic bone pain (Sm-153, Re-186, Re-188, Sr-89, Sn-117m…).

- However, while the number of accelerators – mainly cyclotrons – for the production of medical radioisotopes is increasing, the supply of reactor-produced medical radioisotopes relies on a **limited number** of research reactors.

- This is especially the case for the production of **Mo-99**, a very crucial radioisotope as it decays into **Tc-99m** which is used in **80% of diagnostic** nuclear imaging procedures carried out worldwide annually, i.e. **30 million** examinations yearly.

1. Introduction

- **High-Flux Reactors**
  - **SM3** (Dimitrovgrad; Russia); thermal neutron flux (E_n < 0.5 eV) up to **3.0 10^{15} n/cm².s**
  - **HFIR** (Oak Ridge; USA); thermal neutron flux (E_n < 0.5 eV) up to **2.5 10^{15} n/cm².s**
  - **BR2** (Mol; Belgium); thermal neutron flux (E_n < 0.5 eV) up to **1.0 10^{15} n/cm².s**
- **Medium-Flux Reactors**
  - **MURR** (Columbia; USA); thermal neutron flux (E_n < 0.5 eV) up to **5.0 10^{14} n/cm².s**
  - **HANARO** (Daejeon; South Korea); thermal neutron flux (E_n < 0.5 eV) up to **4.0 10^{14} n/cm².s**
  - **HFR** (Petten; NL); thermal neutron flux (E_n < 0.5 eV) up to **3.0 10^{14} n/cm².s**
- **Low-Flux Reactors**
  - Thermal neutron flux (E_n < 0.5 eV) below **1.0 10^{14} n/cm².s**

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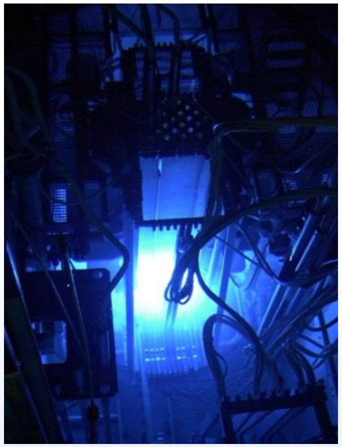
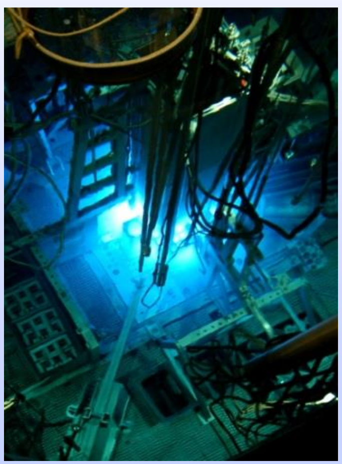
1. Introduction





Reactors	Countries	First criticality	MW	Φ_{th} [e+14 n/cm².s]	Days / year
SM-3	Russia	1961	100	30	?
HFIR	United States	1965	100	25	170
BR2	Belgium	1961	120	10	140
~~NRU~~	~~Canada~~	~~1957~~	~~135~~	~~4~~	~~300~~
MURR	United States	1966	10	4	300
MARIA	Poland	1974	30	4	240
HANARO	Rep Korea	1995	30	4	220
HFR	Netherlands	1961	45	3	280
SAFARI	South Africa	1965	20	3	300
OPAL	Australia	2006	20	3	300
~~OSIRIS~~	~~France~~	~~1966~~	~~70~~	~~2~~	~~180~~
LVR-15	Czech Rep	1957	10	2	200
FRM-II	Germany	2004	20	2	240

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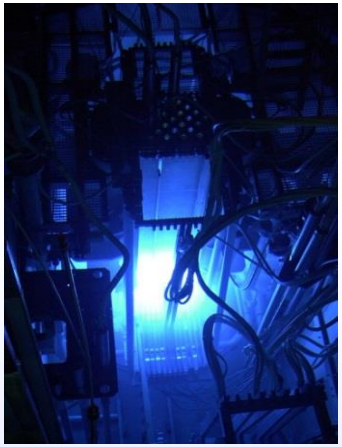

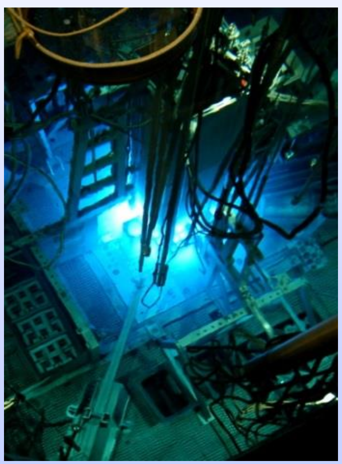

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- Current **research reactors are ageing**, expensive to replace and - due to safety and financial issues - a continuing source of public and political debate as it is currently the case in:
  - France (no bridge between shutdown OSIRIS and start JHR reactor)
  - Belgium (replacement of the BR2 reactor by MYRRHA)
  - The Netherlands (replacement of the HFR reactor by PALLAS)
  - Canada (definitive shutdown of the NRU reactor end of March 2018)
- The research reactors will continue to fulfill their active role in the development of **new radioisotope production routes** for nuclear medicine but their availability with appropriate **neutron fluxes** and significant **operating time** is an important issue to ensure a reliable supply in future.
- The current situation in the **Mo-99/Tc-99m** supply chain is already a major concern, especially after the definitive shutdowns of the **OSIRIS** (France) and **NRU** (Canada) reactors.

2. Production of radioisotopes for diagnostic

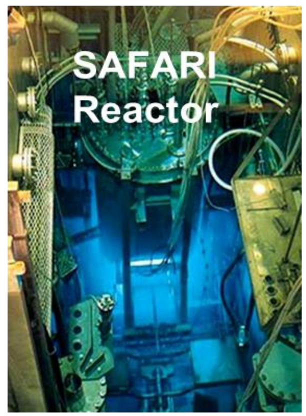
- Nine reactors are currently represented in the **AIPES Security of Supply Working Group**: **BR2** (Belgium), **HFR** (The Netherlands), **SAFARI** (South Africa), **MARIA** (Poland), **LVR-15** (Czech Republic), **OPAL** (Australia), **RA-3** (Argentina), **FRM-II** (Germany; currently not irradiating targets for Mo-99; start 2020) and **RJH** (France; not operating yet).
- The estimated **Mo-99 production capacities** of the current irradiators are:

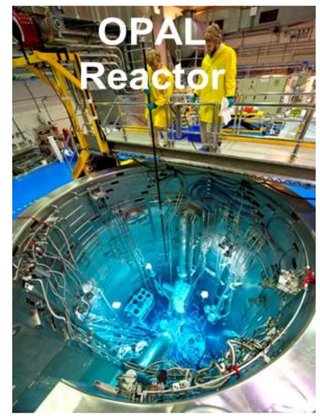
Reactors	Countries	Targets	Operating weeks / year	Irradiation capacities / week [6-day Ci]	Irradiation capacities / year [6-day Ci]	End of operation
BR2	Belgium	HEU/LEU	21	6 500 – 7 800	136 500 – 163 800	> 2026
HFR	The Netherlands	HEU/LEU	39	6 200	241 800	2026
SAFARI	South Africa	LEU	44	3 000	130 700	2030
LVR-15	Czech Republic	HEU	30	3 000	90 000	2028
MARIA	Poland	LEU	36	2 200	79 200	2030
OPAL	Australia	LEU	43	3 500 (2019)	150 500 (2019)	2057
RA-3	Argentina	LEU	46	400	18 400	2027

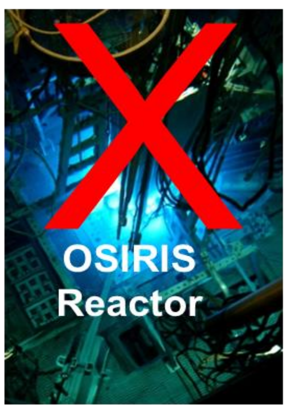
Ref: Nuclear Energy Agency, NEA/SEN/HLGMR (2018)3, August 2018, www.oecd-nea.org

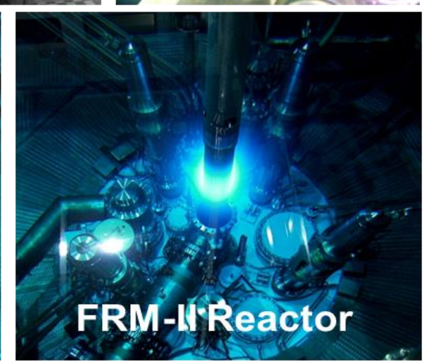
2. Production of radioisotopes for diagnostic

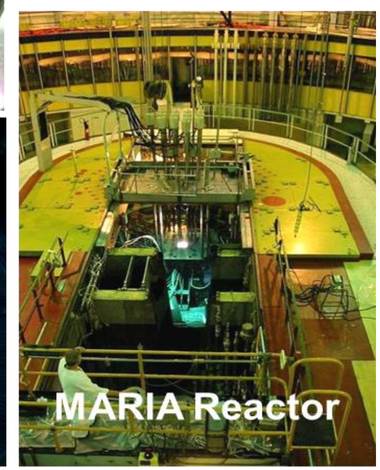
Research Reactors involved in the Mo-99 Global Supply Chain



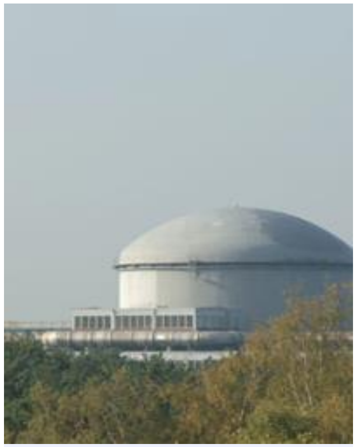


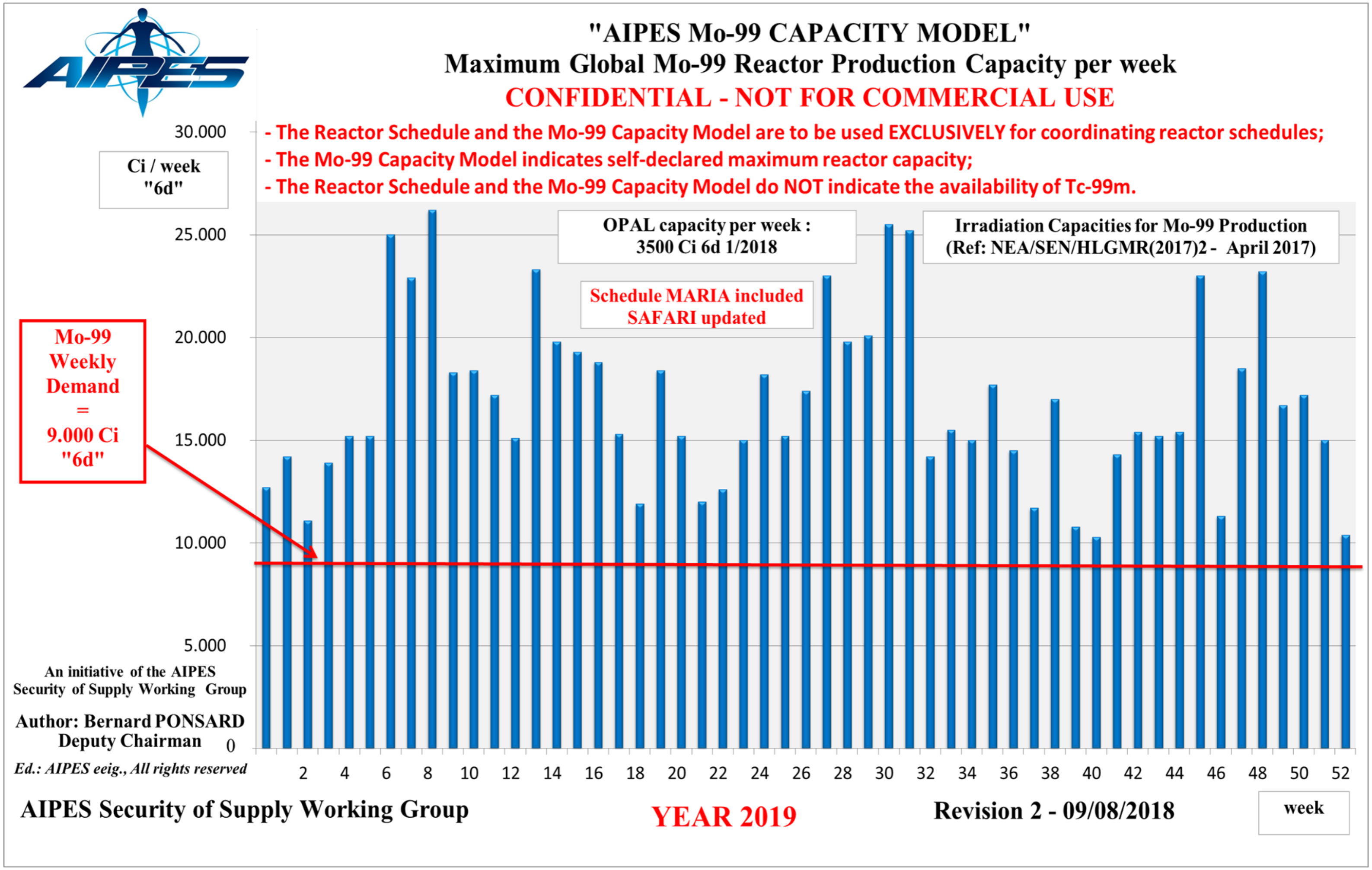






2. Production of radioisotopes for diagnostic





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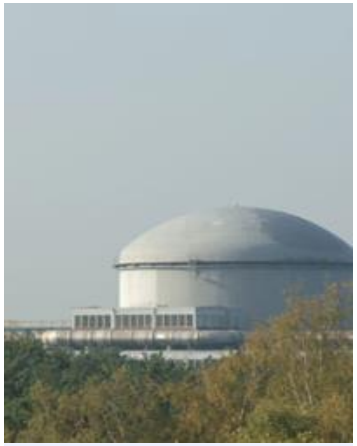
3. Production of radioisotopes for therapy



- Research reactors are **not only** producing Mo-99.
- They are also routinely producing **Ir-192** (T1/2=74.2 d) for curietherapy and several radioisotopes for metastatic bone pain palliation as **Re-186** (T1/2=3.8 d), **Sm-153** (T1/2=46.7 h), **Y-90** (T1/2=64 h), **Sr-89** (T1/2=50.5 d), ...
- The very attractive **Lu-177** (T1/2=6.7 d) for targeted therapy of small tumours (prostate, …) and metastatic bone pain palliation can be produced by both direct and indirect routes in research reactors:
  - **Direct route**: ^{176}Lu (n_{th} , γ) ^{177}Lu; yield = 30 Ci/mg at "EOI"
  - **Indirect route**: ^{176}Yb (n_{th} , γ) ^{177}Yb $\rightarrow$ ^{177}Lu; yield = 0.07 Ci/mg ^{176}Yb at "EOI"
- Special attention is currently given for the production of **new** β^- (Ho-166, Sc-47, Tb-161, …) and α (Ac-227/Ra-223, …) emitters for the development of the **personalized medicine** based on **"theranostics"** (Sc-44/Sc-47, Tb-149/Tb-161, Tb-152/Tb-161, Tb-155/Tb-161, …).

3. Production of radioisotopes for therapy

Direct Route

Lu-176 (98.5% enriched) — n, γ — σ = 2090 barn → **Lu-177** (6.71 days) + **Lu-177*m*** (160 days)

Indirect Route by Beta Decay

Yb-176 — n, γ — σ = 2.85 barn → **Yb-177** (1.9 hours) — β^- → Lu-177

Carrier-Free route

Improved/optimized separation required

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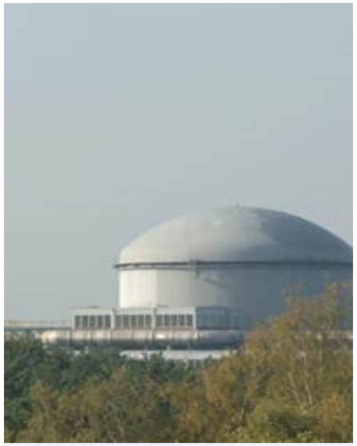
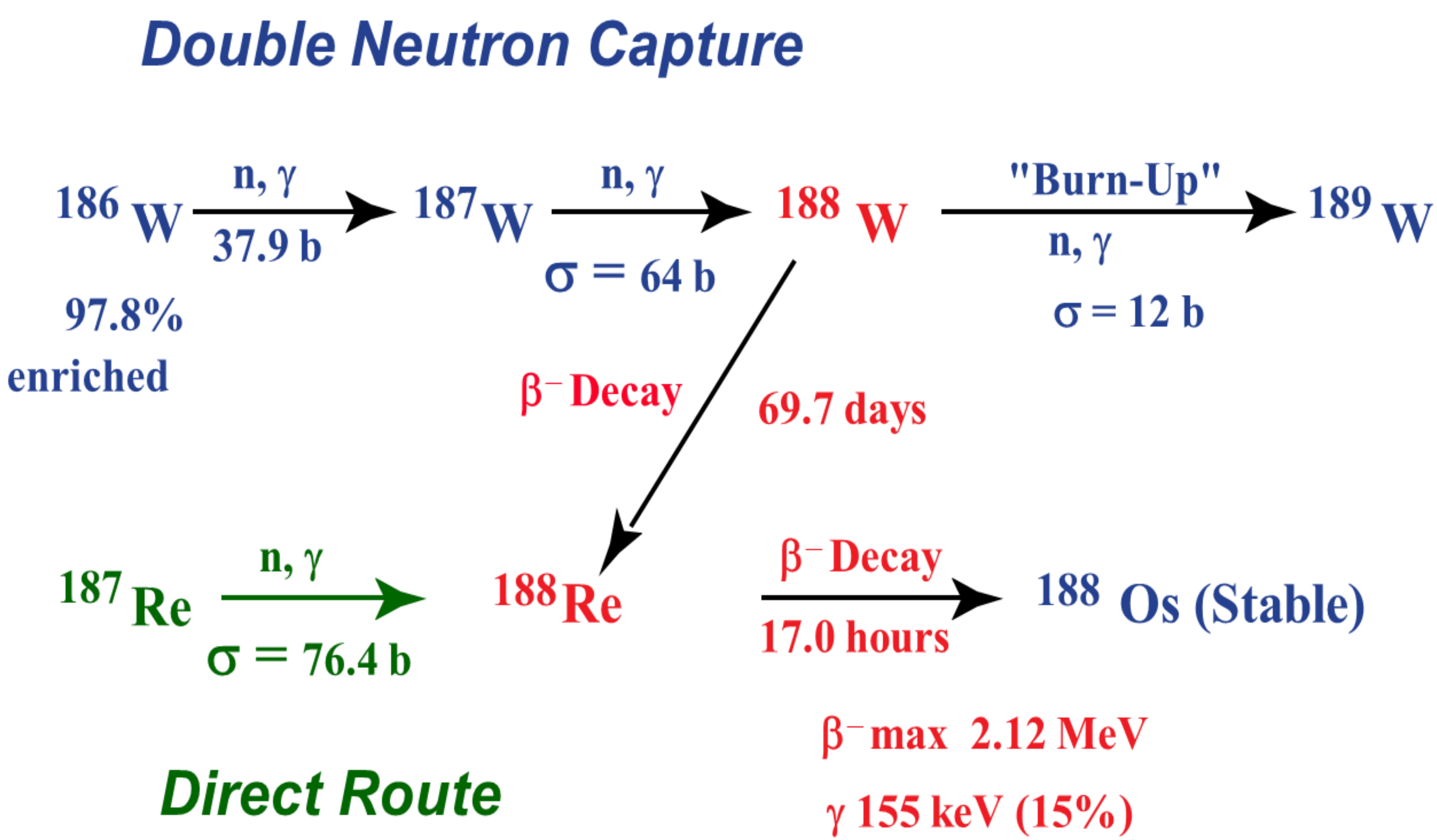
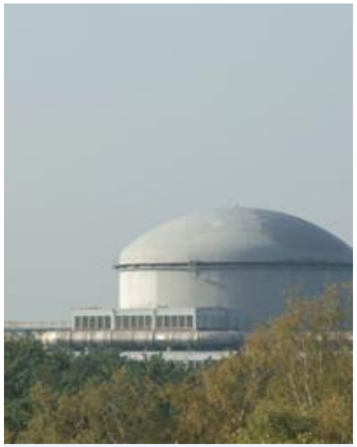
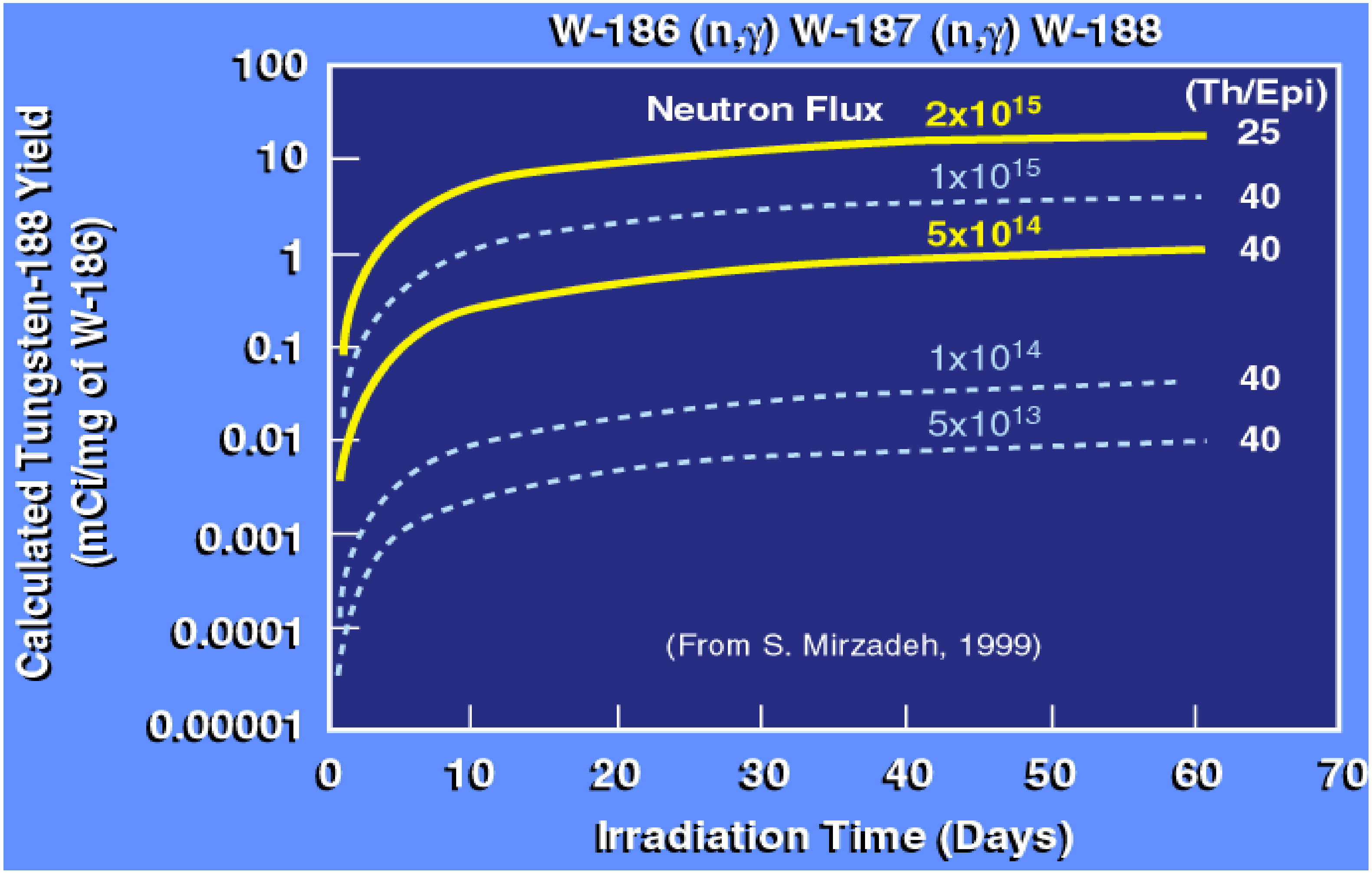
3. Production of radioisotopes for therapy





3. Production of radioisotopes for therapy





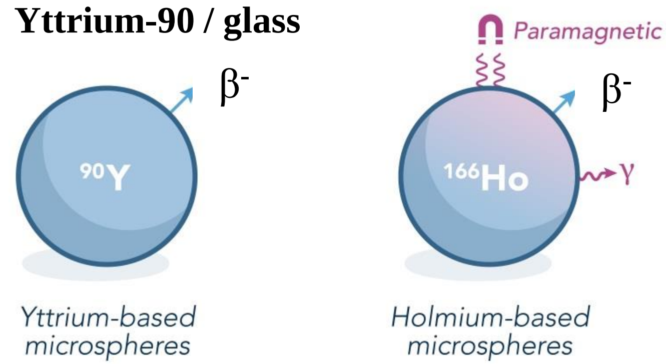
3. Production of radioisotopes for therapy

- Studies have found promizing results for the treatment of metastatic **liver cancer** by **Y-90** and **Ho-166 microspheres**.

Isotopes	Half-life $T_{1/2}$	Decay mode	Average Energy β^-	Average Energy γ
Y-90	64,2 h	β^-	0,94 MeV	-
Ho-166	26,8 h	β^-	1,84 MeV	81 keV

- **Y-90** and **Ho-166** both emit **high energy beta** particles for tumor eradication
- **Y-90** is a **pure beta emitter**
- **Ho-166** also emits **gamma** radiation which allows for quantitative nuclear imaging
- **Holmium** is **paramagnetic** and therefore visible on MRI

BTG TheraSphere® : Yttrium-90 / glass



SIR-Spheres® : Yttrium-90 / resin

QuiremSpheres® : Holmium-166 / PLLA

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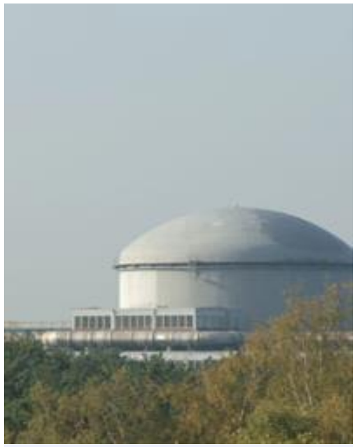
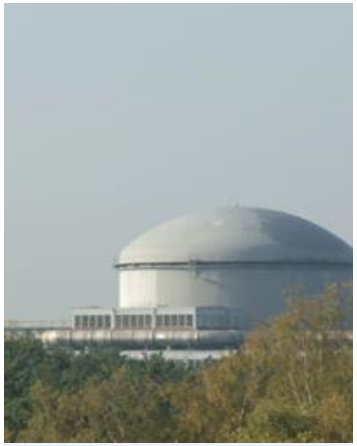
4. Perspectives



- Europe plays the **leading role** in the supply of Mo-99/Tc-99m because it hosts the largest, most coherent and coordinated supply chain from target manufacturing to medical applications.
- The **European Observatory** and **AIPES** are the leading bodies for this coordinated approach in Europe.
- The **main strategic objectives** are:
  - to support a secure supply of medical radioisotopes
  - to ensure that the issue of medical radioisotopes supply is given high political visibility
  - to establish periodic reviews of the supply capacities and demand
- In the **next decade**, it is expected that several research reactors will shut down in Europe.

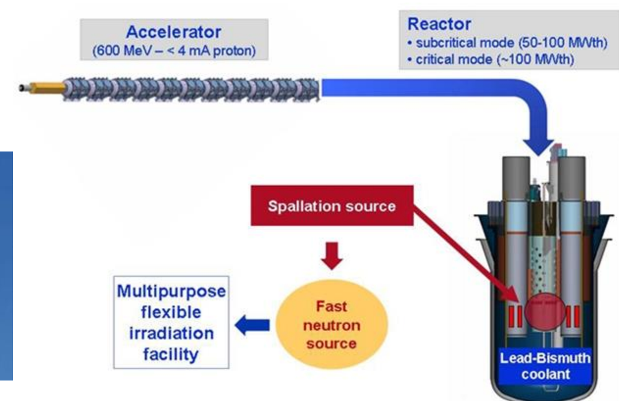
5. Conclusions



- Besides the already mentioned five reactors **BR2** (Belgium), **HFR** (The Netherlands), **MARIA** (Poland), **LVR-15** (Czech Republic) and **FRM-II** (Germany) which are providing irradiation services for medical radioisotopes production, the upcoming irradiation capacity of the **JHR** (France) reactor will be urgently needed for the mid-term but to maintain a European sustainable supply in the long-term, the replacement projects **HFR/PALLAS** and **BR2/MYRRHA** need to be materialized.

JHR

PALLAS



MYRRHA

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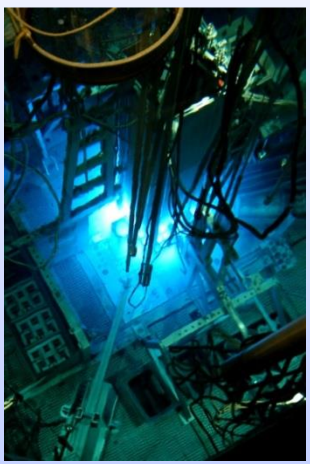

Thank you for your attention …

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Registered Office: Avenue Herrmann-Debrouxlaan 40 – BE-1160 BRUSSEL
Operational Office: Boeretang 200 – BE-2400 MOL