Medical Radioisotope Production
Where Next?

Eleodor Nichita
Faculty of Energy Systems & Nuclear Science
University of Ontario Institute of Technology

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CNS Toronto Branch

Nuclear Medicine

- Use of radioactive isotopes for diagnostic
- Use of radioactive isotopes for treatment

Definitions

- Z (atomic number) – Number of Protons in a nuclide
- N- Number of neutrons in a nuclide
- A (mass number)=Z+N
- Isobars – Nuclides with the same A
- Isotopes – Nuclides with the same Z
- Isotones – Nuclides with the same N
- Isomers – different energy states of the same nuclide
- Symbol: $^{A}_{Z}X$

Radioactive Decay

$$ {}^{A}_{Z}X \rightarrow {}^{A-m}_{Z-n}Y + {}^{m}_{n}P $$

(Parent Nucleus Daughter Nucleus + Emitted Particle)

- Common types of decay
  - Alpha (${}^{4}_{2}\alpha$), Helium nucleus emission
  - Beta (${}^{0}_{-1}\beta$), electron emission
  - Beta plus (${}^{0}_{1}\beta$) positron emission
  - Gamma (${}^{0}_{0}\gamma$), photon emission (no change in nuclear species)
  - Electron capture (an electron is "captured" rather than emitted)

Radioactive Decay

- Balancing the equation

$$^{11}_{5}B \rightarrow {}^{A}_{Z}X + {}^{4}_{2}\alpha$$

$$11 = A + 4$$

$$5 = Z + 2$$

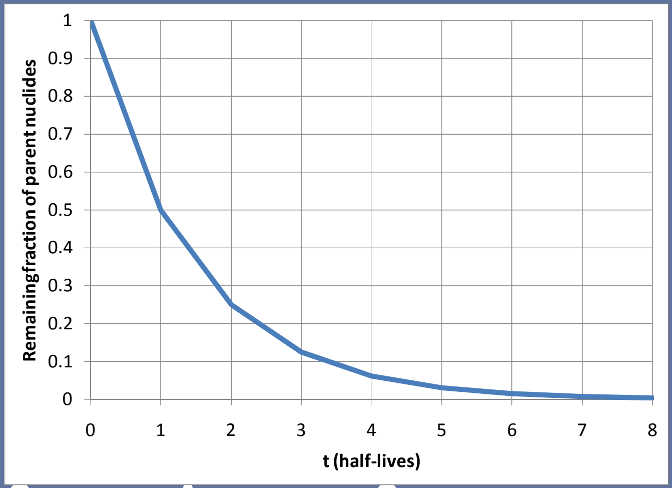
$$^{A}_{Z}X = {}^{7}_{3}Li$$

Radioactive Decay

- Remaining number of parent nuclides

$$N = N_0 \times e^{-\lambda(t-t_0)}$$

$$N = N_0 \times \frac{1}{2^{\frac{t-t_0}{T_{1/2}}}}$$



- λ Decay constant = fraction of radioactive nuclides decaying per unit time
- $T_{1/2} = \ln 2 / \lambda$ Half-life = time after which the number of parent nuclides is halved

Activity

- Number of decays per unit time

$$\Lambda = \lambda N$$

- 1dps = 1 Bq (Becquerel)
- 1Ci = $3.7\mathrm{x}10^{10}$ Bq

Medical Applications of Radioisotopes

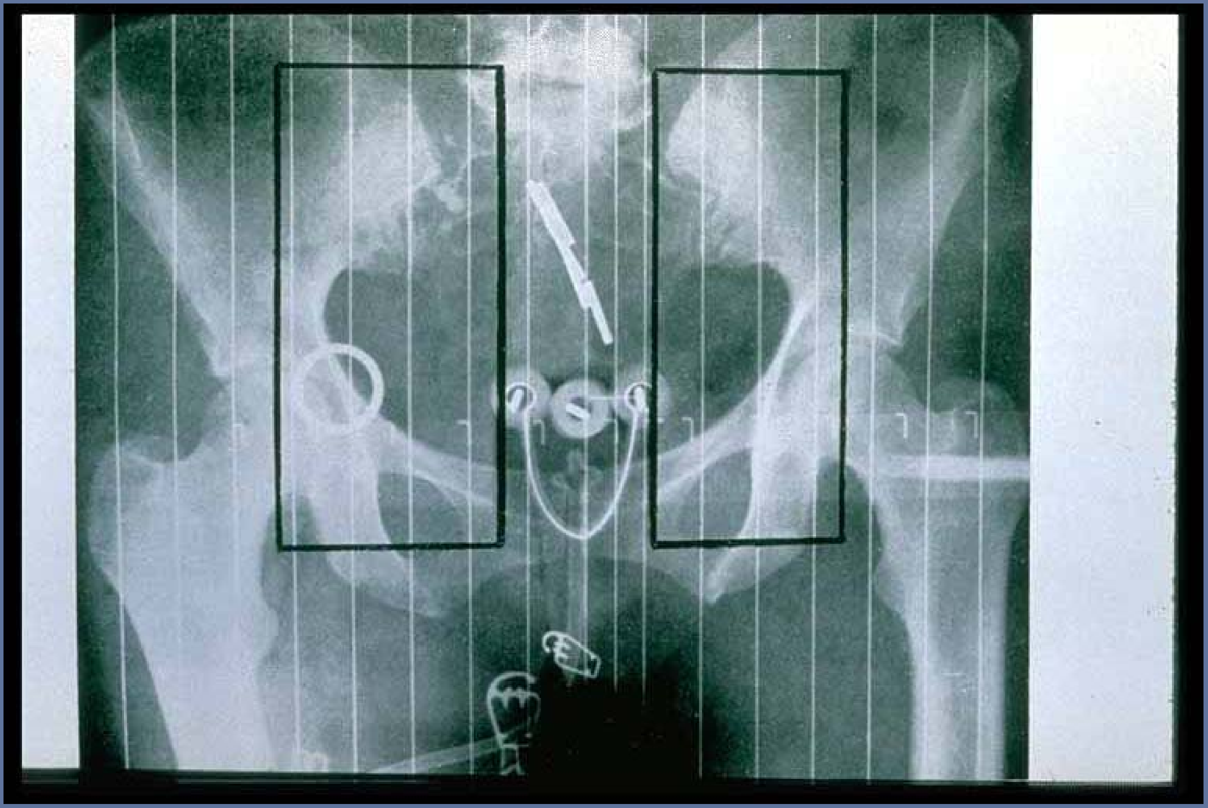
- Therapy
- Diagnostic (Imaging)

Radiotheraphy – Cancer Cell Killing by Ionizing Radiation

- ^{60}Co Tele-Therapy Unit (External Beam)

Brachytherapy

- Used for:
  - Uterus
  - Cervix
  - Prostate
  - Intraocular
  - Skin
  - Thyroid
  - Bone



Radioisotopes for Radiotherapy

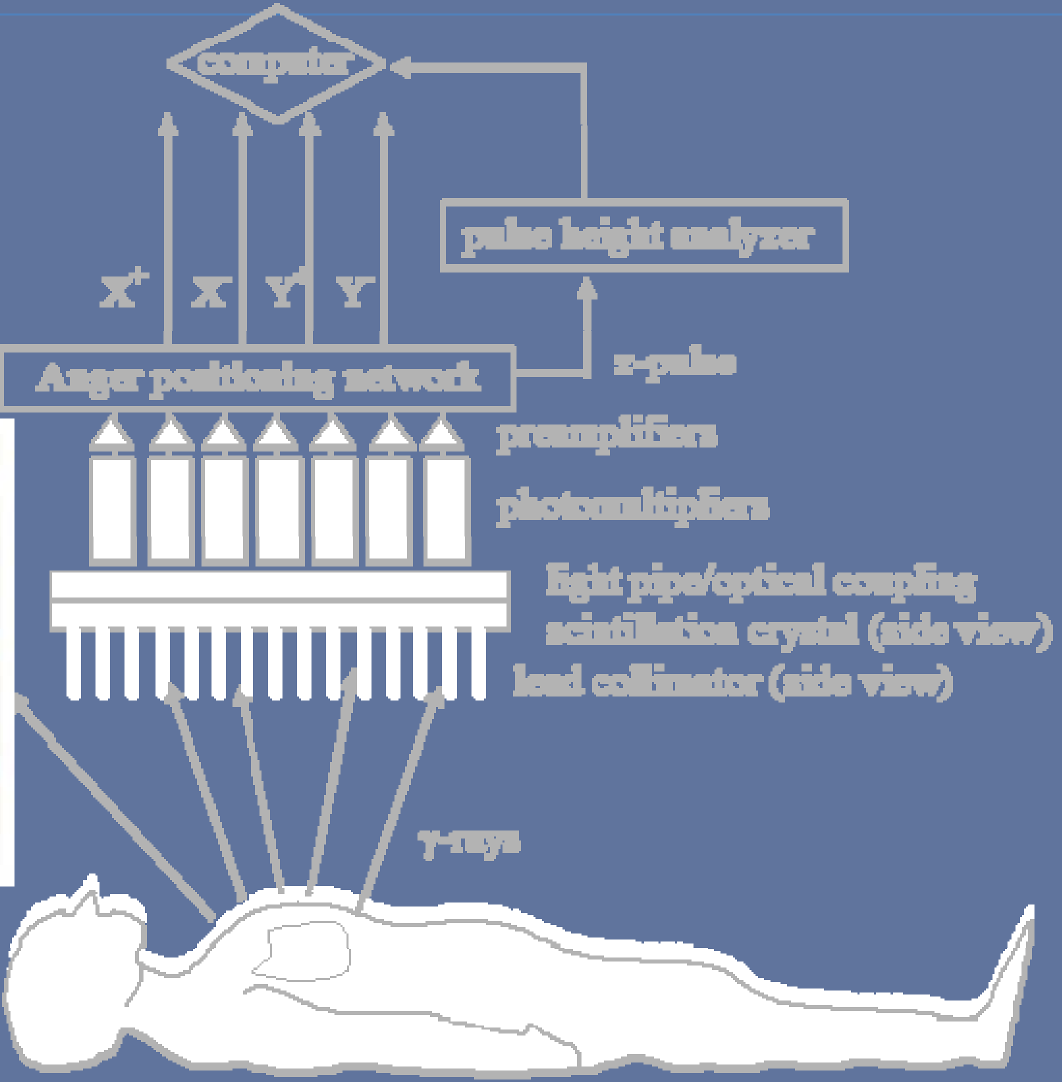
Isotope	avg. ph. energy (MeV)	Half-life
^{60}Co	1.25	5.26 y
^{131}I (thyroid)	0.364	8 d
^{137}Cs	0.66	30 y
^{198}Au	0.41	2.7 d
^{192}Ir	0.38	73.8 d
^{125}I	0.028	60 d
^{103}Pd	0.021	17 d

Nuclear Medicine Imaging

- Medical imaging technique that uses radioisotopes introduced into the patient's body (by ingestion, injection, or inhalation).
- Images do not depict the anatomical structure of the body.
- Images depict distribution of radiopharmaceutical, representative of biochemical processes.
- Radiopharmaceutical = Chemical Substrate + Radioactive Isotope
- Chemical substrate is chosen to identify specific pathology.
- Contrary to X-Ray CT, nuclear medicine maps the distribution of sources rather than that of the attenuation coefficient.

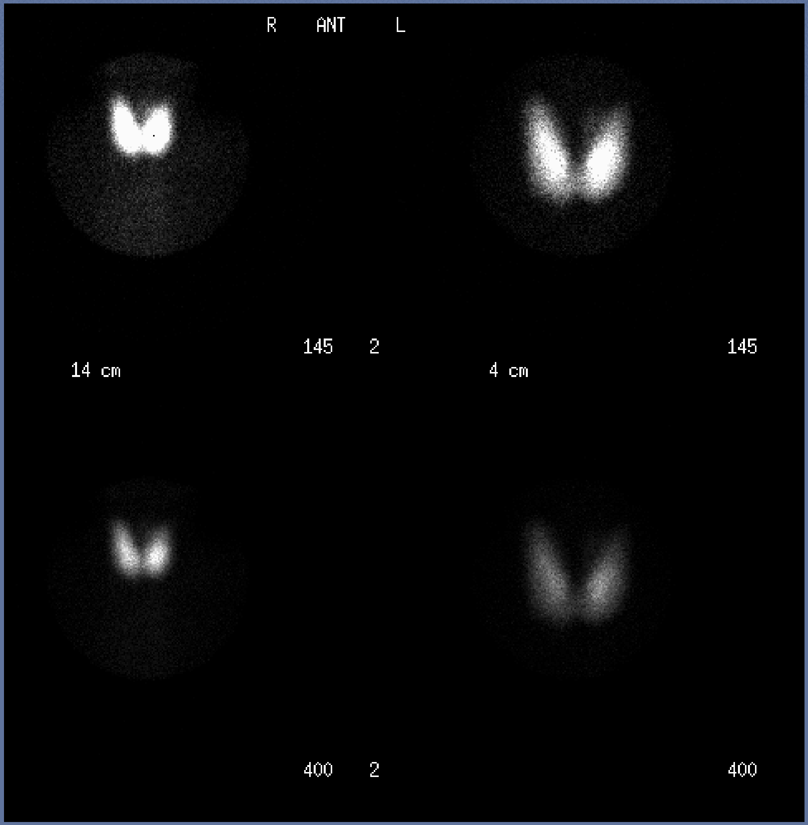
Nuclear Medicine Imaging

- NM Scan
- PET
- SPECT

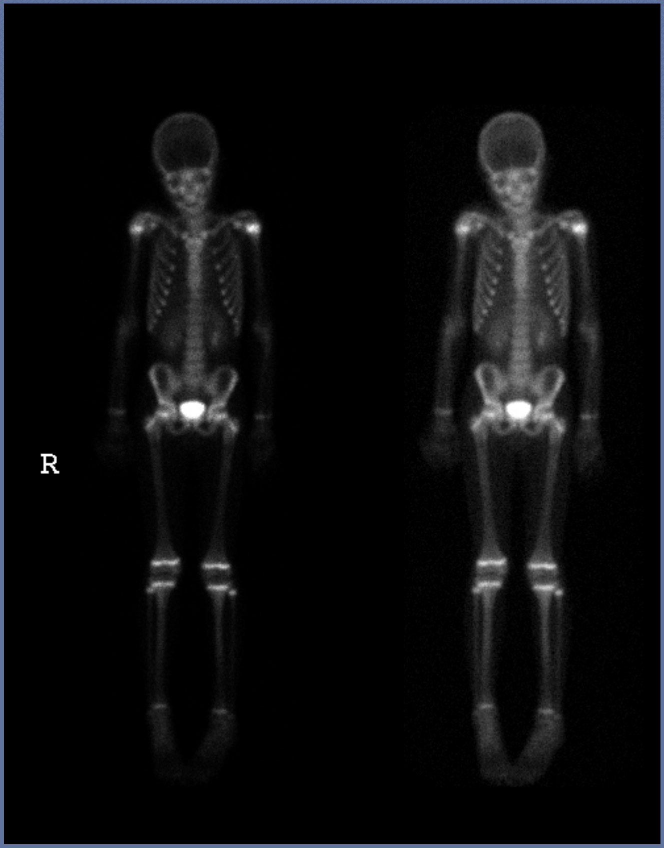


Nuclear Medicine Scan

Thyroid



Bone



Characteristics of Isotopes for Imaging

- Half-life long-enough to allow imaging procedure
- Half-life short-enough so there is little residual dose to the patient after the imaging procedure is finished.
- Gamma emitter with little or no beta or alpha emission (beta and alpha are absorbed in the patient and hence contribute to the dose, without contributing to image formation)

Radioisotopes for Imaging

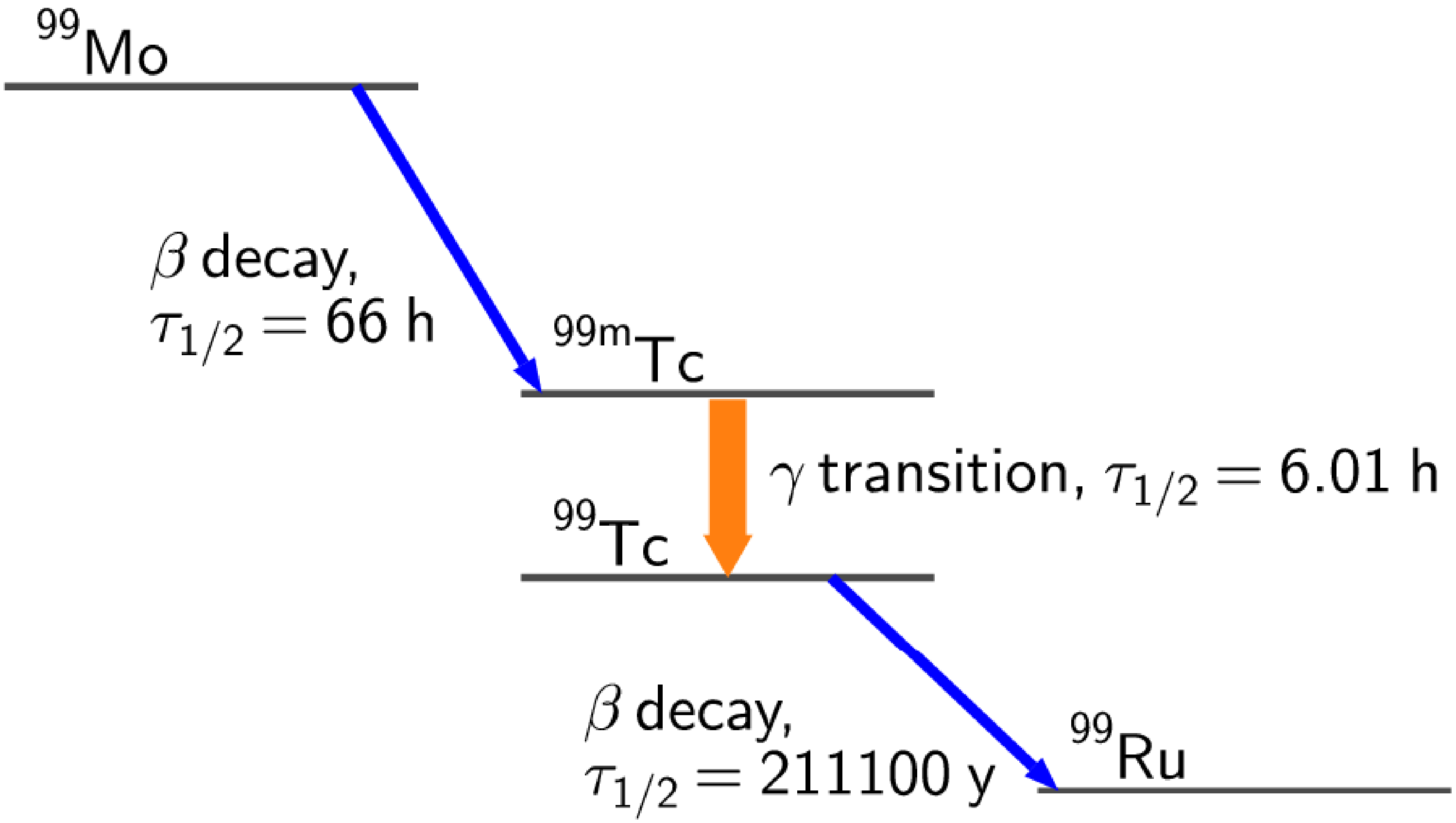
Radionuclide	Half-life	γ-ray Energy (keV)
^{99m}Tc	6.02h	140
^{67}Ga	3.2d	93, 185, 300, 394
^{201}Tl	3.0d	68-82
^{133}Xe	5.3d	81
^{111}In	2.8d	171, 245
^{131}I	8d	364
^{123}I	13h	159

^{99m}Tc

- Extremely versatile for diagnostic
- Combined with chemical substrate
- Substrate determines body distribution

Radiopharmaceutical	**Clinical Application**
^{99m}Tc-macroaggregated albumin	Pulmonary perfusion
^{99m}Tc-diphosphonate	Skeletal
^{99m}Tc-glucoheptonate	Brain tumors
^{99m}Tc-sulfur colloid	Liver and spleen, sentinel node location
^{99m}Tc-DTPA	Renal, pulmonary ventilation
^{99m}Tc-HMPAO	Brain perfusion
^{99m}Tc-Sestamibi	Myocardial perfusion
^{99m}Tc-MAG_3	Renal

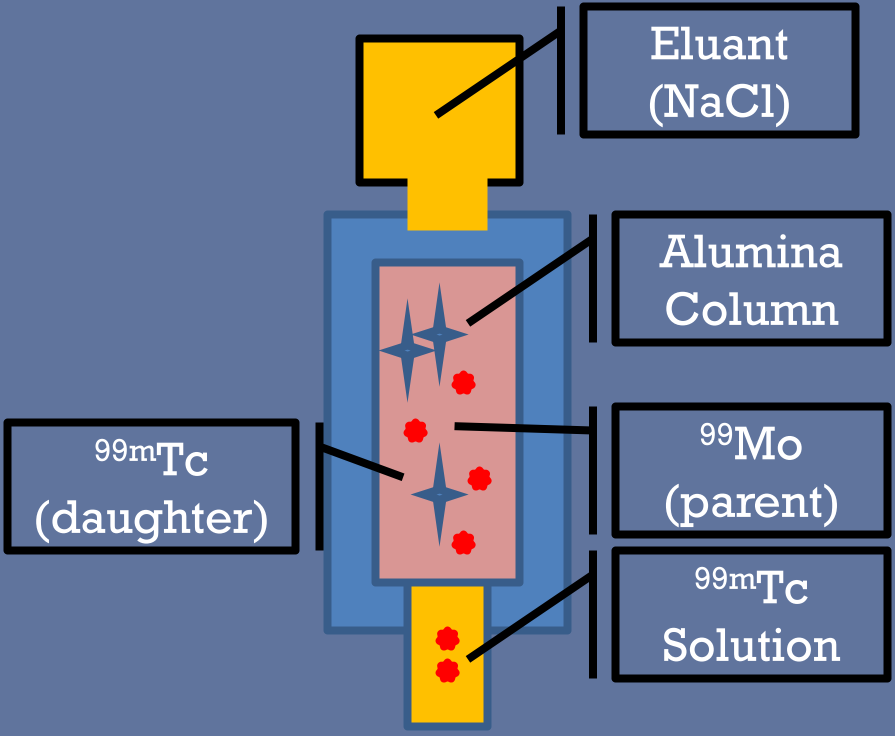
^{99m}Tc


^{99}Mo
β decay, $\tau_{1/2} = 66$ h
^{99m}Tc
γ transition, $\tau_{1/2} = 6.01$ h
^{99}Tc
β decay, $\tau_{1/2} = 211100$ y
^{99}Ru

^{99m}Tc Generator (Cow)

- ^{99}Mo is adsorbed in alumina column.
- ^{99}Mo decays into ^{99m}Tc
- ^{99m}Tc is eluted with saline .
- Subsequently, ^{99m}Tc is chemically combined with the substrate and given to the patient.
- When little ^{99m}Tc is left, Mo *breakthrough* occurs.

$$^{99}_{42}Mo \xrightarrow{T_{1/2}=66h} \beta^- + ^{99m}_{43}Tc$$



^{99m}Tc Generator (Cow)

- First generator (BNL)

- Modern generator

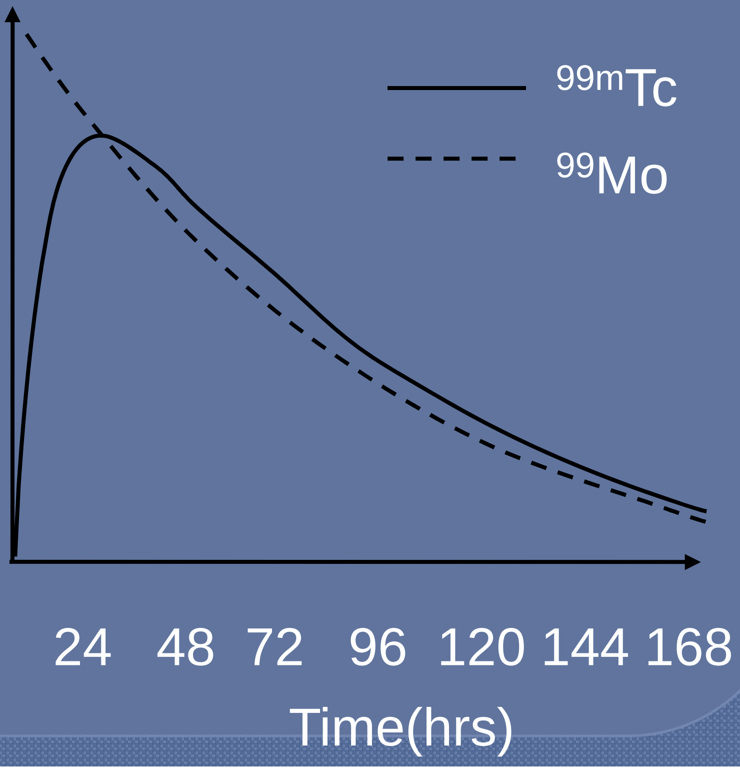
“Milking”

$$^{99}_{42}Mo \xrightarrow{\lambda_1=0.015h^{-1}} \beta^- + {}^{99m}_{43}Tc \xrightarrow{\lambda_2=0.166h^{-1}} \gamma + {}^{99}_{43}Tc$$

- ^{99m}Tc decays as it is being created
- ^{99m}Tc activity (transient equilibrium)

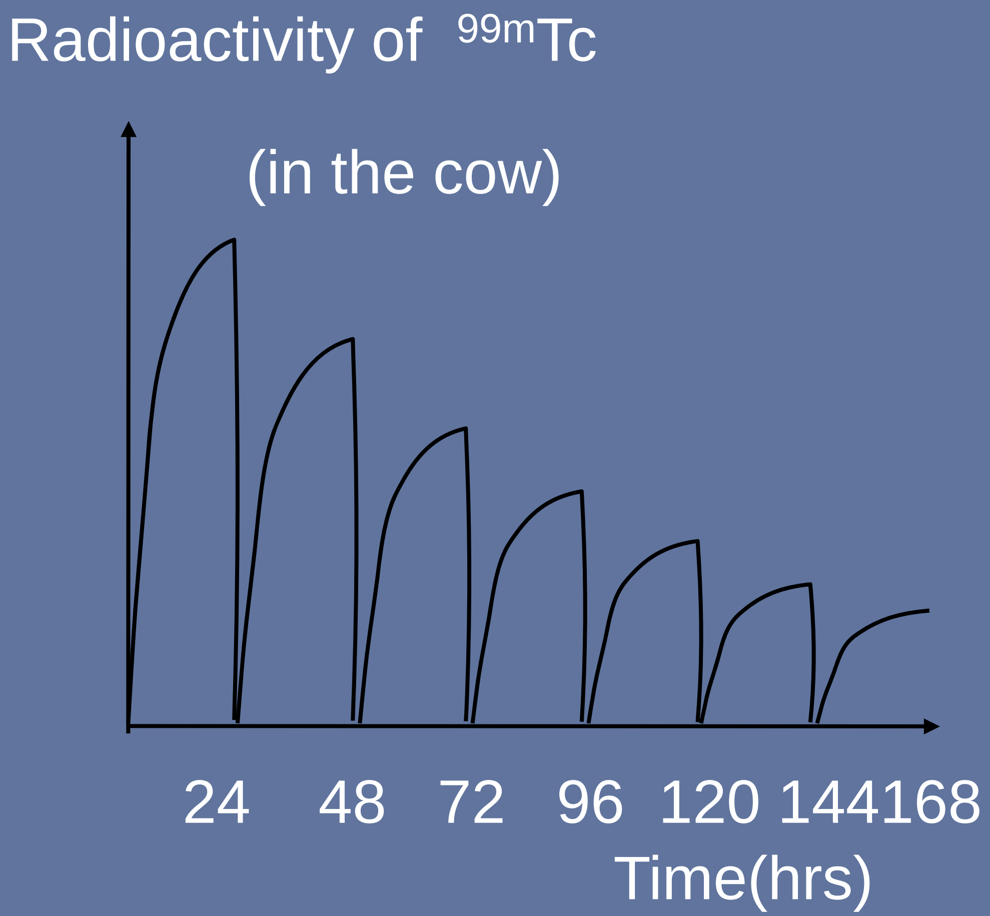
$$A_2 = \frac{\lambda_2 \lambda_1 N_0}{\lambda_2 - \lambda_1}\left(e^{-\lambda_1 t} - e^{-\lambda_2 t}\right)$$

- Once milked, ^{99m}Tc decays fast ($T_{1/2}$=6h)
- Needs to be produced (milked) on-site



Once a Day "Milking"

- After a week, the cow is exhausted.
- Weekly delivery schedule needed.
- ^{99}Mo half-life is 2.75 days, enough to allow transportation around the world.



The Physics of Isotope Production

- Production rate density

$$R_p \cong N_{T0}\sigma_p \eta \Phi$$

- Loss rate density

$$R_L = \lambda N_p$$

- Time evolution of fraction of target nuclei turned into product.

$$\frac{N_P(t)}{N_{T0}} \cong \frac{\sigma_p \eta \Phi}{\lambda}\left(1 - e^{-\lambda t}\right) = \frac{\sigma_p \eta \Phi}{\lambda}\left(1 - \frac{1}{2^{\frac{t}{T_{1/2}}}}\right)$$

The Physics of Isotope Production

- Saturation (production rate = loss rate)

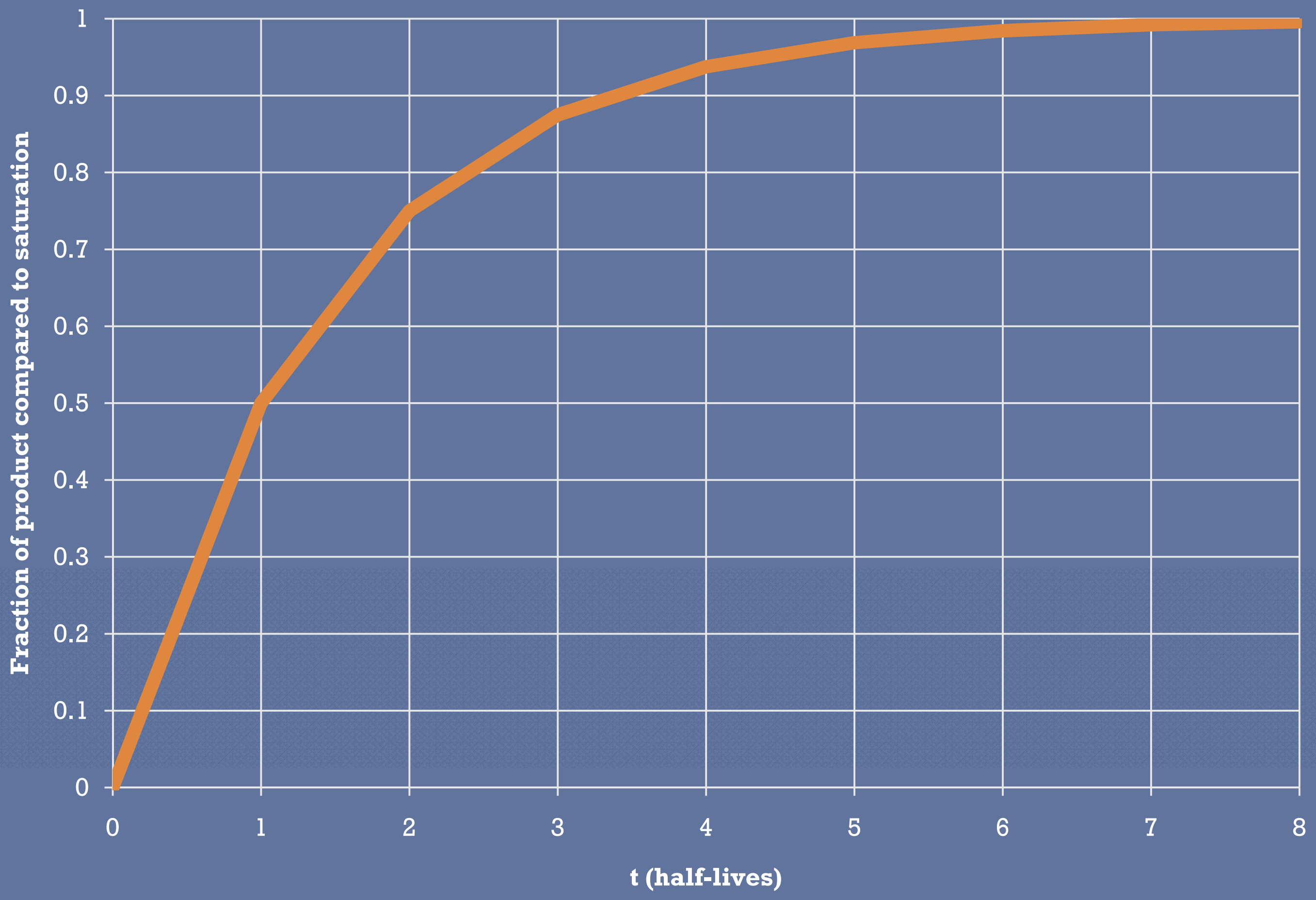
$$\frac{N_{sat}}{N_{T0}} = \frac{\sigma_p \eta \Phi}{\lambda}$$ occurs after approx. 5 $T_{1/2}$

- Saturation activity density

$$\Lambda_{d-sat} = \lambda N_{sat} = N_{T0} \sigma_p \eta \Phi = R_p$$

$$\Lambda_{d-sat} = \frac{\rho_{T0}}{A_{T0}} N_A \sigma_p \eta \Phi$$

Product Concentration Curve



The Physics of Isotope Production

- Irradiated Volume for Required Total Saturation Activity

$$V = \frac{\Lambda_{total}}{\Lambda_{d-sat}} = \frac{\Lambda_{total}}{R_p} = \frac{\Lambda_{total}}{N_{T0}\sigma_p \eta \Phi}$$

- Power production in the target at saturation

$$P = E_p R_P V = E_p \Lambda_{total}$$

^{99}Mo Production

- Neutron-induced Fission

$$ {}^{235}_{92}U + n \rightarrow {}^{99}_{42}Mo + {}^{133}_{50}Sn + 4n \quad (\sigma = 580b) $$

- Neutron Activation

$$ {}^{98}_{42}Mo + n \rightarrow {}^{99}_{42}Mo + \gamma \quad (\sigma = 0.13b) $$

- Accelerator (proton)

$$ {}^{100}_{42}Mo + p \rightarrow {}^{99}_{42}Mo + p + n \quad (\sigma = 0.1b) $$

- Photo-fission

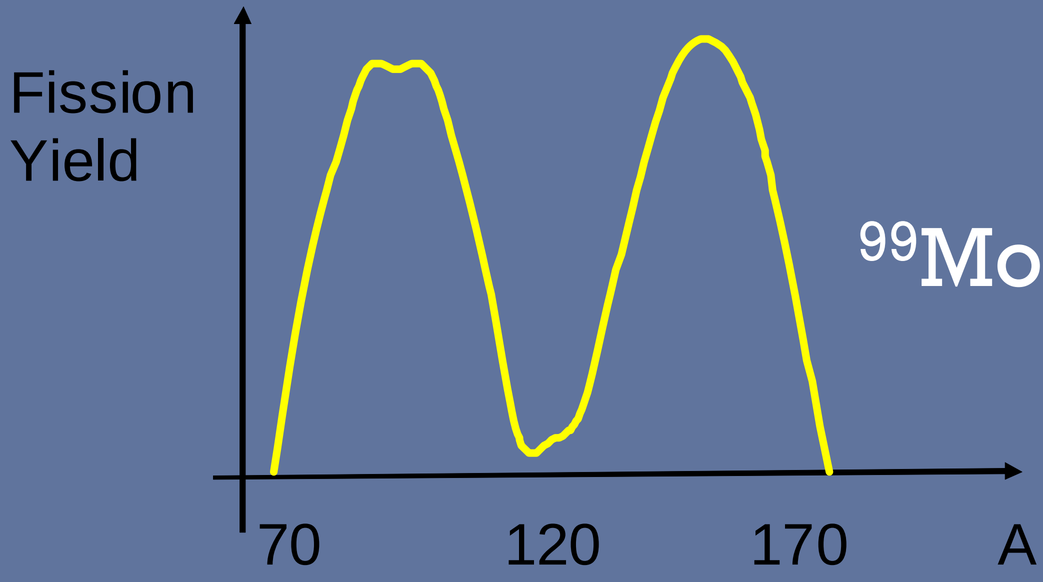
$$ {}^{238}_{92}U + \gamma \rightarrow {}^{99}_{42}Mo + {}^{133}_{50}Sn + 6n \quad (\sigma = 0.2b) $$

^{99}Mo Production by Neutron-Induced Fission in ^{235}U

- Reaction

$$^{235}_{92}U + n \rightarrow ^{99}_{42}Mo + ^{133}_{50}Sn + 4n \quad (\sigma = 580b)$$

- Fission Fragment Mass Distribution



^{99}Mo yield: 6.1%

^{99}Mo Production by Neutron-Induced Fission in ^{235}U

- Time-dependence of fraction of target nuclei turned into product (^{99}Mo)

$$\frac{N_P(t)}{N_{T0}} \cong \frac{\sigma_f \eta \Phi}{\lambda}\left(1 - \frac{1}{2^{\frac{t}{T_{1/2}}}}\right) \quad ; \quad \left[\eta = \eta_m \frac{235}{99}\right]$$

- Saturation occurs after approx. 5 half-lives, i.e. 2 weeks (no need to irradiate longer)

$$\frac{N_{sat}}{N_{T0}} = \frac{\sigma_f \eta \Phi}{\lambda}$$

Better to have high enrichment and high flux

^{99}Mo Production by Neutron-Induced Fission in ^{235}U

- Ratio of product/target nuclei (enrichm 50%)

$$\frac{N_{sat}}{N_{U0}} = \frac{N_{sat}}{N_{T0}/r} = \frac{r\sigma_f \eta \Phi}{\lambda} =$$

$$\frac{0.5 \times 580b \times 0.061 \frac{235}{99} \times 1.5 \times 10^{14} n/cm^2 - s}{2.92 \times 10^{-6} s^{-1}} =$$

$$0.0021$$

  - If natural U was used, then fraction = 0.00003
  - ^{99}Mo can be separated chemically since target consists of other species.

^{99}Mo Production by Neutron Activation of ^{98}Mo

- Reaction $^{98}_{42}Mo + n \rightarrow ^{99}_{42}Mo + \gamma \quad (\sigma = 0.13b)$
- Time-dependence of fraction of target nuclei turned into product (^{99}Mo)

$$\frac{N_P(t)}{N_{T0}} \cong \frac{\sigma_c \Phi}{\lambda}\left(1 - \frac{1}{2^{\frac{t}{T_{1/2}}}}\right)$$

- Saturation occurs after approx. 5 half-lives, 82% achieved after 2.5 half-lives

$$\frac{N_{sat}}{N_{T0}} = \frac{\sigma_c \Phi}{\lambda}$$

Better to have high flux

^{99}Mo Production by Neutron Activation of ^{98}Mo

- Ratio of product/target nuclei

$$\frac{N_{sat}}{N_{T0}} = \frac{\sigma_c \Phi}{\lambda} =$$

$$\frac{0.13b \times 1.5 \times 10^{14} n/cm^2 - s}{2.92 \times 10^{-6} s^{-1}} = 0.000007$$

- Impossible to separate, by simple chemical processes because same species

^{99}Mo Production by (p, pn) reaction

- Reaction $^{100}_{42}Mo + p \rightarrow {}^{99}_{42}Mo + p + n \quad (\sigma = 100mb)$
- Time-dependence of fraction of target nuclei turned into product (^{99}Mo)

$$\frac{N_P(t)}{N_{T0}} \cong \frac{\sigma_{p,pn}\Phi_p}{\lambda}\left(1 - \frac{1}{2^{\frac{t}{T_{1/2}}}}\right)$$

- Saturation occurs after approx. 5 half-lives, i.e. 2 weeks (no need to irradiate longer)

$$\frac{N_{sat}}{N_{T0}} = \frac{\sigma_{p,pn}\Phi_p}{\lambda}$$

Better to have high flux

^{99}Mo Production by Photon-Induced Fission in ^{238}U

- Time-dependence of fraction of target nuclei turned into product (^{99}Mo)

$$\frac{N_P(t)}{N_{T0}} \cong \frac{\sigma_{pf}\eta\Phi_{ph}}{\lambda}\left(1-\frac{1}{2^{\frac{t}{T_{1/2}}}}\right) \quad ; \quad \left[\eta = \eta_m \frac{235}{99}\right]$$

- Saturation occurs after approx. 5 half-lives, i.e. 2 weeks (no need to irradiate longer)

$$\frac{N_{sat}}{N_{T0}} = \frac{\sigma_{pf}\eta\Phi_{ph}}{\lambda}$$

Better to have high enrichment and high flux

Comments on ^{99}Mo production by (p,pn)

- (p,pn)

$$\frac{N_{sat}}{N_{T0}} = \frac{\sigma_{p,pn}\Phi_p}{\lambda}$$

- Cross section 0.1b, comparable to neutron activation.
- Needs intense proton flux over a large spatial region.

Comments on ^{99}Mo production by photofission in ^{238}U

- (p,pn)

$$\frac{N_{sat}}{N_{U0}} = \frac{(1-r)\sigma_{pf}\eta\Phi_{ph}}{\lambda}$$

- Cross section 0.2b vs. 580b for neutron-induced fission.
- Needs intense photon flux over a large spatial region.
- Photon production by Bremsstrahlung very inefficient.
- Can use natural U, with r=0.007

Estimated World Needs of ^{99}Mo

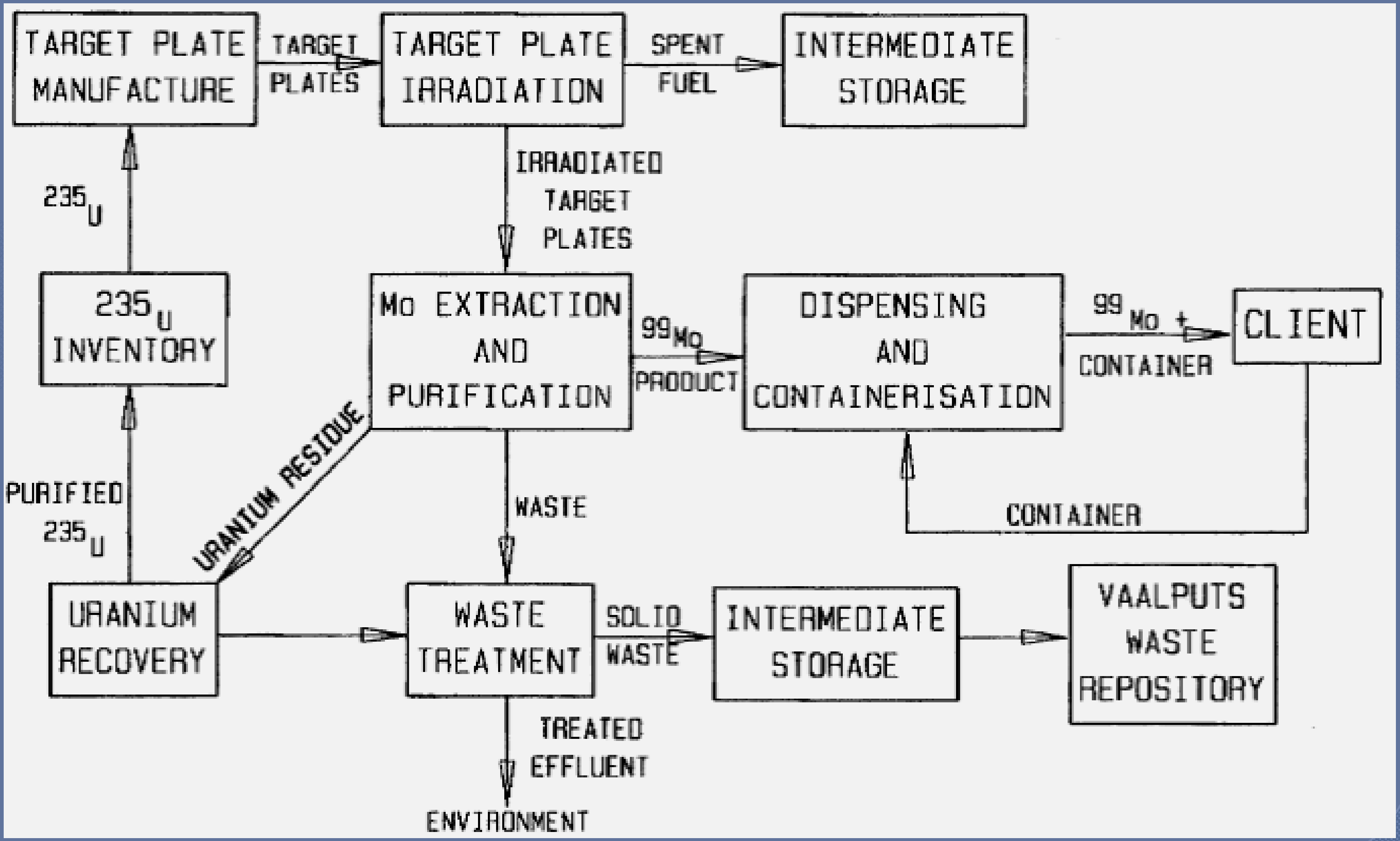
Region	6-day Ci / week	Ci / week
North America	6,000	28,000
South America	500	2,300
Japan	2,400	11,200
Europe	3,600	78,000
Rest of World	1,200	5,600
Total	13,700	64,000

- 1kW x 1 week -> 42 Ci
- Total power (in targets, allowing for 3 days processing) is approx. 3MW

^{99}Mo Production Reactors

- NRU, Chalk River, Canada
- HFR, Petten, The Netherlands
- SAFARI-1, Pelindaba, South Africa
- BR2, Mol, Belgium
- Osiris, Saclay, France

Reactor ^{99}Mo Production (SAFARI-1)



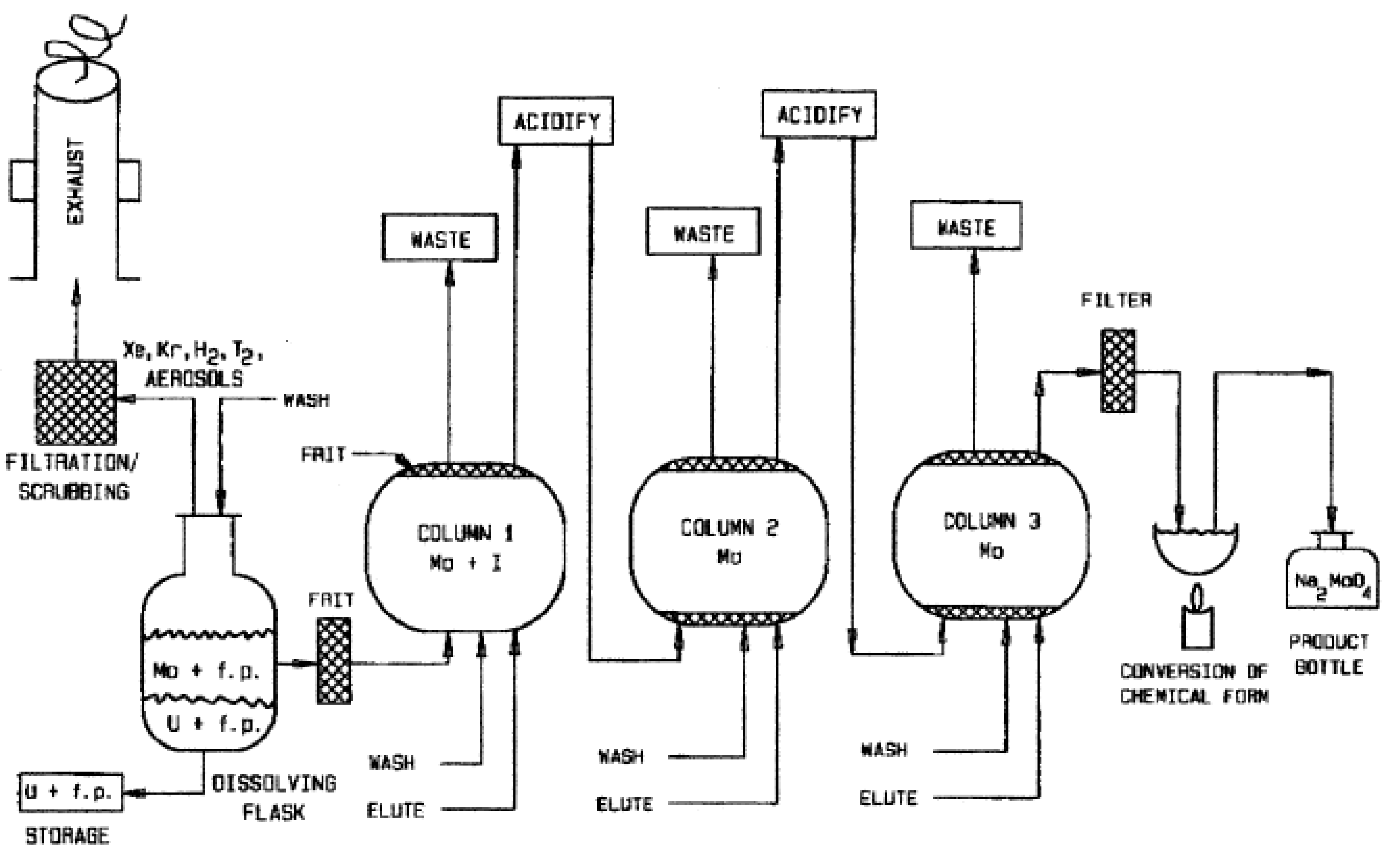
Targets (SAFARI-1)

- Uranium/Aluminum alloy (45% ^{235}U)
- Clad in Aluminum.
- 4.2 g ^{235}U in each 200 mm × 45 mm target plate
- 6 irradiation positions x 7 plates each
- Irradiation time up to 8 days @ 1.5E14 n/cm^{2}-s.
- ^{99}Mo activity per plate at 8 days
  - approx 500Ci

Chemical Processing (SAFARI-1)

- Irradiated target plates dissolved in concentrated NaOH.
  - Nuclides of only few elements are dissolved with Mo
- Purification (two anion exchange resins and one chelating resin)
  - sorption of Mo
  - washing to remove residual source solution
  - elution of Mo
  - eluate from the third column is filtered, evaporated to dryness, and re-dissolved in 0.2 M NaOH to convert to sodium molybdate (Na_2MoO_4).

Chemical Processing (SAFARI-1)



Chemical Processing (hot cells)

- dissolver cell
  - dissolution vessel for irradiated target plates
  - first ion exchange column
  - waste tanks
- purification cell
  - second and third purification columns
- filtration cell
  - evaporator and other equipment for the filtration sampling and bottling of the ^{99}Mo solution;
- dispensing cell
  - ionization chamber for the quantification of the product
- packaging cell
  - product bottles placed into transport containers

^{99}Mo Product

- Purity (radionuclide)
  - ^{131}I/99Mo < 5 × 10-5
  - ^{103}Ru/99Mo < 5 × 10-5
  - ^{89}Sr/99Mo < 6 × 10-7
  - ^{90}Sr/99Mo < 6 × 10-8
  - other alpha/99Mo < 1 × 10-9
  - other beta/99Mo < 1 × 10-4
- Radiochemical purity
  - >95% as Na_2MoO_4)
- Activty
  - >1 Ci/cm^3 at calibration time.
- Product solvent
  - 0.2 M NaOH,
- Calibration date
  - 3 to 7 days after shipment to the customer.
- Shelf-life
  - 7 days after the calibration date.

SAFARI-1 Reactor, Pelindaba, South Africa

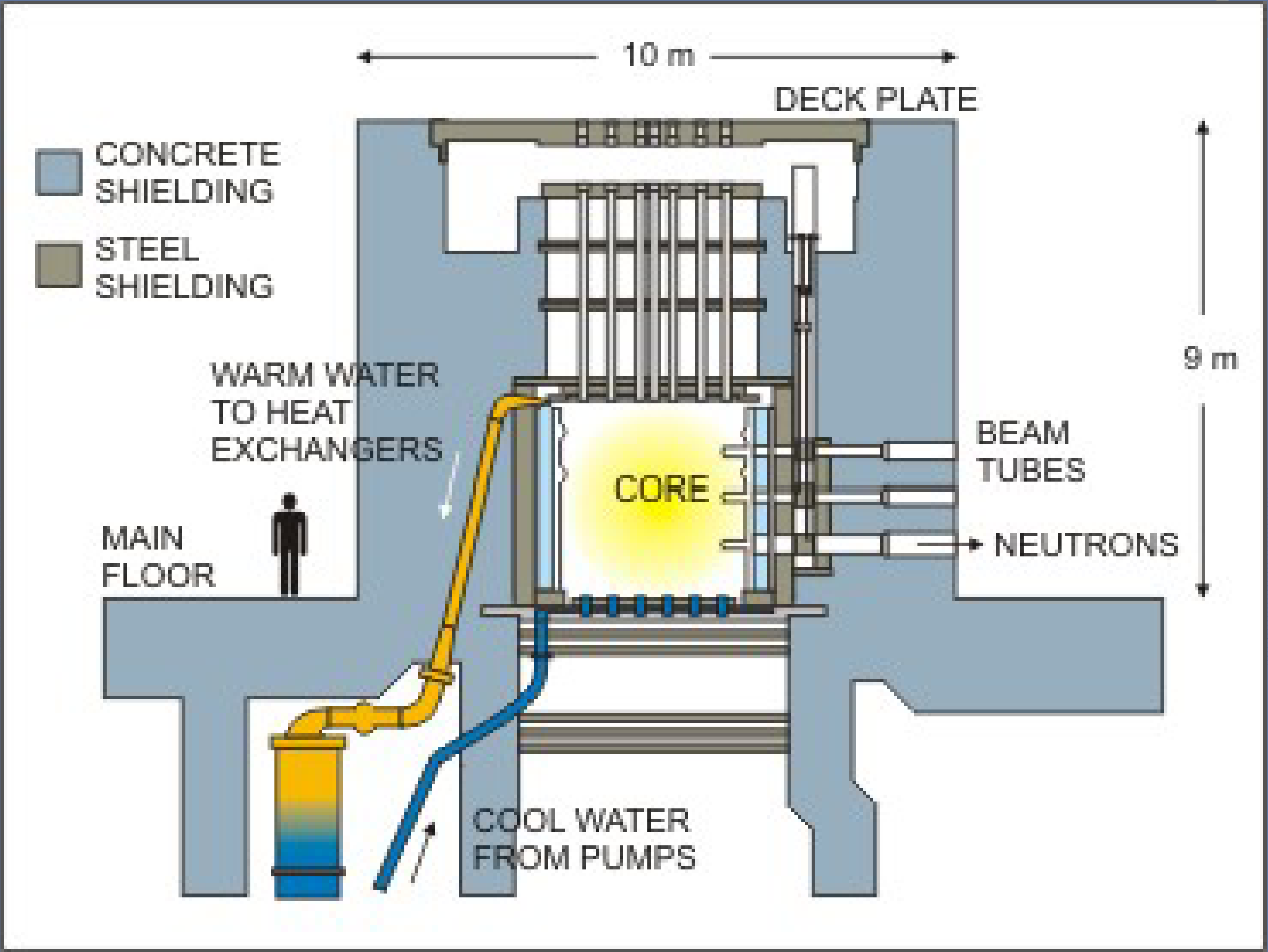
- Oak Ridge Design
- 20 MW
- In service since 1965

NRU

- **N**ational **R**esearch **U**niversal
- Power
  - 130MW
- Coolant
  - Heavy water
- Moderator
  - Heavy water
- Vertical fuel channels
- In service since 1957

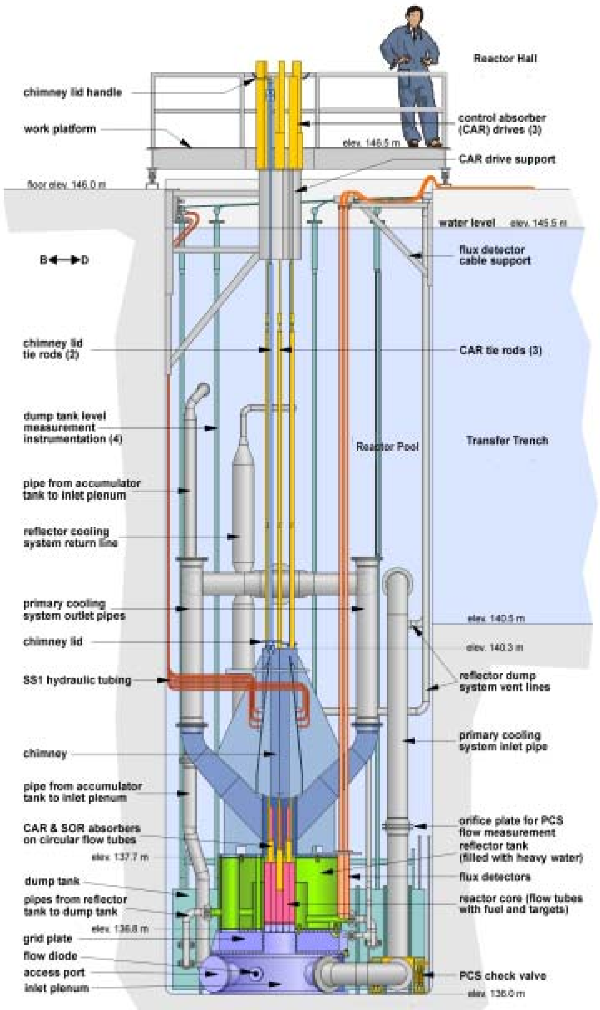
NRU

NRU


10 m
DECK PLATE
CONCRETE SHIELDING
STEEL SHIELDING
WARM WATER TO HEAT EXCHANGERS
9 m
BEAM TUBES
CORE
NEUTRONS
MAIN FLOOR
COOL WATER FROM PUMPS

MAPLE

- **M**ultipurpose **A**pplied **P**hysics **L**attice **E**xperiment
- Type
  - Open-tank-in-pool
- Thermal power
  - 10 MW
- Coolant
  - Light water
- Reflector
  - Heavy water
- Fuel material



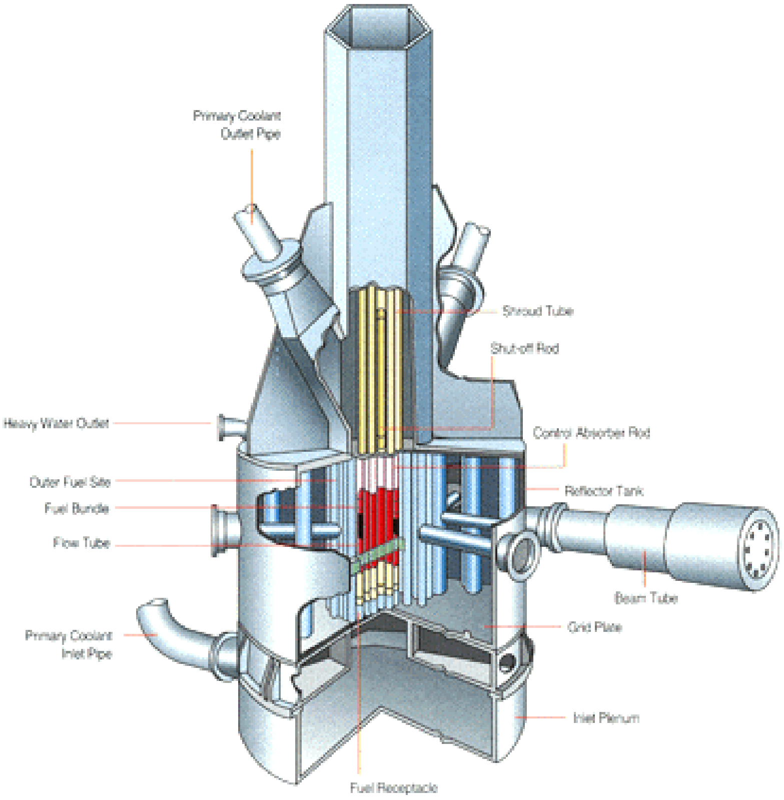
MAPLE reactor

MAPLE 2 80% Power

- First criticality, 2003-10-09

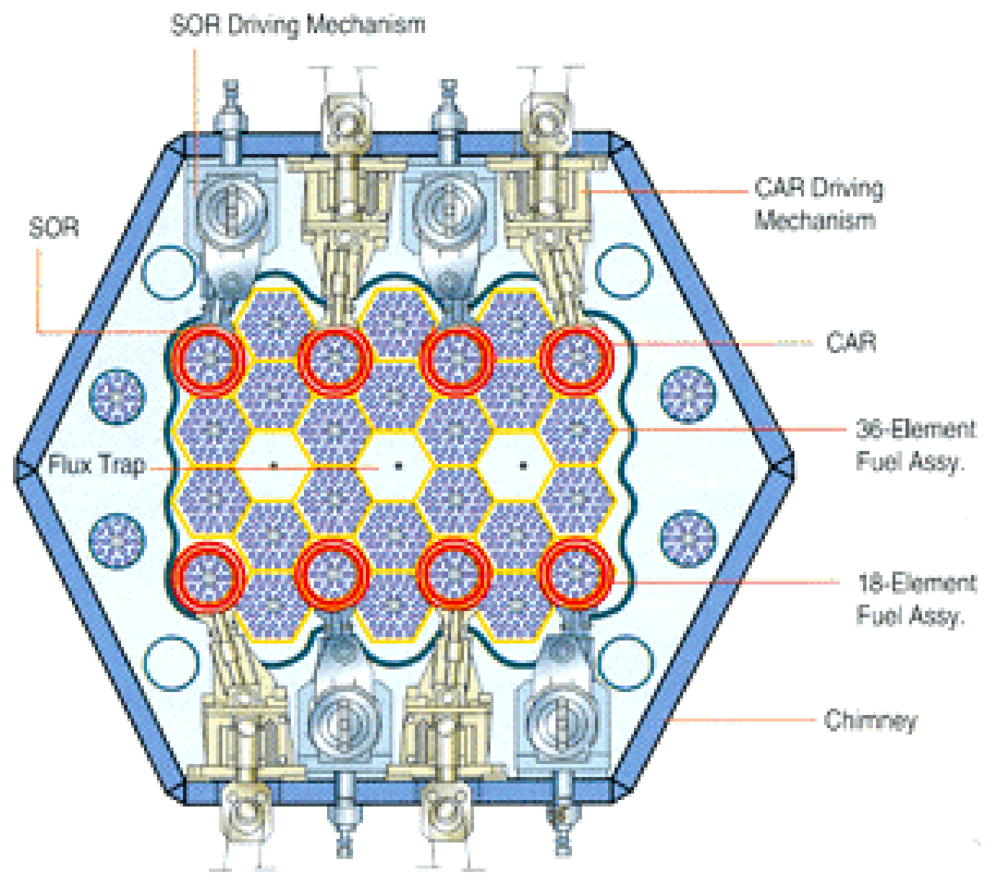
HANARO (MAPLE Design)

- **H**igh-flux **A**dvanced **N**eutron **A**pplication **R**eactor
- Type
  - Open-tank-in-pool
- Max thermal power
  - 30 MW
- Coolant
  - Light water
- Reflector
  - Heavy water
- Fuel
  - U_3Si_2 in aluminum matrix, 19.75% enriched
- Absorber material
  - Hafnium
- Secondary cooling
  - Cooling tower
- In service since 1995



Reator structure assembly

HANARO


SOR Driving Mechanism
SOR
CAR Driving Mechanism
CAR
36-Element Fuel Assy.
Flux Trap
18-Element Fuel Assy.
Chimney

HANARO Fuel

HANARO fuel assemblies, 36-element hexagonal fuel assembly and 18-element circular fuel assembly, with three spacers on each fuel assembly.

The Trouble with Chalk River MAPLEs

- A thing called Power Reactivity Coefficient (PCR)
- Calculations predicted a small, negative PCR.
- Commissioning measurements found a small positive PCR.
- WHY?!

Remember Engineering?

- Engineering is the art of modelling materials we do not wholly understand, into shapes we cannot precisely analyse, so as to withstand forces we cannot properly assess, in such a way that the public has no reason to suspect the extent of our ignorance.
- I.E. Design so that it works without requiring exact knowledge.

Chalk River MAPLEs

- Small positive or negative PCR is insignificant in the big scheme of things.
- Nice to know why the prediction was off (More knowledge doesn't hurt.)
- So, again, Why?
- According to HS, 3 possibilities:
  - bowing target
  - bowing fuel elements
  - heating of water between reflector wall and flow tubes
- 3 tests necessary to elucidate the cause
- Plug pulled after first 2, on May 16, 2008.

Realistically Speaking

- Reactor production of ^{99}Mo by fission only one economical at this point.
- Accelerator-based methods are not economical.
- World in dire need of medical radioisotopes.
- Market will bear a slightly higher price to amortize additional expenses with MAPLE reactors.

Conclusion

- Restart of MAPLEs best solution.
- If not:
  - CANDUs
  - Some research reactors (McMaster)
  - New Reactors for Isotope Production
    - Annular Core Research Reactor (ACRR) Sandia
  - (Currently) exotic methods
    - Photofission
    - Proton activation
    - Fission in accelerator-driven systems

References

- ^{99}Mo Production process reproduced from: IAEA-TECDOC-1340 Manual for reactor produced radioisotopes
- Images of reactors reproduced from respective reactors' web sites and the Canadian Nuclear FAQ.