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Nuclear Data for Medical Radionuclide Production: Present Status and Future Needs

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Outline

- **Introduction**
- **Commonly used radionuclides**
  - status of nuclear data
  - standardisation of production data
- **Research oriented radionuclides**
  - non-standard positron emitters
  - novel therapeutic radionuclides
- **Changing trends in production and application**
  - alternative routes for production of ^{99m}Tc
  - new directions in radionuclide applications
- **Future data needs**
- **Summary and conclusions**

Nuclear Data Research for Radionuclide Applications

Aim

- Provide database for optimum production and application of radionuclides
  - remove discrepancies in existing data
  - search alternative production routes of established radionuclides
  - develop novel radionuclides

Areas of work

- Experimental measurements
- Nuclear model calculations
- Standardisation and evaluation of data

Considerable effort is invested worldwide in nuclear data research

Decay Data of Medical Radionuclides

- Choice of a radionuclide depends on decay data

Considerations: - suitability for imaging

- radiation dose

Demands:

Diagnosis: minimum dose (γ or β^+ emitters)

Therapy: suitable localised dose (β^- or α-particle emitters)

- Status of decay data good; occasional discrepancies in
  - weak γ-ray intensities
  - β^+ emission branching
  - Auger electron spectra

Major references

MRID: Radionuclide Data and Decay Schemes (2007)

NNDC: Evaluated Decay Data Files

Nuclear Reaction Data

Aim

- **Optimisation of production procedure**
  - maximise product yield
  - minimise radioactive impurity level

Types of data

- **Neutron data for production in a nuclear reactor,** e.g.

  (n,γ), (n,f) and (n,p) reactions

- **Photonuclear data for production at an accelerator,** e.g.

  (γ,n) and (γ,p) reactions

- **Charged particle data for production at a cyclotron,** e.g.

  p, d, ^{3}He- and α-particle induced reactions

Radionuclides Commonly used in Nuclear Medicine

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Diagnostic Radionuclides

- **For SPECT**

  γ-emitters (100 – 250 keV)

  ^{99m}Tc, ^{123}I, ^{201}Tl

(used worldwide)

- **For PET**

  β^+ emitters

  ^{11}C, ^{13}N, ^{15}O, ^{18}F,

  ^{68}Ge (^{68}Ga), ^{82}Sr (^{82}Rb)

  (fast developing technology)

Therapeutic Radionuclides (in-vivo)

- β^--emitters (^{32}P, ^{90}Y, ^{131}I, ^{153}Sm, ^{177}Lu)
- α-emitter (^{211}At)
- Auger electron emitters (^{111}In, ^{125}I)
- X-ray emitter (^{103}Pd)

(increasing significance)

Status of nuclear data is generally good

Standardisation of Production Data

- Neutron data extensively evaluated, mainly for energy research; also useful in reactor production of radionuclides
-
- Charged particle data evaluation methodology is developing, mainly co-ordinated by IAEA. It involves

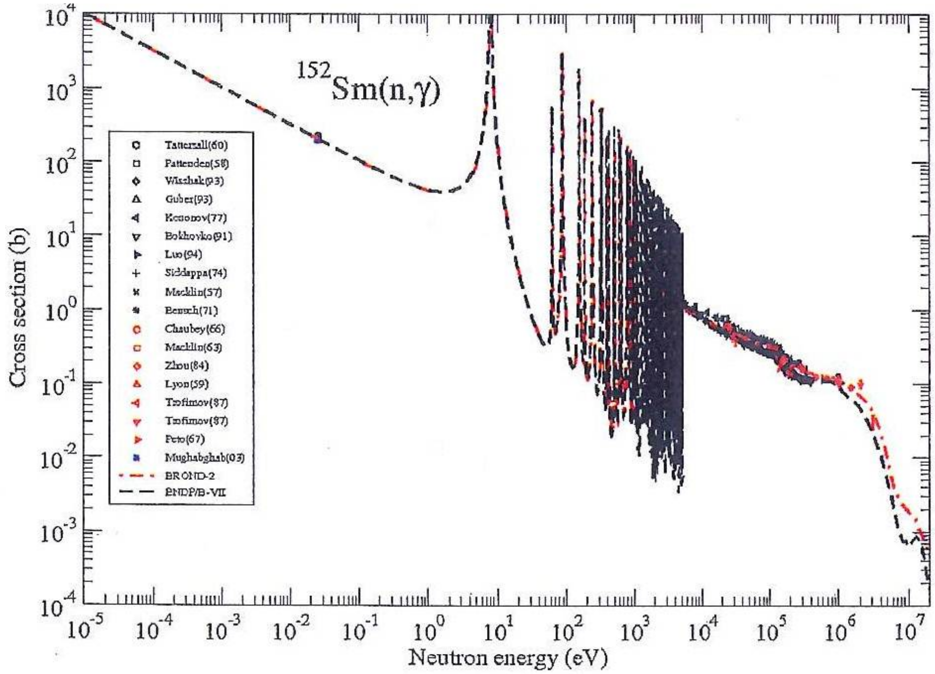
  - compilation of data (EXFOR)
  - normalisation of data (decay data, monitor cross section, etc.)
  - nuclear model calculation
  - statistical fitting of data

Role of nuclear model calculations

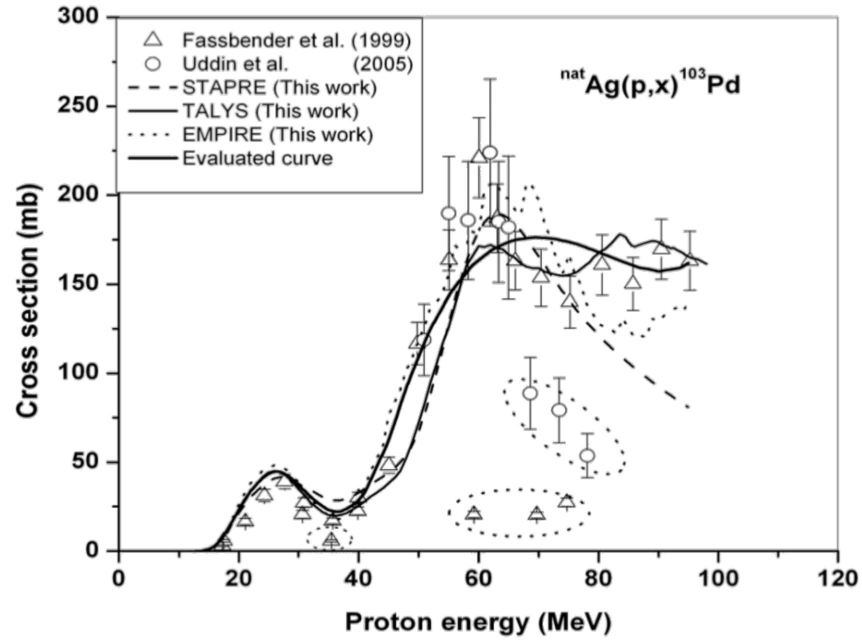
- Validation of experimental data
- Guidance in rejection of inaccurate data
- Prediction of unknown data

Examples of Evaluated Data

$^{152}Sm(n,\gamma)^{153}Sm$ Qaim et al., IAEA-Technical Report – 473 (2011)



$^{nat}Ag(p,x)^{103}Pd$ Hussain et al., ARI **67**, 1842 (2009)



- Neutron data generally well evaluated
- Evaluation of charged particle data partially successful
  (often based on data fitting procedures)

Evaluated Data for Production of Commonly used Radionuclides

Diagnostic radionuclides

Gul, Hermanne, Mustafa, Nortier, Oblozinsky, Qaim (Chairman), Scholten, Shubin, Takács, Tárkányi, Zhuang,
IAEA-TECDOC-1211(2001); pp. 1 - 285

Therapeutic radionuclides

Qaim, Tárkányi, Capote (Editors),
IAEA Technical Report Series No.473 (2011); pp. 1 - 358

Evaluation of data for production of emerging radionuclides is continuing

Research Oriented Radionuclides

- Non-standard positron emitters
  - to study slow metabolic processes
  - to quantify targeted therapy

- Novel low-range highly ionising radiation emitters for internal radiotherapy
  - for targeted therapy

Emphasis is on metal radionuclides

Production Routes of ^{64}Cu

Nuclear process	Optimum energy range [MeV]	Thick target yield [MBq/µA·h]
^{64}Ni(p,n)^{64}Cu a)	12 → 8	304
^{64}Ni(d,2n)^{64}Cu a)	17 → 11	430
^{68}Zn(p,αn)^{64}Cu a)	30 → 21 b)	116
^{66}Zn(p,2pn)^{64}Cu a)	52 → 37	316
^{64}Zn(d,2p)^{64}Cu a)	20 → 10	27.1
^{66}Zn(d,α)^{64}Cu a)	13 → 5	13.8
^{nat}Zn(d,x)^{64}Cu	25 → 10 c)	57.0

a) Using highly enriched target material, low enrichment leads to impurities

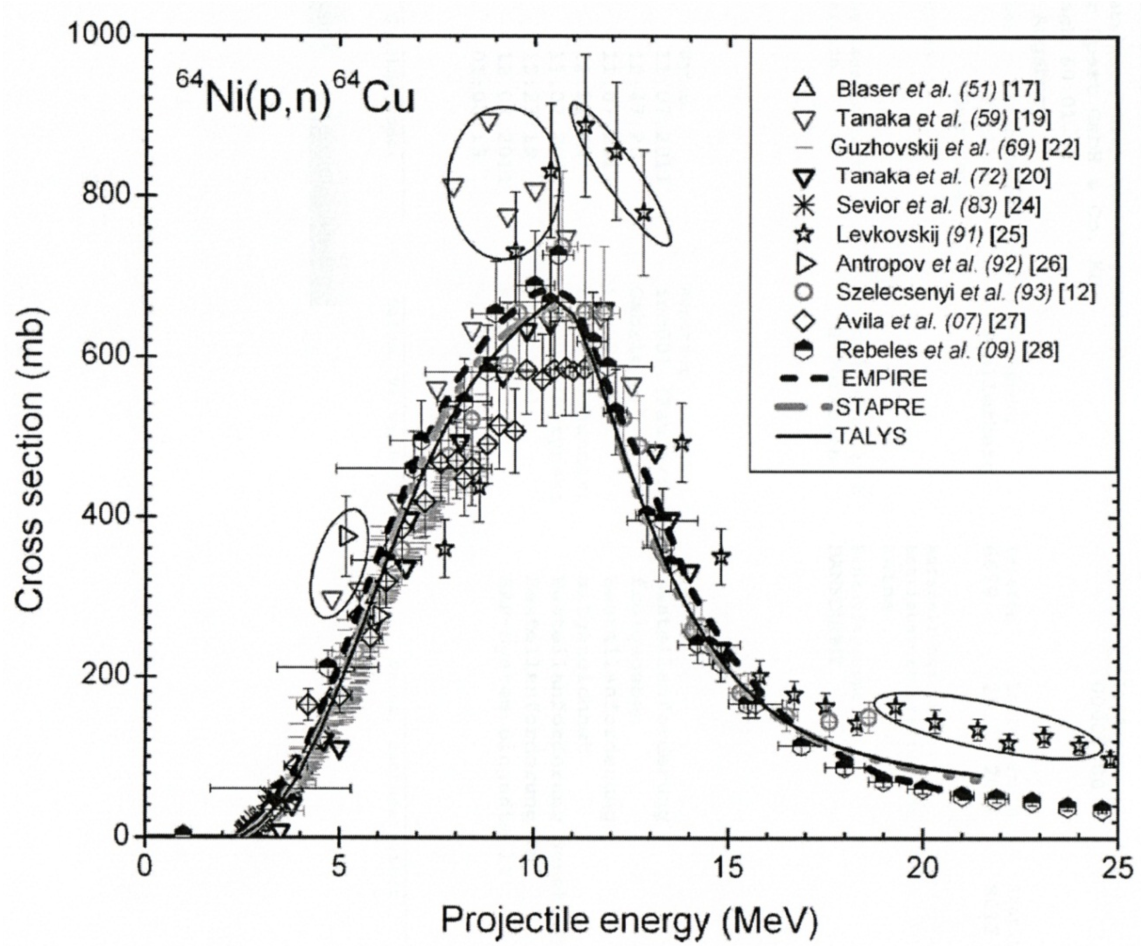
b) Below threshold of ^{67}Cu impurity via the ^{68}Zn(p,2p)^{67}Cu reaction

c) Below thresholds of ^{61}Cu and ^{67}Cu impurities via the ^{64}Zn(d,αn)^{61}Cu and ^{68}Zn(d,2pn)^{67}Cu reaction, respectively

Extensive studies performed at Brussels, Cape Town, Debrecen, Jülich and Segrate

For review cf. Aslam et al., RCA **97**, 669 (2009)

Excitation Function of $^{64}Ni(p,n)^{64}Cu$ Reaction



Production method developed at Jülich (1993)

Data evaluated by
Aslam et al, RCA **97**, 669 (2009)

Optimum energy range for production of ^{64}Cu

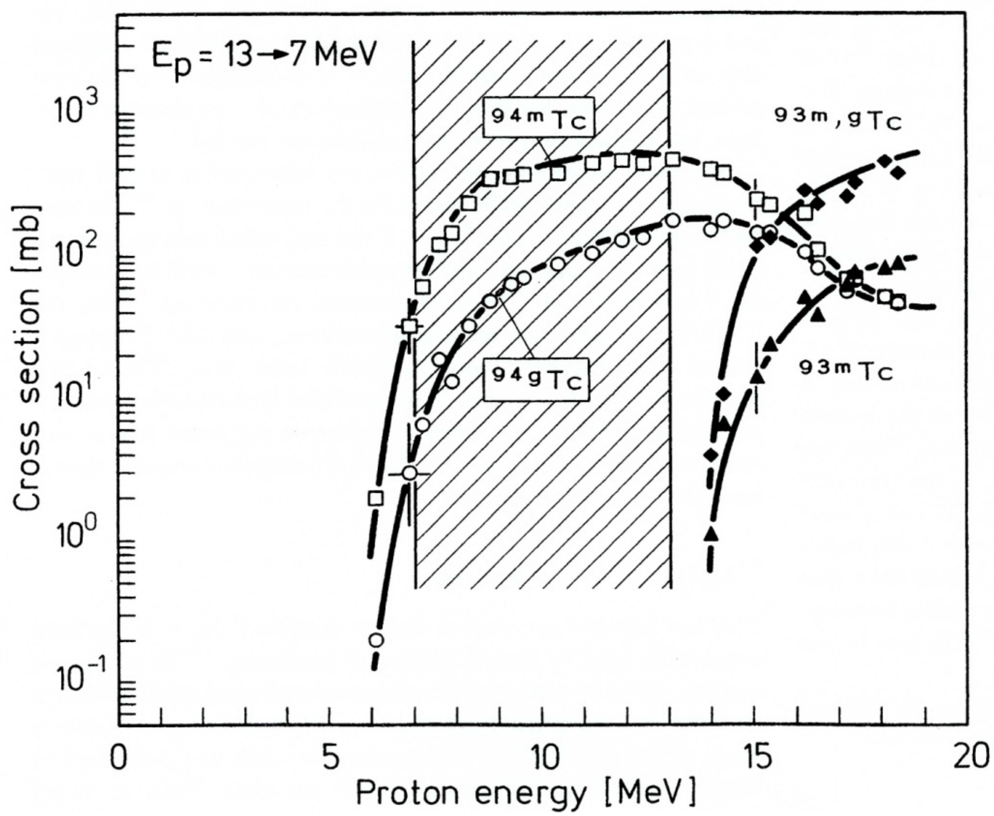
E_p: 12 → 8 MeV
Yield: 304 MBq/µAh

Radionuclide useful for PET

Formation of Isomeric States

- Occasionally unavoidable isomeric impurity
- Level depends mainly on type of reaction

Example : ^{94}Mo(p,n)^{94m,g}Tc



Qaim, NMB **27**, 323 (2000).

^{94g}Tc impurity in ^{94m}Tc

^{94}Mo(p,n)	: 6%
^{93}Nb(^{3}He,2n)	: 25%
^{92}Mo(α,pn)	: 30%

Extensive investigations mandatory

For theoretical discussion,
cf. Strohmaier et al.,
Phys. Rev. C 56, 2654 (1997).

Novel Positron Emitters for Medical Applications Produced via Low Energy Reactions (E ≤ 20 MeV)

Qaim, RCA **99**, 611 (2011)

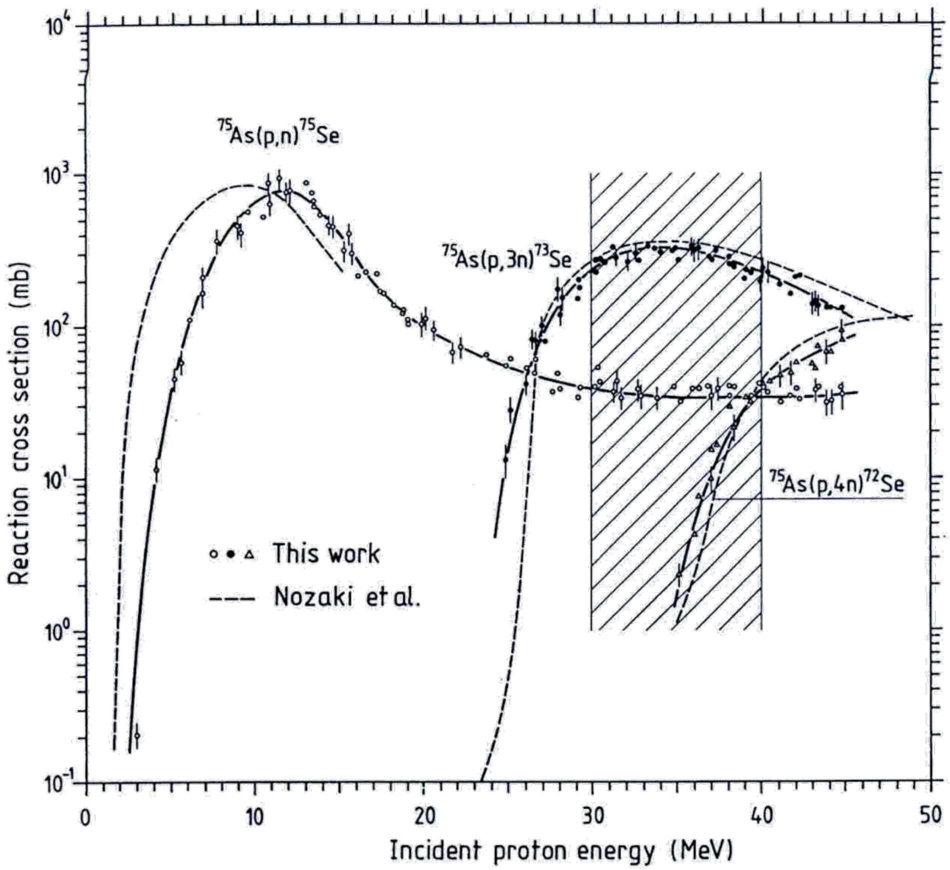
Nuclide	Major production route	Energy range [MeV]	Application
^{55}Co (17.6 h)	^{58}Ni(p,α) ^{54}Fe(d,n)	15 $\rightarrow$ 7 10 $\rightarrow$ 5	Tumour imaging; neuronal Ca marker
^{64}Cu (12.7 h)	^{64}Ni(p,n)	14 $\rightarrow$ 9	Radioimmunotherapy
^{66}Ga (9.4 h)	^{66}Zn(p,n)	13 $\rightarrow$ 8	Quantification of SPECT
^{72}As (26.0 h)	^{nat}Ge(p,xn)	18 $\rightarrow$ 8	Tumour localisation; immuno-PET
^{76}Br (16.0 h)	^{76}Se(p,n)	15 $\rightarrow$ 8	Radioimmunotherapy
^{82m}Rb (6.2 h)	^{82}Kr(p,n)	14 $\rightarrow$ 10	Cardiology
^{86}Y (14.7 h)	^{86}Sr(p,n)	14 $\rightarrow$ 10	Therapy planning
^{89}Zr (78.4 h)	^{89}Y(p,n)	14 $\rightarrow$ 10	Immuno-PET
^{94m}Tc (52 min)	^{94}Mo(p,n)	13 $\rightarrow$ 8	Quantification of SPECT
^{120}I (1.3 h)	^{120}Te(p,n)	13.5 $\rightarrow$ 12	Iodopharmaceuticals
^{124}I (4.2 d)	^{124}Te(p,n)	12 $\rightarrow$ 8	Tumour targeting; dosimetry

Some cross section data are discrepant; further work is essential.

Non-standard Positron Emitters Produced via Intermediate Energy Reactions

- Intermediate energy reactions give higher yields but lower radionuclidic purity; yet they are used for production of some positron emitters.

Example: $^{75}As(p,3n)^{73}Se$ Mushtaq et al., ARI **39**, 1085 (1988).



- Optimum energy range for production of ^{73}Se: $E_p = 40 \rightarrow 30$ MeV
- Yield : 1.4 GBq/µA·h
- $^{72,75}Se$ impurity: < 0.2 %

The higher the projectile energy, the more are competing reactions, and the greater are nuclear data needs.

Novel Therapeutic Radionuclides

^{47}**Ca** ($T_{½}$ = 3.4 d; E_{β^-} = 610 keV)

^{67}**Cu** ($T_{½}$ = 2.6 d; E_{β^-} = 577 keV)

^{186}**Re** ($T_{½}$ = 3.7 d; E_{β^-} = 1070 keV)

^{225}**Ac** ($T_{½}$ = 10.0 d; E_{α} = 5830 keV)

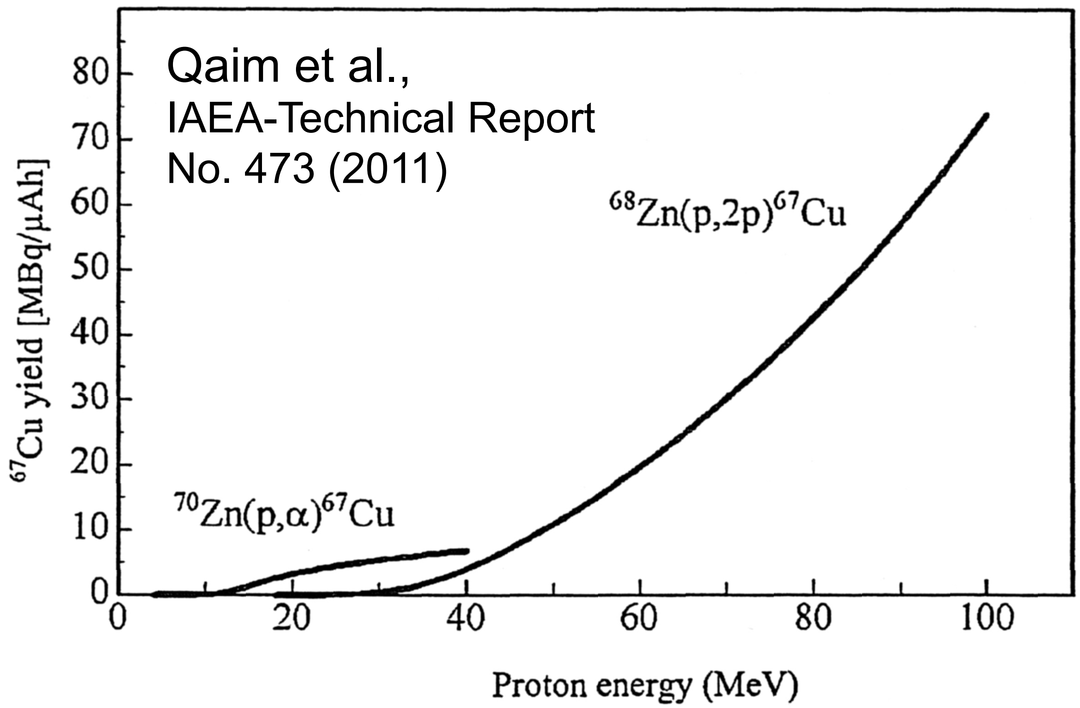
^{131}**Cs** ($T_{½}$ = 9.7 d; X-rays)

^{117m}**Sn** ($T_{½}$= 13.6 d; Conversion electrons)

^{193m}**Pt** ($T_{½}$ = 4.3 d; Auger electrons)

Production of Copper-67

Routes: ^{70}Zn(p,α); ^{68}Zn(p,2p); ^{68}Zn(γ,p); ^{67}Zn(n,p)



^{68}Zn(γ,p)^{67}Cu

Yield: 1 MBq/(g•kW•h)
for Zn target
Starovoitova et al., ARI **85**, 39 (2014).

^{67}Zn(n,p)^{67}Cu

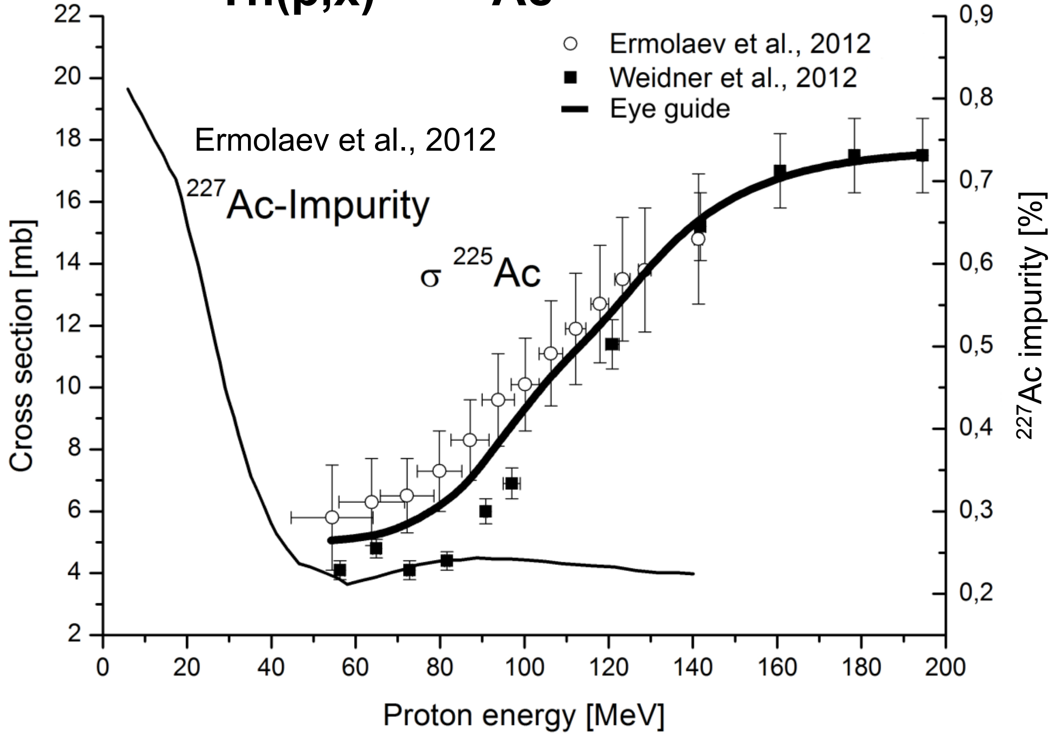
Yield: 4.4 MBq/(g•h for 10^{14} n cm^{-2} s^{-1})
for Zn target
Uddin et al., RCA **102**, 473 (2014).

- Reaction ^{68}Zn(p,2p)^{67}Cu at E_p = 80 → 30 MeV most promising; but strong disturbance from ^{68}Zn(p,2n)^{67}Ga reaction; good chemical separation mandatory

Production of Actinium-225

Routes: a) Separation from nuclear waste — Transuranium Lab., Karlsruhe
b) $^{226}Ra(p,2n)^{225}Ac$ — Apostolidis et al., ARI **62**, 383 (2005).
c) $^{232}Th(p,x)^{225}Ac$ — Ermolaev et al., RCA **100**, 223 (2012); Weidner et al., ARI **70**, 2602 (2012).

$^{232}Th(p,x)^{225,227}Ac$



$^{232}Th(p,x)^{225}Ac$

E_p = 140 → 60 MeV

^{225}Ac yield:

4 MBq/μAh

$^{226}Ra(p,2n)^{225}Ac$

E_p = 22 → 10 MeV

^{225}Ac yield:

7 MBq/μAh

(radioactive target)

All methods of ^{225}Ac production need further development

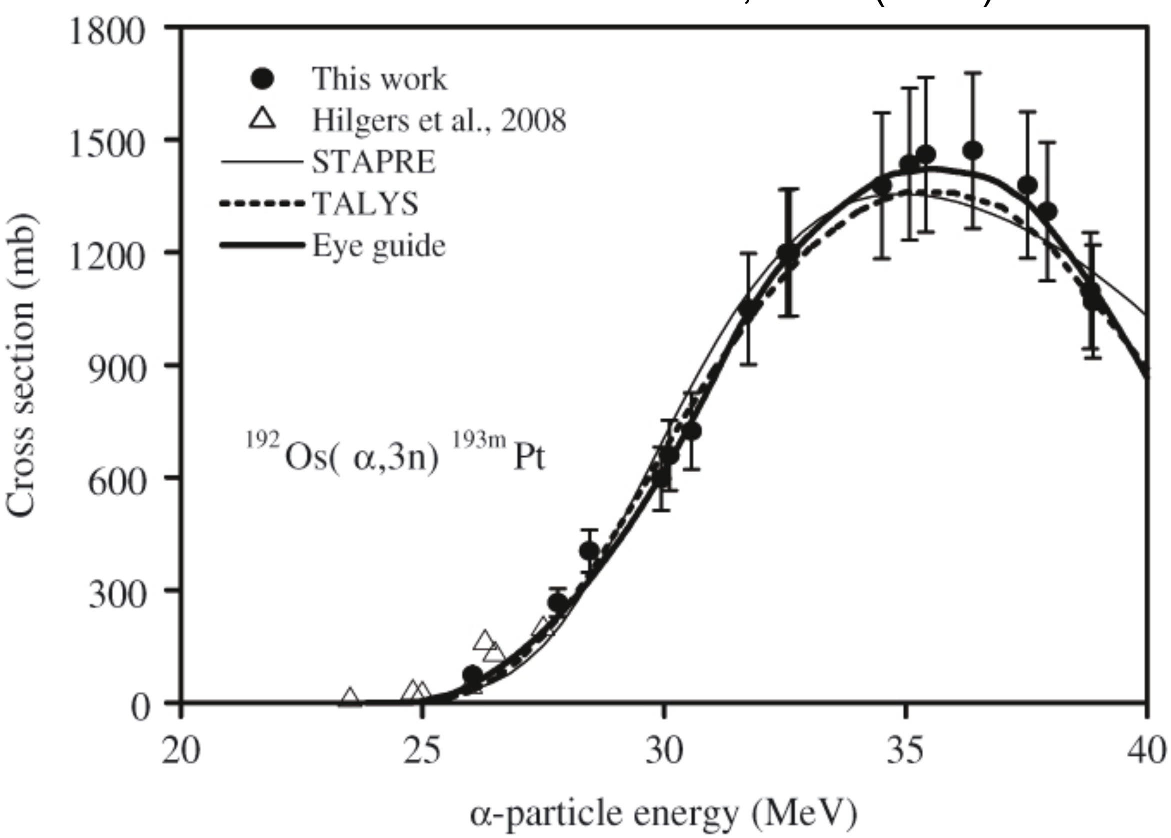
Production of Pt-193m

High-spin isomer ($I = 13/2^+$)
(Auger electrons ~ 33 per decay)

Production Method: $^{192}Os(\alpha,3n)^{193m}Pt$
X-ray spectrometry

Excitation Function

Uddin et al.,
ARI **68**, 2001 (2010).



^{193m}Pt yield:

$E_\alpha = 40 \rightarrow 30$ MeV

10 MBq/µA·h

Production of high-specific activity ^{193m}Pt in sufficient quantity is feasible

Alternative Routes for Production of Tc-99m ($T_{½}$ = 6.1 h)

Due to ageing reactors, production via $^{235}U(n,f)$-route is in jeopardy. Alternative suggested routes include:

$^{nat}U(\gamma,f)^{99}Mo$	(σ = 160 mb at 15 MeV)	Detailed data needed
$^{232}Th(p,f)^{99}Mo$	(σ = 34 mb at 22 MeV)	Detailed data needed
$^{100}Mo(\gamma,n)^{99}Mo$	(σ = 150 mb at 14 MeV)	Detailed data needed
$^{100}Mo(n,2n)^{99}Mo$	(σ = 1500 mb at 14 MeV)	More data needed
$^{100}Mo(p,pn)^{99}Mo$	(σ = 150 mb at 40 MeV)	Evaluated data available
$^{100}Mo(p,2n)^{99m}Tc$	(σ = 284 mb at 17 MeV)	Evaluated data available

For reviews, cf.

Ruth,
Nature **457**, 536 (2009);

Van der Marck et al.
Eur. J. Nucl. Med. Mol. Imaging **37**, 1817 (2010);

Qaim,
JRNC, DOI 10.1007 (2014).

$^{nat}U(n,f)^{99}Mo$ process with **spallation neutrons** appears interesting, but cross section is unknown.

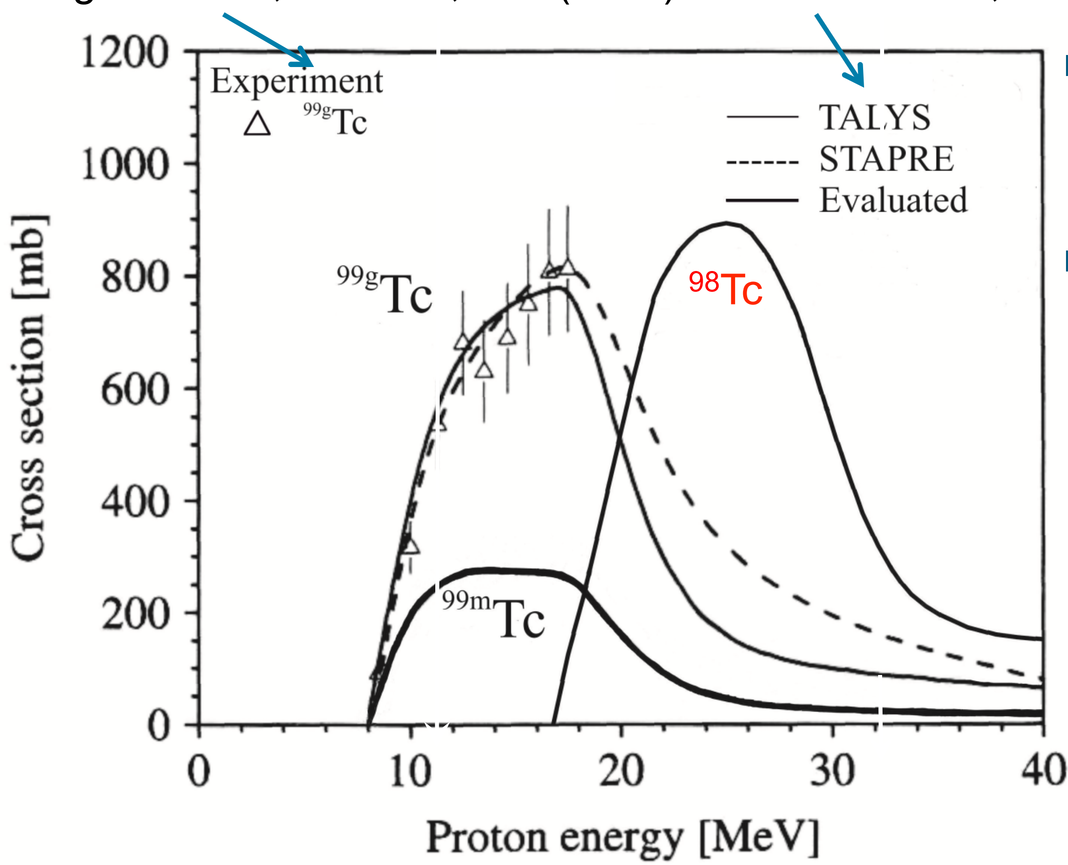
Presently the most promising route is the $^{100}Mo(p,2n)^{99m}Tc$ reaction; other processes need further investigation.

Long-lived Impurities in Cyclotron Production of ^{99m}Tc

$^{100}Mo(p,2n)^{99g}Tc$ ($T_{½} = 2.1 \times 10^5$ a); $^{100}Mo(p,3n)^{98}Tc$ ($T_{½} = 4.2 \times 10^6$ a)

Experimental values via mass-spectrometric measurement of ^{99g}Tc reported; theoretical predictions done.

Gagnon et al., NMB **38**, 907 (2011). Qaim et al., ARI **85**, 101 (2014).



- Experimental ^{99g}Tc data up to 18 MeV agree with theory.
- **Detailed data required to**
  - estimate Tc-metal content in product
  - estimate radioactive impurities from isotopes other than ^{100}Mo

New Directions in Radionuclide Applications

- **Quantification of SPECT agents**

  (combination of PET/SPECT) $^{94m}Tc/^{99m}Tc$, $^{120}I/^{123}I$, etc.

- **Multimode imaging**

  (combination of PET/CT and PET/MRI)

  Positron emitters needed: ^{52}Mn, ^{52}Fe, ^{57}Ni, ^{64}Cu, etc.

- **Theragnostic pairs**

  (combination of PET/Therapy)

  $^{44}Sc/^{47}Sc$, $^{64}Cu/^{67}Cu$, $^{86}Y/^{90}Y$, $^{124}I/^{131}I$, etc.

- **Radioactive nanoparticles**

  Better delivery of radionuclide to tumour?

Continuous nuclear data research is mandatory

Future Data Needs

Considerations

- *Demands on quality of radionuclides*

  (yield, radionuclidic and chemical purity, specific activity)
- *Changing trends in medical applications*

  (multimode imaging, theragnostic approach, targeted therapy, radioactive nanoparticles)
- *Developments in accelerator technology*

cf. Report: IAEA-INDC(NDS)-0596 (2011), describes some data needs

Nuclear data research to concentrate on

- Charged particle induced reactions
- High energy photon induced reactions
- Fast neutron induced reactions

Charged Particle Reaction Data

Low-energy region (E < 30 MeV)

Non-standard β^+ emitters

- Evaluate existing data
- Validate evaluated data through integral yield measurements
- Strengthen database via measurements and calculations.

Examples :

^{45}Sc(p,n)^{45}Ti; ^{52}Cr(p,n)^{52}Mn; ^{54}Fe(d,n)^{55}Co; ^{67}Zn(p,α)^{64}Cu; ^{72}Ge(p,n)^{72}As; ^{74}Se(d,n)^{75}Br; ^{86}Sr(p,n)^{86}Y; ^{120}Te(p,n)^{120}I, and many other potentially useful reactions.

Accompanying impurities must be determined. Use of highly enriched targets is strongly recommended.

β^+ emission intensities in decay of ^{66}Ga, ^{86}Y, ^{120}I, etc. need to be accurately determined.

Charged Particle Reaction Data

Intermediate-energy region (30 – 100 MeV and beyond)

Non-standard β^+ emitters

- Strengthen database. ***Examples:***

^{55}Mn(p,4n)^{52}Fe; ^{59}Co(p,3n)^{57}Ni; ^{68}Zn(p,αn)^{64}Cu; ^{75}As(p,3n)^{73}Se; ^{85}Rb(p,3n)^{83}Sr; ^{88}Sr(p,3n)^{86}Y; ^{125}Te(p,2n)^{124}Te, and many other potentially useful reactions.

SPECT radionuclides and generator parents

- Strengthen database. ***Examples*:**

(a) ^{124}Xe(p,pn)^{123}Xe $\rightarrow$ ^{123}I; ^{124}Xe(p,2p)^{123}I SPECT
(b) (p,x) reactions on $^{94-98}$Mo to determine possible impurities in cyclotron produced ^{99m}Tc SPECT
(c) ^{45}Sc(p,2n)^{44}Ti; ^{69}Ga(p,2n)^{68}Ge; ^{75}As(p,4n)^{72}Se; ^{nat}Br(p,x)^{72}Se; ^{nat}Rb(p,xn)^{82}Sr (Parents of β^+ emitters)

Charged Particle Reaction Data

Intermediate-energy region (cont’d)

Therapeutic nuclides

- Strengthen database. ***Examples:***

$^{68}Zn(p,2p)^{67}Cu$; $^{70}Zn(p,\alpha)^{67}Cu$; $^{107}Ag(p,\alpha n)^{103}Pd$; $^{232}Th(p,x)^{225}Ac$;
$^{181}Ta(p,spall)^{149}Tb$, ^{152}Tb, ^{155}Tb (1.4 GeV irradiation and ISOLDE/CERN)
Investigation of impurities absolutely necessary

Deuteron-induced reactions possibly more useful for production of ^{103}Pd and ^{186}Re. More data are needed.

Alpha-particle induced reactions very useful for production of high-spin isomers, e.g.

$^{116}Cd(\alpha,3n)^{117m}Sn$; $^{192}Os(\alpha,3n)^{193m}Pt$, etc. More data are needed.

Some work possible also with ^{7}Li and heavier ions

Intermediate-energy multi-particle accelerators have great potential for medical radionuclide production.

High Energy Photon Induced Reactions

- Considerable progress in technology for photon production

Types of nuclear reactions

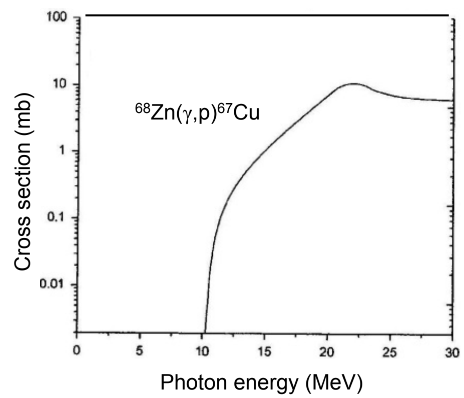
(γ,n), (γ,p), (γ,2n), (γ,f), etc.

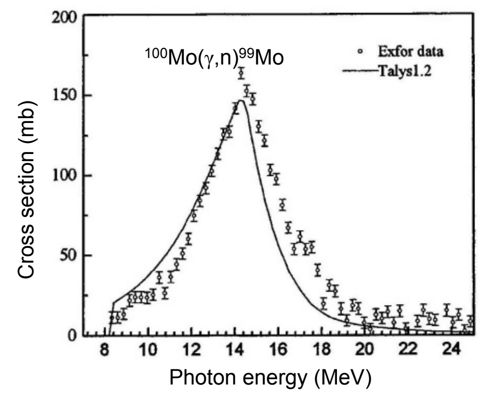
Available database is weak

cf. Report IAEA-TECDOC-1178 (2000)

- Data needs. ***Examples:***

Excitation functions





^{68}Zn(γ,p)^{67}Cu; ^{100}Mo(γ,n)^{99}Mo; ^{104}Pd(γ,n)^{103}Pd; ^{124}Xe(γ,n)^{123}Xe; ^{232}Th(γ,f)^{99}Mo; ^{238}U(γ,f)^{99}Mo, and several other reactions

Targetry is simple, but yield is rather low.

Extensive efforts needed to improve database;
but limited application to medical radionuclide production.

Fast Neutron Induced Reactions

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- Fission neutrons extensively used for medical radionuclide production. Special data needs will always arise.
- d/Be beak-up and spallation neutrons could be advantageously used for radionuclide production, especially for neutron threshold reactions

  cf. Spahn et al., RCA **92**, 183 (2004); Al-Abyad et al., ARI **64**, 717 (2006)

Examples: **β^-** emitters

$^{32}S(n,p)^{32}P$; $^{47}Ti(n,p)^{47}Ca$, $^{64}Zn(n,p)^{64}Cu$; $^{67}Zn(n,p)^{67}Cu$; $^{89}Y(n,p)^{89}Sr$; $^{105}Pd(n,p)^{105}Rh$; $^{149}Sm(n,p)^{149}Pm$, $^{153}Eu(n,p)^{153}Sm$, $^{159}Tb(n,p)^{159}Gd$; $^{161}Dy(n,p)^{161}Tb$; $^{166}Er(n,p)^{166}Ho$; $^{169}Tm(n,p)^{169}Er$; $^{175}Lu(n,p)^{175}Yb$; $^{177}Hf(n,p)^{177}Lu$, and several other reactions

- Some α-emitting radionuclides, such as **^{225}Ac, ^{223}Ra, ^{227}Th**, etc. can also be produced using spallation neutrons
- Spallation neutrons could be used to induce **fission** of ^{232}Th or ^{238}U to produce ^{99}Mo (avoid criticality problem)

Fast neutron spectral sources need to be developed for medical radionuclide production; data needs are extensive.

Summary and Conclusions

- Radionuclide production technology is rapidly progressing.
- Accurate knowledge of nuclear data is absolutely necessary for production and application of radionuclides in medicine.
- Nuclear data needs are more stringent in accelerator production of radionuclides than in reactor production.
- Constant nuclear data research is necessary to meet changing trends in medical applications.
- Future needs of production data will be related to extensive use of intermediate-energy charged particle accelerators, some selective use of high-intensity photon generators, and enhancing use of spallation neutron sources.