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Nuclear Data for Medical Applications: An Overview

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Outline

- Introduction
- Types of data for medical use
- Commonly used radionuclides
- Research oriented radionuclides
  - non-standard positron emitters
  - novel therapeutic radionuclides
- New directions in radionuclide applications
- New developments in irradiation technologies
- Future data needs
- Summary and conclusions

Introduction
Nuclear Data Research for Medical Use

Aim

- Provide fundamental database for
  - external radiation therapy
  - internal radionuclide applications

Areas of work

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

Considerable effort is invested worldwide in nuclear data research.

Data for External Radiation Therapy

Types of Therapy

- ***Photon therapy***: use of ^{60}Co or linear accelerator
  (*low-LET radiation*) **most common**
- ***Fast neutron therapy***: accelerator with E_p or E_d above 50 MeV
  (*high-LET radiation*) **being abandoned**
- ***Proton beam therapy***: accelerators with E_p = 70 -250 MeV
  (*treatment of deep-lying, tumours*) **increasing significance**
- ***Heavy-ion beam therapy***
  (*rather specialized)* **limited application**

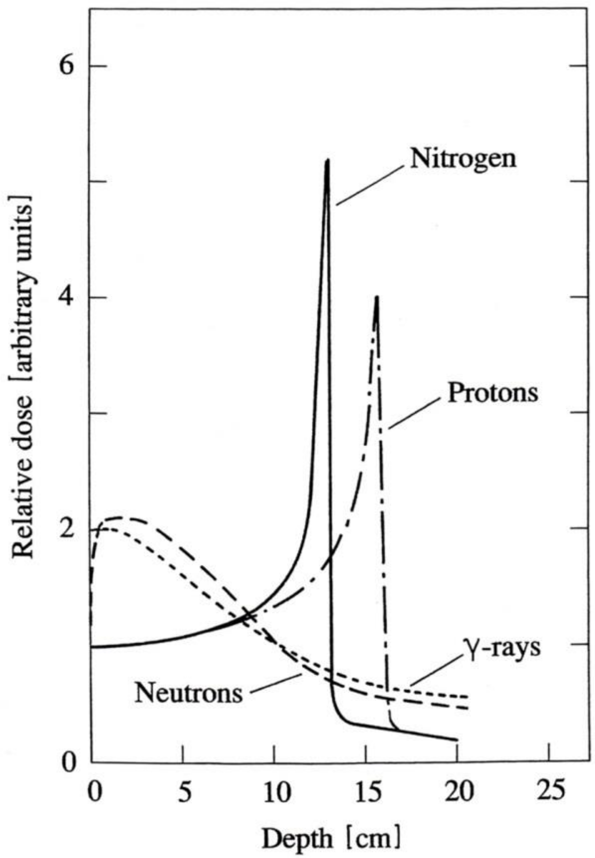
Nuclear data are important in fast neutron therapy; in other cases atomic and molecular data are more relevant.

Radiation Therapy
(Cont´d)

Atomic and molecular data required to

- calculate radiation transport
- calculate the absorbed dose

Nuclear data needs in charged-particle therapy



- Total and non-elastic cross sections
- Production yields, average energies and angular distributions of emitted n, p, d, α, γ
- Formation of radioactive products

(Kettern, et al., RPC **78**, 380, 2009).

Major references

IAEA-TECDOC-799,1995
ICRU Report 63,Bethesda,2000

Data for *in vivo* Applications

Decay Data

- Choice of a radionuclide depends on decay data

Considerations: - suitability for imaging
(Scintigraphy; SPECT; PET)
- radiation dose

Demands:

Diagnosis: minimum dose (γ or β^+ emitters)
Therapy: suitable dose (β^- or α-particle emitters)

Major references

Radionuclide Data and Decay Schemes (MRID)

Evaluated Nuclear Structure Decay Data (ENSDF)

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

Major interest is in neutron and charged-particle data

Commonly Used Radionuclides

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; yet more information on low-energy electrons is needed

(cf. INDC(NDS)-0638, 2013).

Standardisation of Production Data

- **Neutron data** extensively evaluated, mainly for energy research; also useful in reactor production of radionuclides

Major reference: ENDF/B-VII

- **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

Major references

Diagnostic radionuclides: IAEA – TECDOC - 1211 (2001)
Therapeutic radionuclides: IAEA - Technical Report - 473 (2011)

Alternative Routes for Production of Tc-99m ($T_{1/2}$ = 6.1 h)

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

For reviews, cf.

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

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

Qaim
JRNC **305**, 233 (2015).

$^{235}U(n,f)^{99}Mo$ process with **spallation neutrons** appears interesting, but cross section is unknown.

Presently the $^{100}Mo(p,2n)^{99m}Tc$ reaction is most promising , but extensive data on formation of impurities are needed.

This route will not solve the world shortage.

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.

Copper-64

($T_{½}$ = 12.7 h; $E_{\beta+}$ = 0.66 MeV; $I_{\beta+}$ = 17.8 %)

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Production Routes

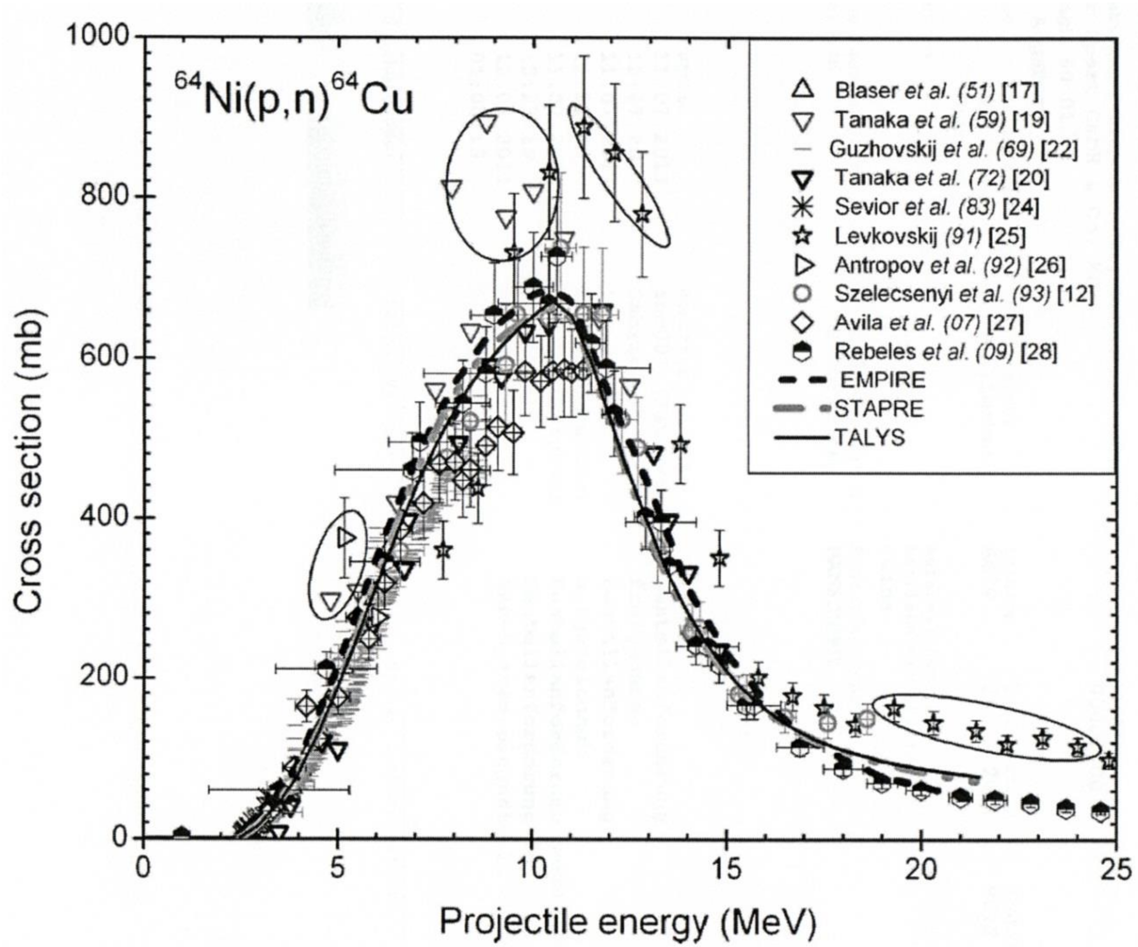
Nuclear process	Optimum energy range [MeV]	Thick target yield [MBq/µA·h]
^{64}Ni(p,n)^{64}Cu [a)]	12 → 8	304
^{64}Ni(d,2n)^{64}Cu [a)]	17 → 11	430
^{68}Zn(p,αn)^{64}Cu [a)]	30 → 21	116
^{66}Zn(p,2pn)^{64}Cu [a)]	52 → 37	316
^{64}Zn(d,2p)^{64}Cu [a)]	20 → 10	27
^{66}Zn(d,α)^{64}Cu [a)]	13 → 5	14
^{nat}Zn(d,x)^{64}Cu	25 → 10	57

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

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)

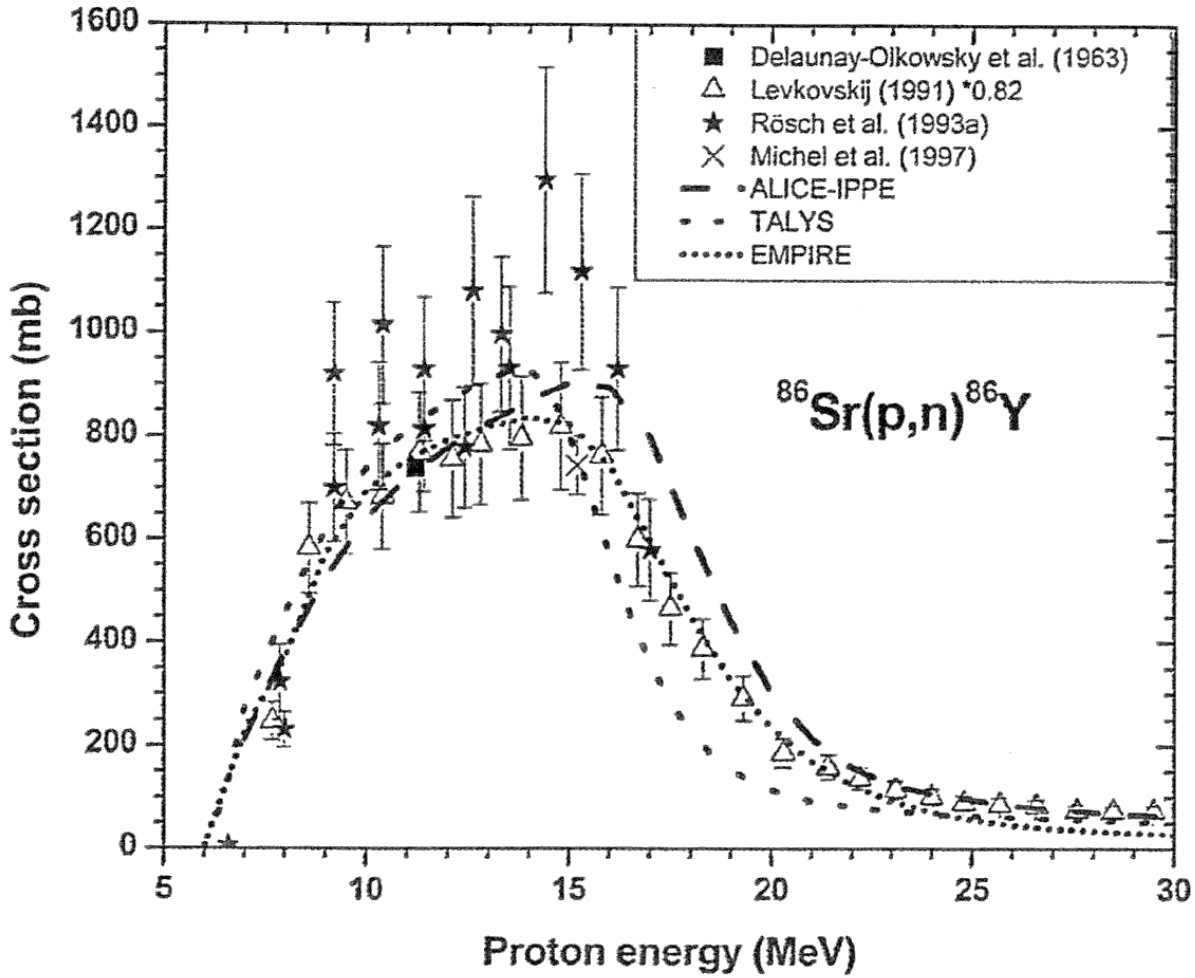
Optimum energy range for production of ^{64}Cu

E_p: 12 → 8 MeV
Yield: 304 MBq/µAh

Yttrium-86

($T_{½}$ = 14.7 h; $E_{\beta+}$ = 1.6 MeV; $I_{\beta+}$ = 34 %)

Excitation Function



Production method developed at Jülich (1993)

Data evaluated by Zaneb et al, ARI **104**, 232 (2015)

Considerable discrepancy suggests need of more precise measurement.

Non-standard Positron Emitters for Medical Applications Produced via Low Energy Reactions

Qaim, JRNC **305**, 233 (2015)

Nuclide	Major production route	Energy range [MeV]	Application
^{52}Mn (5.6 d)	^{52}Cr(p,n)	16 → 8	Multimode imaging (PET + MRI)
^{55}Co (17.6 h)	^{58}Ni(p,α) ^{54}Fe(d,n)	15 → 7 10 → 5	Tumour imaging; neuronal Ca marker
^{64}Cu (12.7 h)	^{64}Ni(p,n)	14 → 9	Radioimmunotherapy
^{66}Ga (9.4 h)	^{66}Zn(p,n)	13 → 8	Quantification of SPECT
^{72}As (26.0 h)	^{nat}Ge(p,xn)	18 → 8	Tumour localisation; immuno-PET
^{76}Br (16.0 h)	^{76}Se(p,n)	15 → 8	Radioimmunotherapy
^{82m}Rb (6.2 h)	^{82}Kr(p,n)	14 → 10	Cardiology
^{86}Y (14.7 h)	^{86}Sr(p,n)	14 → 10	Therapy planning
^{89}Zr (78.4 h)	^{89}Y(p,n)	14 → 10	Immuno-PET
^{94m}Tc (52 min)	^{94}Mo(p,n)	13 → 8	Quantification of SPECT
^{120}I (1.3 h)	^{120}Te(p,n)	13.5 → 12	Iodopharmaceuticals
^{124}I (4.2 d)	^{124}Te(p,n)	12 → 8	Tumour targeting; dosimetry

Internal Radionuclide Therapy

- **Brachytherapy**
  (insertion of sealed sources near the tumour)
  Examples: ^{192}Ir as wire
  ^{103}Pd and ^{125}I as seeds

- **Administration in cavities**
  (for pain palliation)
  Examples: ^{32}P colloid for arthritis
  ^{90}Y, ^{186}Re and ^{188}Re complexes for joint inflammation

- **Metabolic therapy**
  (incorporation of radionuclide via a biochemical path)
  Examples: ^{131}I for thyroid cancer
  ^{89}Sr, ^{186}Re and ^{153}Sm are bone seekers

- **Radioimmunotherapy**
  (administration of a radionuclide chemically conjugated to antibodies)
  Examples: low-energy high-LET value radionuclides

Internal radionuclide therapy is a fast developing field.

Novel Therapeutic Radionuclides

^{47}Sc ($T_{½}$ = 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)

^{149}Tb ($T_{½}$ = 4.1 h; E_{α} = 3970 keV)

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

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

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

^{195m}Pt ($T_{½}$ = 4.0 d; Auger electrons)

Production of Copper-67

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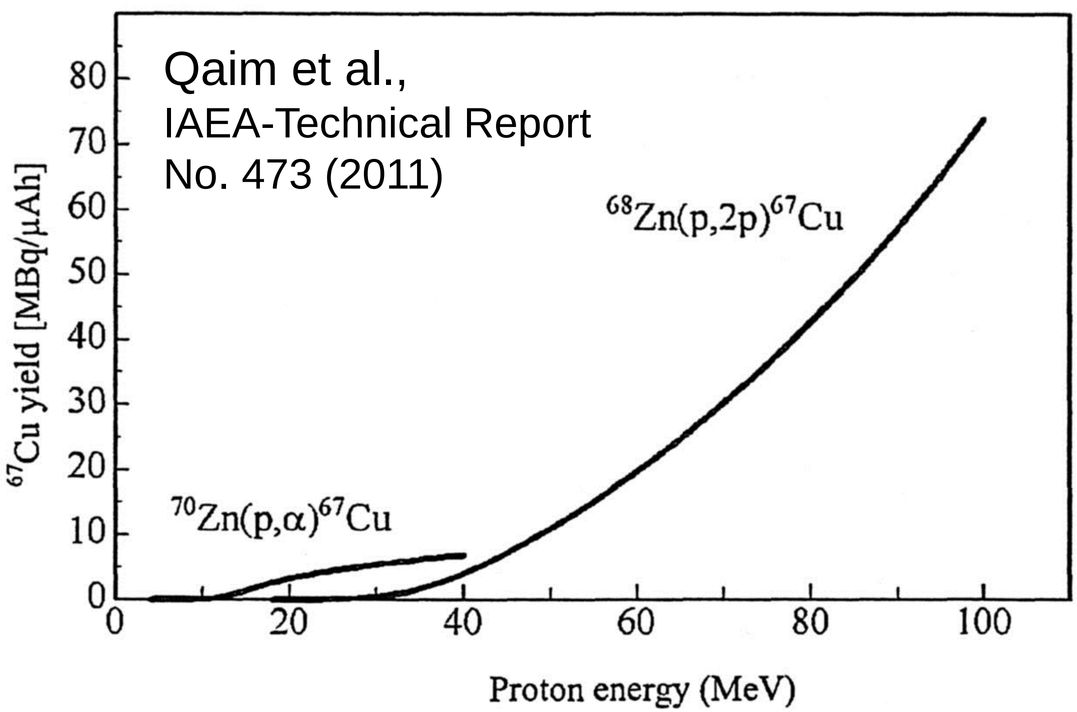
Routes: ^{70}Zn(p,α); ^{68}Zn(p,2p); ^{68}Zn(γ,p); ^{67}Zn(n,p)



^{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

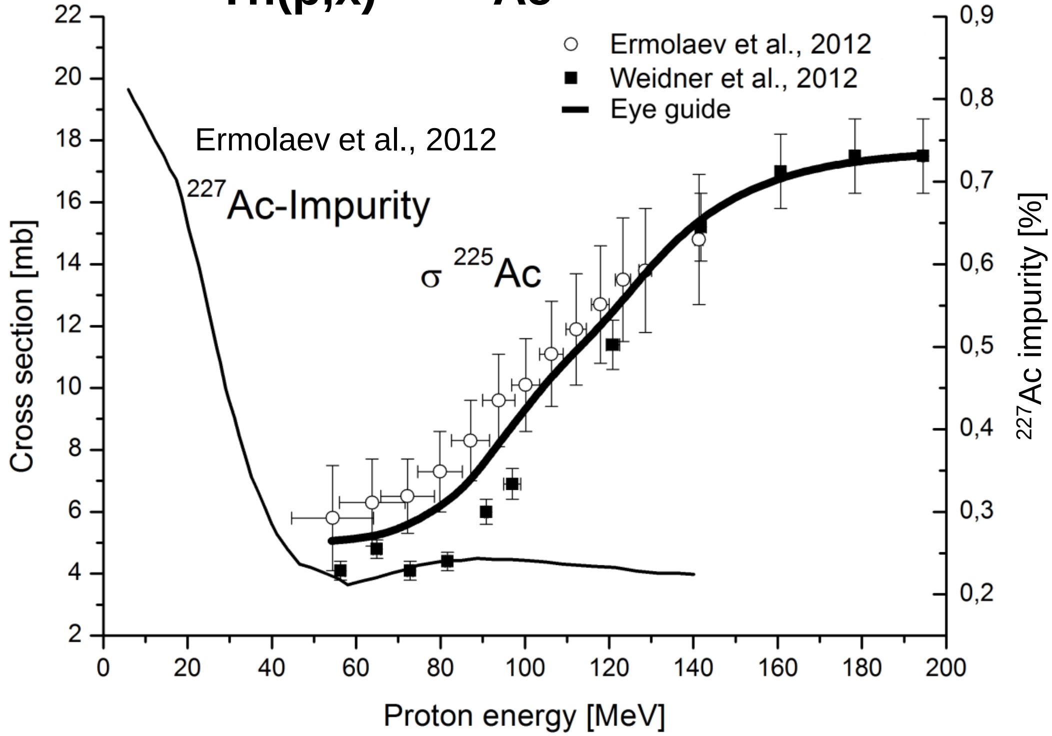
Uddin et al., RCA **102**, 473 (2014).

- 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 Tin-117m

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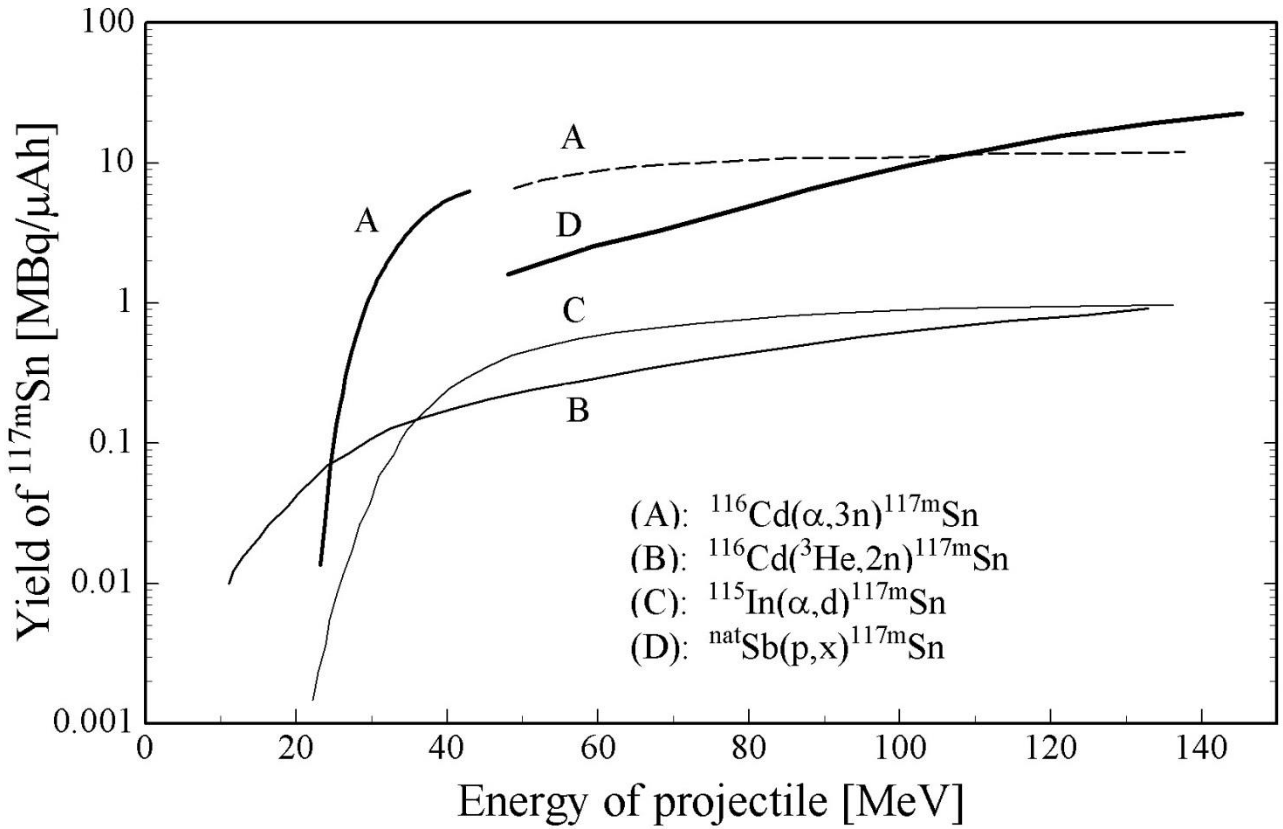
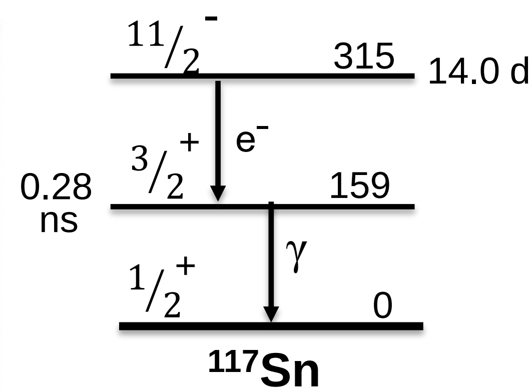
Routes: ^{117}Sn(n,n´γ); ^{116}Cd(α,3n); ^{116}Cd(^{3}He,2n); ^{115}In(α,d); ^{nat}Sb(p,x)

Qaim, NMB (2016), to be published





Qaim, Döhler,
IJARI **25**, 645 (1984)

Adam Rebeles et al.,
NIM **B266**, 4731 (2008)

Ermolaev et al.,
JRNC **280**, 319 (2009)

Due to high spin of ^{117m}Sn, the ^{116}Cd(α,3n)-reaction leads to high-yield (and high-purity) product.

Intermediate-term Data Needs

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(partly defined in IAEA-INDC(NDS)-0596 (2011); additional analysis of emerging needs)

Non-standard β^+ emitters

- Re-evaluate existing mass decay chains
- Determine β^+ emission intensities

  (using improved experimental techniques)
- Evaluate existing charged-particle reaction data
- Strengthen database via measurements and calculations
- Validate evaluated data through integral yield measurements

Novel therapeutic radionuclides

- Re-evaluate intensities of emitted corpuscular radiation
- Improve knowledge of Auger electron spectra
- Strengthen charged-particle database for production

  (via measurements and calculations)

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.

- **Theranostic approach**

  (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 radionuclide research is mandatory

New Developments in Irradiation Technologies

- Small, high-intensity medical cyclotron ($E_p < 20$ MeV)
  (generally two particles; hospital based)
- Medium-sized cyclotron (E= 30 – 40 MeV)
  (multiple particles)
- Intermediate energy accelerator/cyclotron (E = 50 – 100 MeV)
  (mostly single particle; occasionally multiple particles)
- Electron accelerator for high-intensity photons (E < 50 MeV)
- Spallation neutron source

Future Data Needs

Considerations

- *Demands on quality of radionuclides*

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

  (multimode imaging, theranostics, targeted therapy)
- *Developments in accelerator technology*

Major needs defined in

- White Paper on Nuclear Data Needs,

  USDOE-Office of Science, Washington, D.C., USA (2015)
- S.M. Qaim, Review article, NMB (2016), to be published

A summary is presented here according to reaction type.

Charged Particle Induced Reactions

- Deuteron-induced production of ^{103}Pd, ^{186}Re, etc.
- Alpha-particle-induced production of high-spin isomers, e.g. ^{117m}Sn, ^{193m}Pt, etc.
- Proton-induced production of radionuclides over the energy range 50-150 MeV, e.g.

β⁺-emitters

$^{55}Mn(p,4n)^{52}Fe$; $^{59}Co(p,3n)^{57}Ni$; $^{68}Zn(p,\alpha n)^{64}Cu$;
$^{75}As(p,4n)^{72}Se \rightarrow ^{72}As$; $^{88}Sr(p,3n)^{86}Y$; $^{155}Gd(p,4n)^{152}Tb$

Therapeutic radionuclides

$^{68}Zn(p,2p)^{67}Cu$; $^{109}Ag(p,\alpha 3n)^{103}Pd$; $^{232}Th(p,x)^{225}Ac$;
$^{155}Gd(p,7n)^{149}Tb$

Intermediate energy accelerators have great potential for medical radionuclide production; accompanying nuclear data research is essential.

High Energy Photon Induced Reactions

- Considerable progress in technology for photon production

Types of nuclear reactions

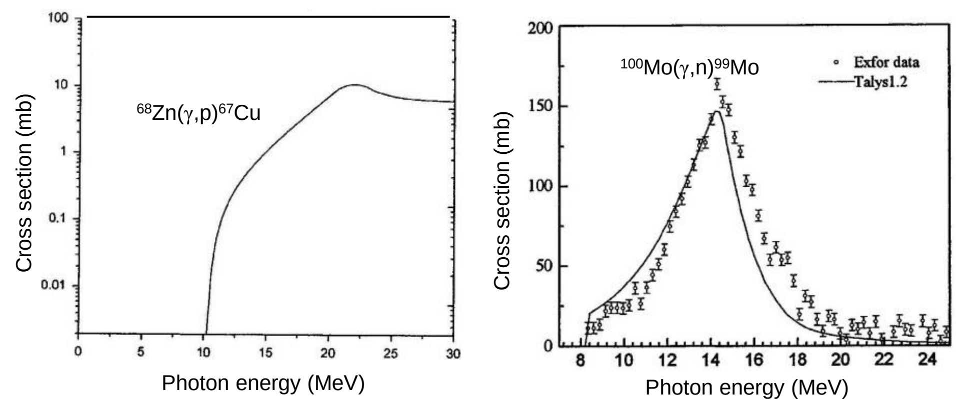
(γ,n), (γ,p), (γ,f), etc.

Available database is weak

cf. Report IAEA-TECDOC-1178 (2000)

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

Excitation functions



^{48}Ti(γ,p)^{47}Sc; ^{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; ^{nat}U(γ,f)^{99}Mo, etc.

Targetry is simple, but yield is rather low.

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

Fast Neutron Induced Reactions

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- **Fission neutrons** extensively used; some data needs always exist.
- d/Be **beak-up** and **spallation neutrons** would be advantageous for radionuclide production via neutron threshold reactions.

cf. Spahn et al., RCA **92**, 183 (2004); Al-Abyad et al., ARI **64**, 717 (2006); DeLorme et al., JNM **55**, 1468 (2014).

Examples: **β^-** emitters

^{32}S(n,p)^{32}P; ^{35}Cl(n,p)^{35}S; ^{47}Ti(n,p)^{47}Sc; ^{64}Zn(n,p)^{64}Cu; ^{67}Zn(n,p)^{67}Cu; ^{89}Y(n,p)^{89}Sr; ^{105}Pd(n,p)^{105}Rh; ^{153}Eu(n,p)^{153}Sm; ^{159}Tb(n,p)^{159}Gd; ^{161}Dy(n,p)^{161}Tb; ^{166}Er(n,p)^{166}Ho; ^{175}Lu(n,p)^{175}Yb, etc.

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

Development of fast neutron spectral sources would involve extensive data needs.

Summary and Conclusions

- In radiation therapy, primary needs exist for atomic and molecular data.
- Accurate knowledge of nuclear data is absolutely necessary for ***in vivo*** diagnosis and internal radiotherapy.
- For routine patient-care studies, the available nuclear database is sufficient (except for some small discrepancies).
- Constant nuclear data research is mandatory with regard to novel radionuclides and increasing quality control demands.
- Future nuclear reaction data needs will be related to enhancing use of charged-particle accelerators, high-intensity photon generators, and spallation neutron sources.