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Fundamentals of metal ion separations: Nuclear Medicine Examples

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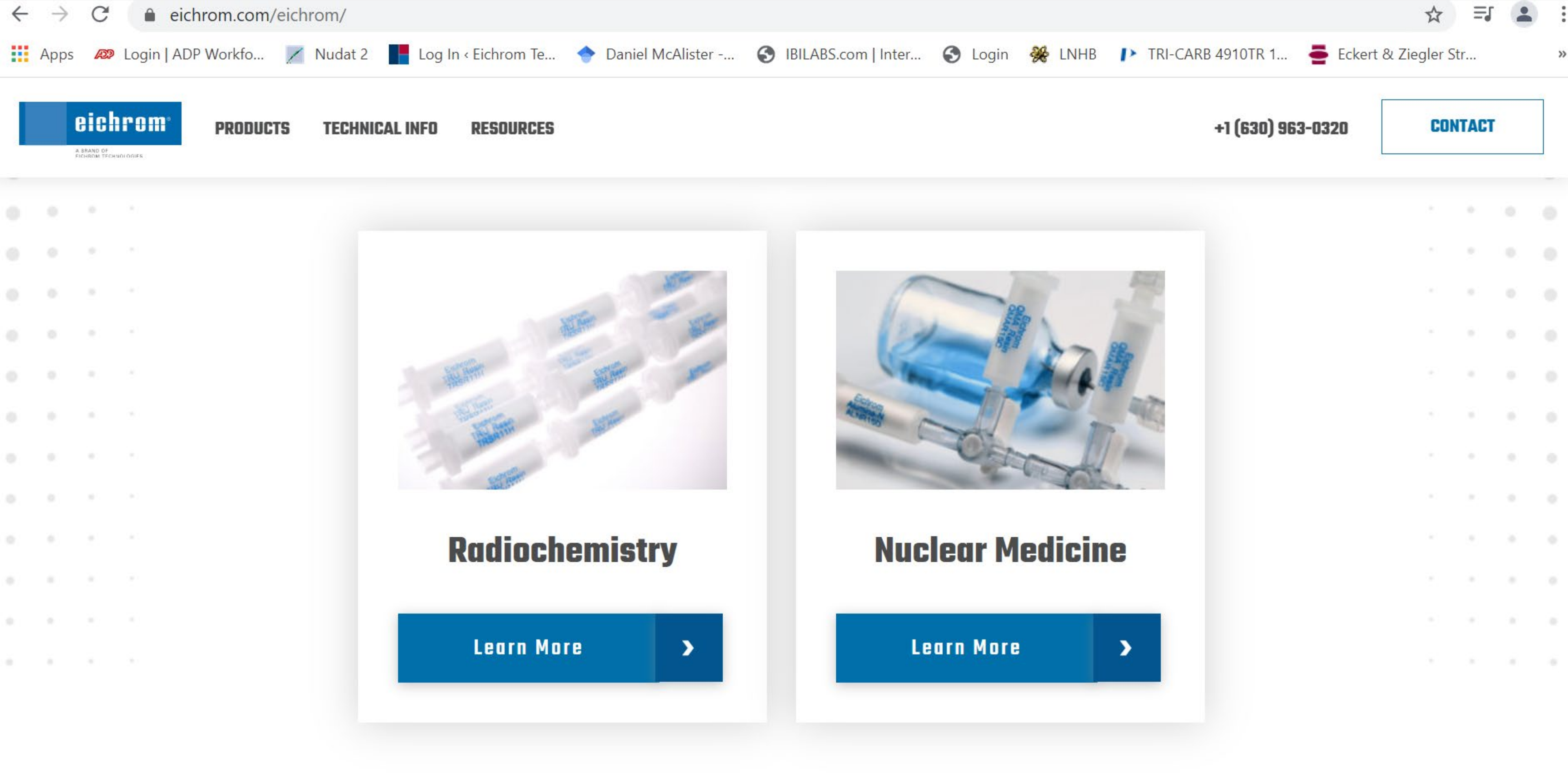
30 April 2021

Outline

- $^{90}Sr/^{90}Y$ and ^{82}Sr (PPT vs IX vs EXC, extractant bleed)
- $^{225}Ac/^{213}Bi$ (Standard COW vs MSIG)
- ^{225}Ac production (Targeting minor component)
- $^{177}Lu/^{161}Tb$ (Low separation factors)
- ^{68}Ga (Inorganic adsorbants and bonded silicas)
- ^{227}Ac from stainless steel encapsulated neutron sources
  - Unique selectivity and synergistic enhancement of extraction

Eichrom Website – Nuclear Medicine



Eichrom Website – Nuclear Medicine

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For more than 25 years, Eichrom scientists and partners have developed chromatographic separations for a wide range of nuclear medicine radionuclides. Click the links below for more information on key radionuclides.

- Actinium-225
- Bismuth-213
- Fluorine-18
- Gallium-68
- Germanium-68
- Indium-111
- Lead-203/212
- Lutetium-177
- Radium-223
- Scandium-44/47
- Strontium-82
- Terbium-161
- Thallium-201 (Lead-201)
- Thorium-227
- Yttrium-86
- Yttrium-90
- Zirconium-89

$^{90}Sr/^{90}Y$ and ^{82}Sr

-Precipitation vs IX vs EXC

-Multicolumn separations

-Extractant Bleed

^{90}Sr Separations

	Fuming HNO3 ppt	Cation Exchange	EXC (Sr Resin)
Method	Evaporate sample. Series of ppt: Fuming HNO_3, $Fe(OH)_3$, $Ba(CrO_4)$.	Load from dilute acid. Rinse with acid gradients to remove impurities. Recover Sr in high acid concentration.	Concentrate sample using IX or ppt. Dissolve in 8M HNO_3. Rinse with HNO3 – oxalic acid. Recover Sr in 0.05M HNO_3.
Limitations	Labor Intensive. Dangerous chemicals.	Low separation factors. Large columns and elution volumes.	Lower capacity than IX. Extractant bleed (1-octanol).
Advantages	???	Less labor. Less hazardous.	High separation factors. Small columns.
Waste	Highly acidic, large volumes. Mixed waste.	Large volumes of acidic aqueous waste. Spent IX resin.	Small volumes of acidic aqueous waste. Spent EXC resin.

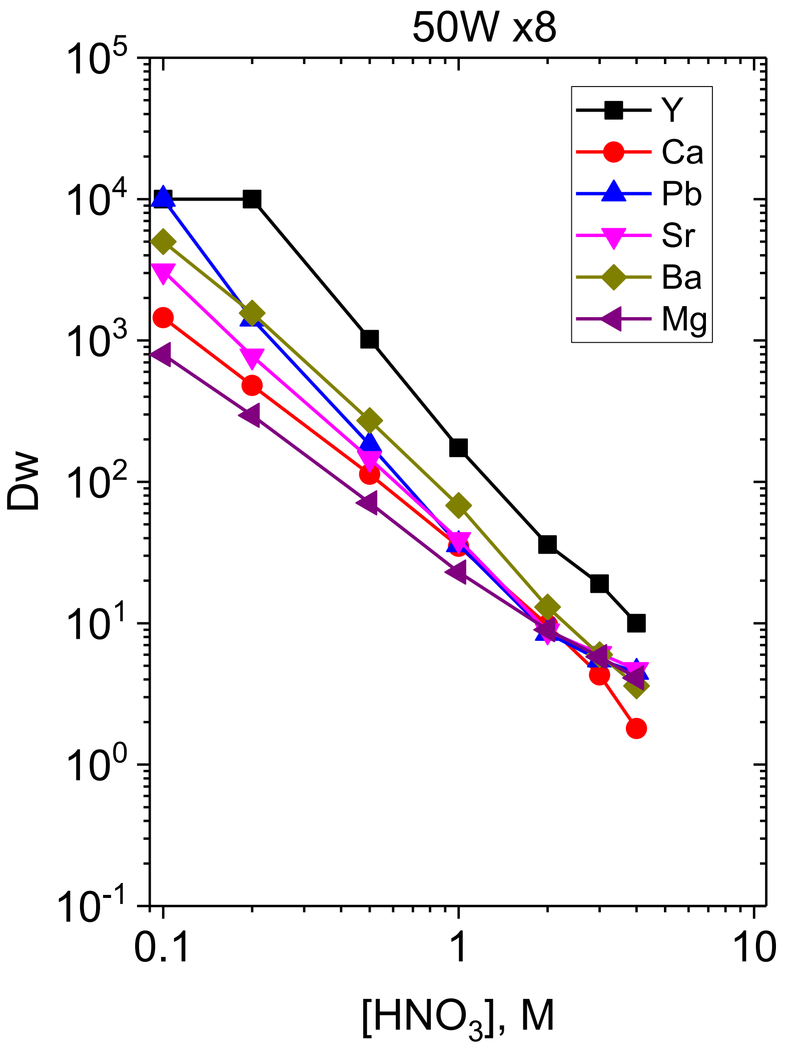
Fuming Nitric Acid (Separation of Sr from Ca, Ba and Fission Products)

1) Add 10 mg Sr, Ba, Ca carriers.
2) Concenrate water samples by evaporation or carbonate ppt.
3) Dissolve sample in enough fuming nitric acid (90-95%) to make 80% HNO3.
4) Mix, heat 5 min. Centrifuge. Decant Supernate
   - Note: **Explosions are likely to occur** if the supernate waste is mixed with other wastes that may contain organic compounds.
5) Repeat 2x
6) Fe(OH)3 ppt to remove Ca (2-3x)
7) Ba(CrO4) ppt to remove Ba (2-3x)
8) Sr-oxalate ppt to concentrate and mount final Sr source.

Simplified scheme needed for separation of $^{90}Sr/^{90}Y$.

Coryell and Sugarman, Radiochemical Studies: The Fission Products (McGraw-Hill Book Co., New York, 1951), N.N.E.S. Div. IV, Vol. 9, Book 3, Paper 236.

Cation Exchange



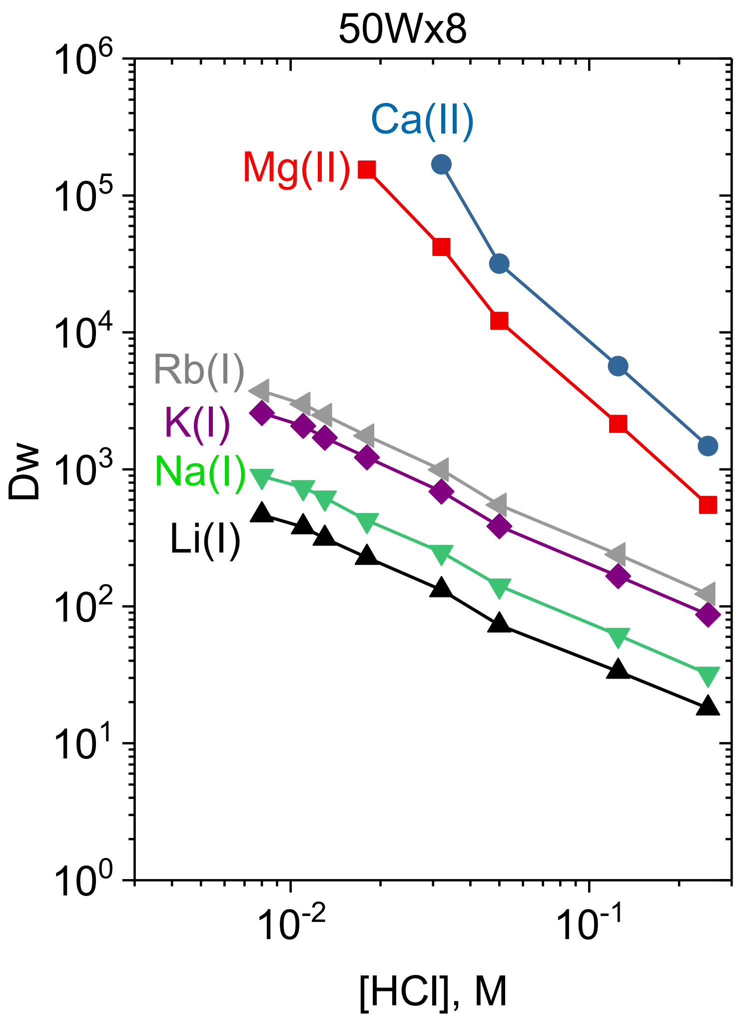
Small separation factors ($\alpha_{Y/Sr}$ ~20)

-Large columns

-Large elution volumes

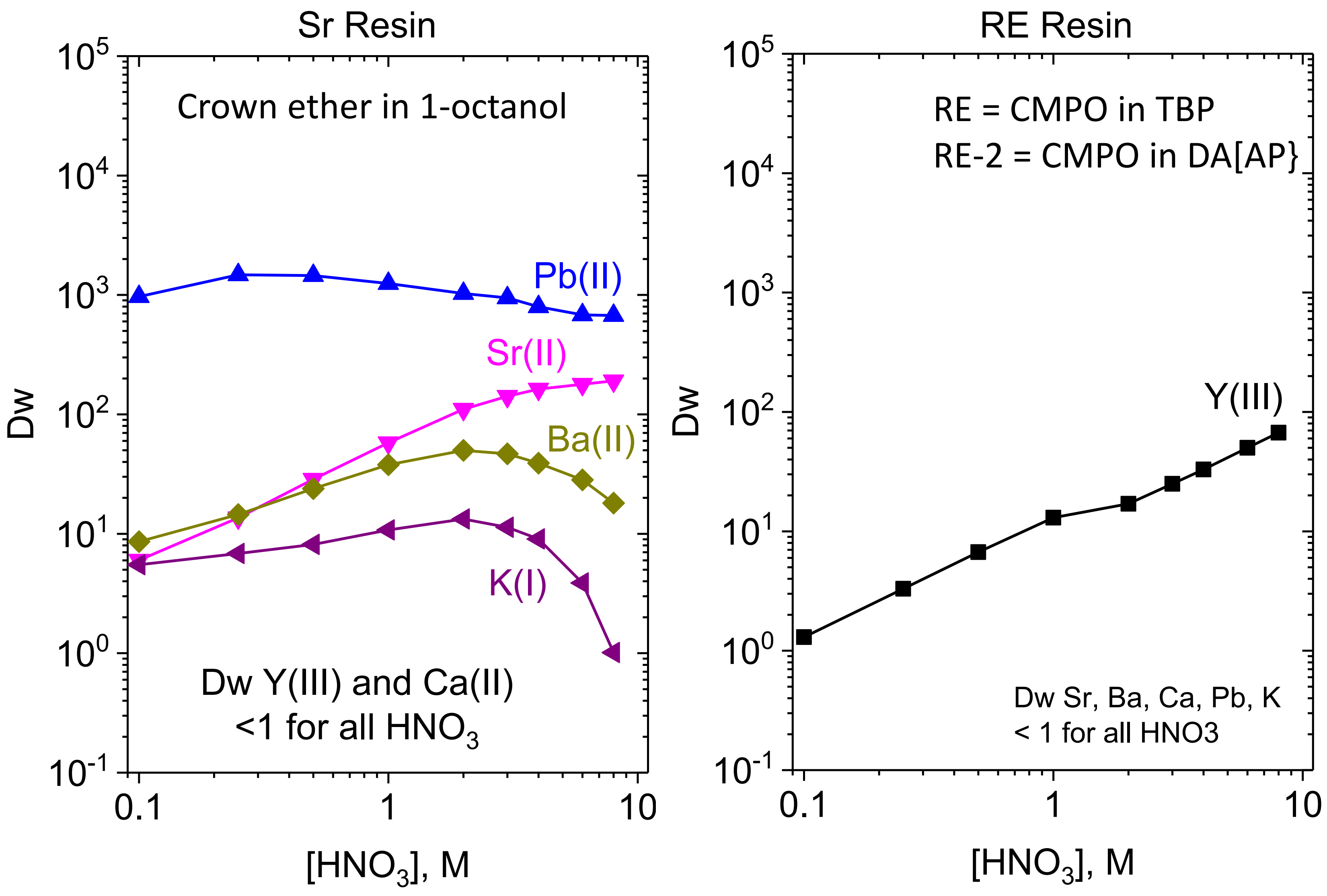
IX very useful for concentrating metal ions from large volumes and convert from low to high acidity.

Remove common matrix ions such as Na^+ and K^+.



^{90}Y (Sr Resin, RE Resin)

Dietz, M.L., Horwitz, E.P., 2000. Applications of extraction chromatography in the development of radionuclide generator systems for nuclear medicine, Ind. Eng. Chem. Res. 39, 3181-3188.



Sr-90 retained on Sr Resin

Sr-90 recovered in 0.05M HNO3.

Y-90 retained on RE Resin.

Y-90 recovered in dilute HCl.

Relatively high extractant bleed (octanol and TBP).

HNO3 and Fe carryover into HCl strip of Y-90.

Options for extractant bleed

- Bonded ion exchangers (Use after EXC)
  - Stable in highly acidic conditions.
- Bonded silica ion exchangers (Use after EXC)
  - Stable from pH ~ 2-10.
- Polymeric scavengers (Use after EXC)
  - Stable in highly acidic conditions
- Bonded silica scavengers (C18, use after EXC)
  - Stable from pH ~2-10
- Alumina / Inorganic ion exchangers (Use after EXC)
  - Can leach metal ions

Relative extractant bleed

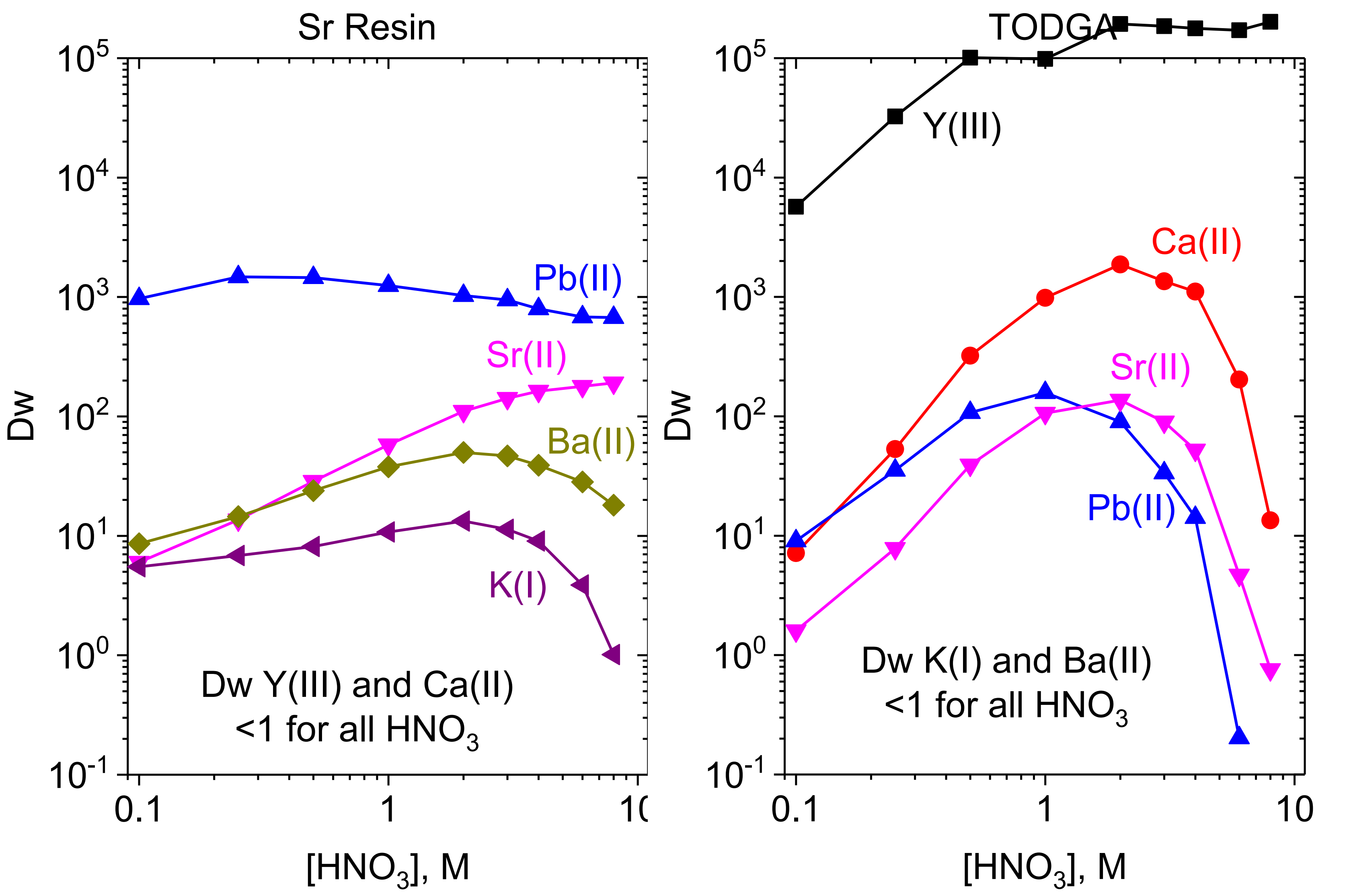
High

Sr Resin	1-octanol	
Pb Resin	isodecanol	
TRU/RE	TBP	
Ac Resin	Dipex	higher at high pH
LN	HDEHP	higher at high pH
LN2	HEH[HEP]	higher at high pH
LN3	H[DTMPP]	higher at high pH
TEVA	Aliquat·336	higher at high pH
UTEVA	DAAP	
DGA, Normal	TODGA	
DGA, Branched	TEHDGA	

Low

^{90}Y (Sr Resin, DGA Resin)

D.R. McAlister, E.P. Horwitz, "Extraction of Selected Metal Ions by Mixtures of Diglycolamides and Crown Ethers," Solv. Extr. Ion Exch., accepted (2020), http://dx.doi.org/10.1080/07366299.2020.1831249.



Sr-90 retained on Sr Resin

Sr-90 recovered in 0.05M HNO3.

Y-90 retained on DGA Resin.

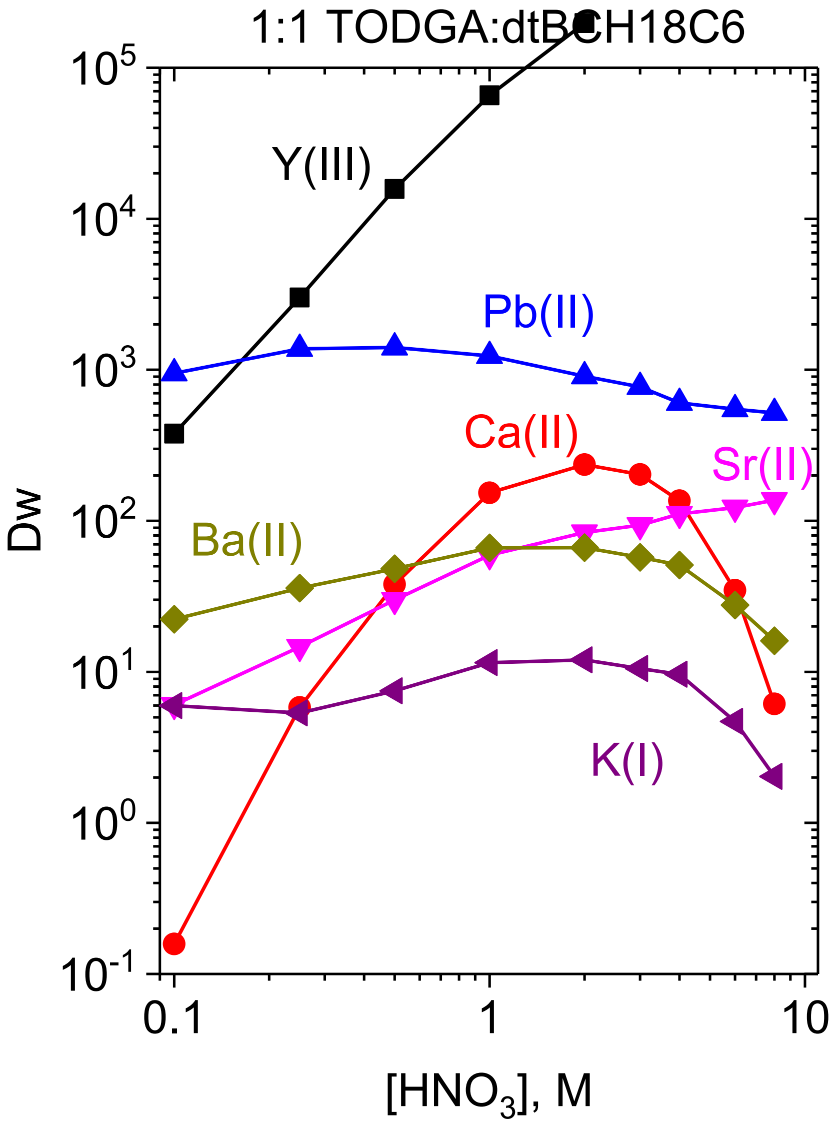
Y-90 recovered in dilute HCl.

Lower extractant bleed (octanol).

2-3M HCl rinse prior to recovery of Y-90 eliminates HNO3 carryover and Sr impurity.

Higher Y retention = smaller columns

^{90}Y (DGA-Sr Resin), TODGA replaces 1-octanol diluent



Sr-90 and Y-90 retained on single resin.

Sr-90 recovered in 2M HCl or 0.05M HNO3.

Y-90 recovered in dilute HCl.

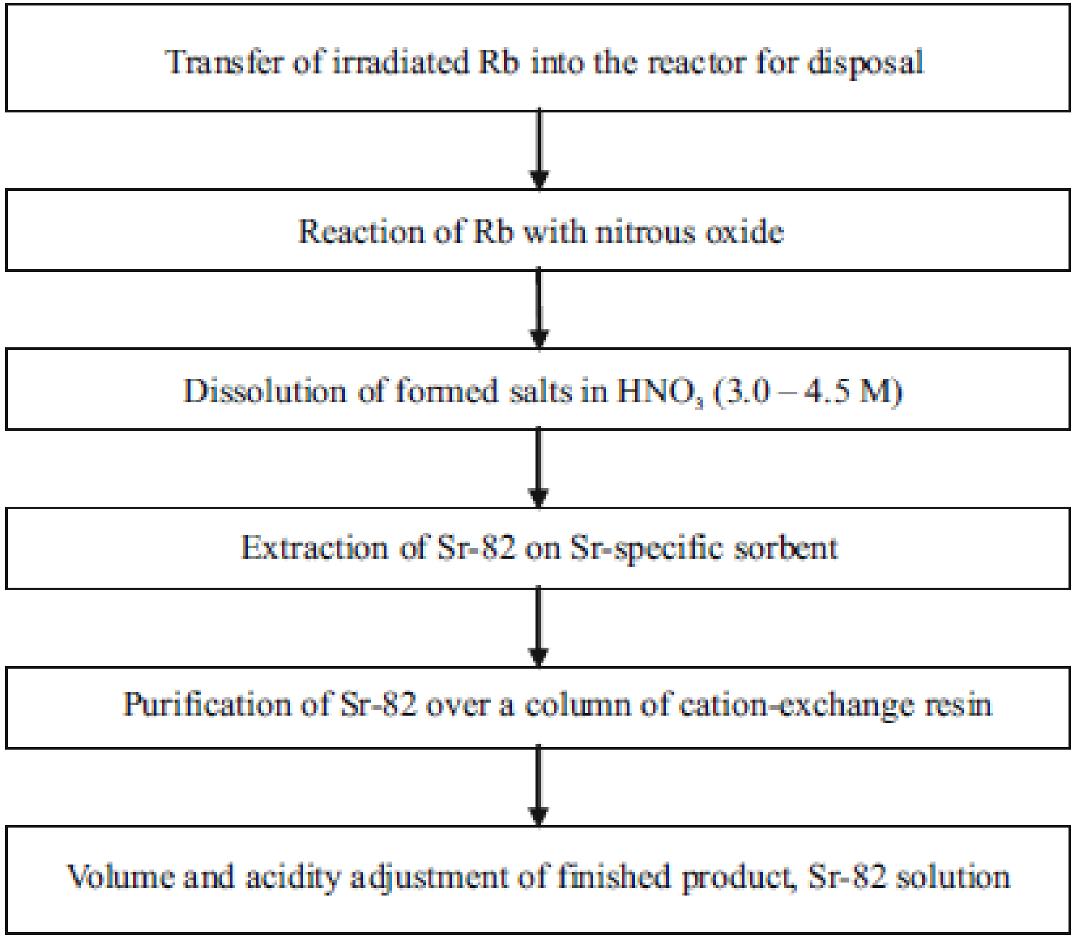
Lowest extractant bleed (no octanol).

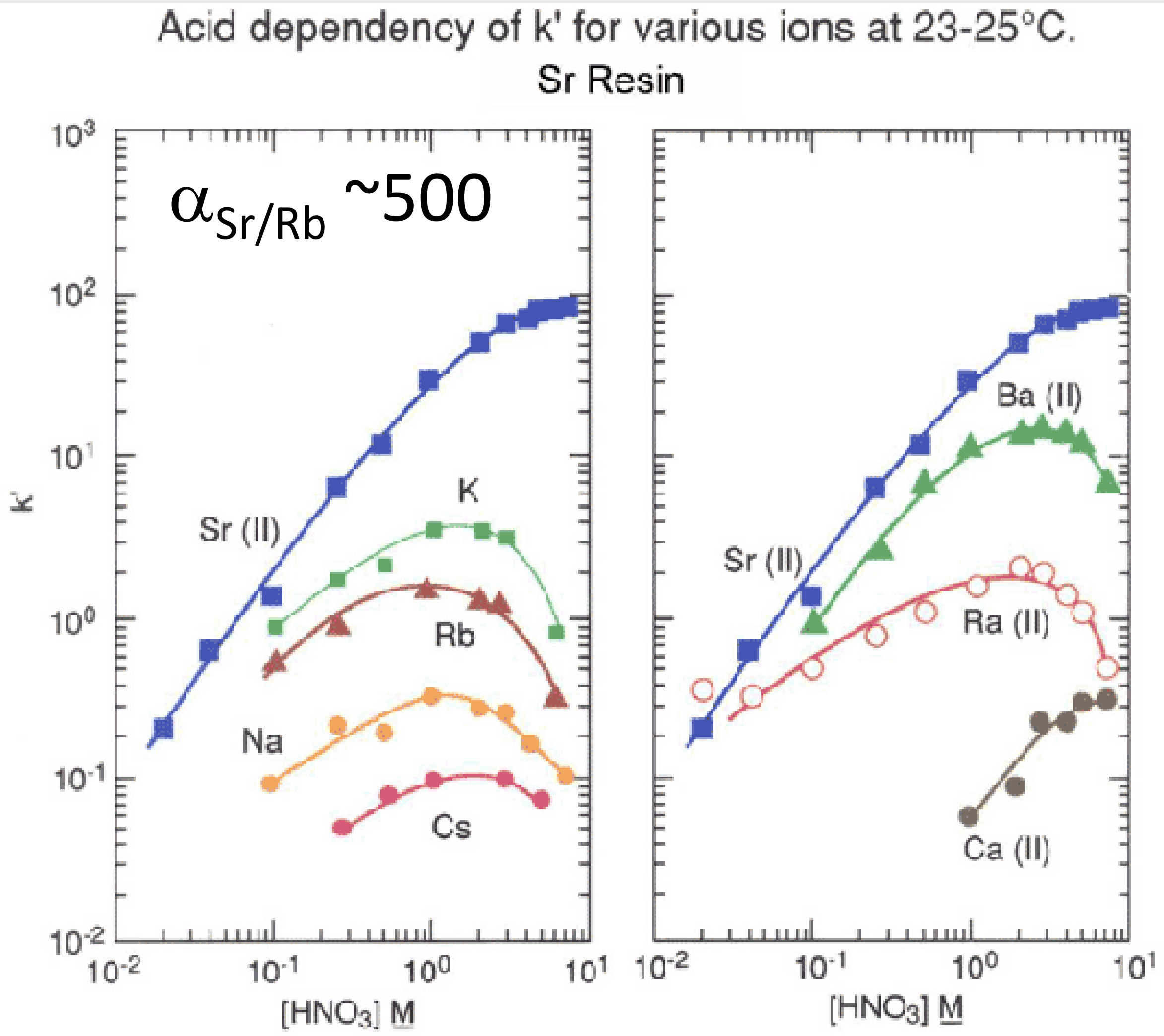
2-3M HCl rinse prior to recovery of Y-90 eliminates HNO3 carryover and Sr impurity.

Higher Y retention = smaller columns

D.R. McAlister, D. Silvestri, E. Rush, E.P. Horwitz, "Extraction of Selected Metal Ions by Mixtures of Diglycolamides and Crown Ethers," *Solv. Extr. Ion Exch.*, 39(2), 184-203 (2021).

Sr-82 Flowsheet (50 grams Rb target)





Dunin, A.V., Nerozin, N.A., Togaeva, N.R., Khamyanov, S.V., Shapovalov, V.V. 2014. Extraction of Sr-82, Raw Material for Radiopharmaceutical Production. Pharmaceutical Chemistry Journal, 48(6), 395-397.

Sr-82 Flowsheet (50 grams Rb target)

TABLE 1. Technical Characteristics of Strontium-82

Parameter	Norm
Specific activity of Sr-82, TBq/g (Ci/g), at least	0.9(25)
Activity concentration of Sr-82, GBq/mL (mCi/mL), at least	2.2(60)
Total chemical impurities, μg/cm^3, less than	20
Radionuclidic impurities, mCi/mCi ^{82}Sr, less than	
Rb-83	0.0015
Rb-84	0.0001
Rb-86	0.0015
Sr-85	0.0001
HCl or HNO_3 concentration	0.05 – 0.5

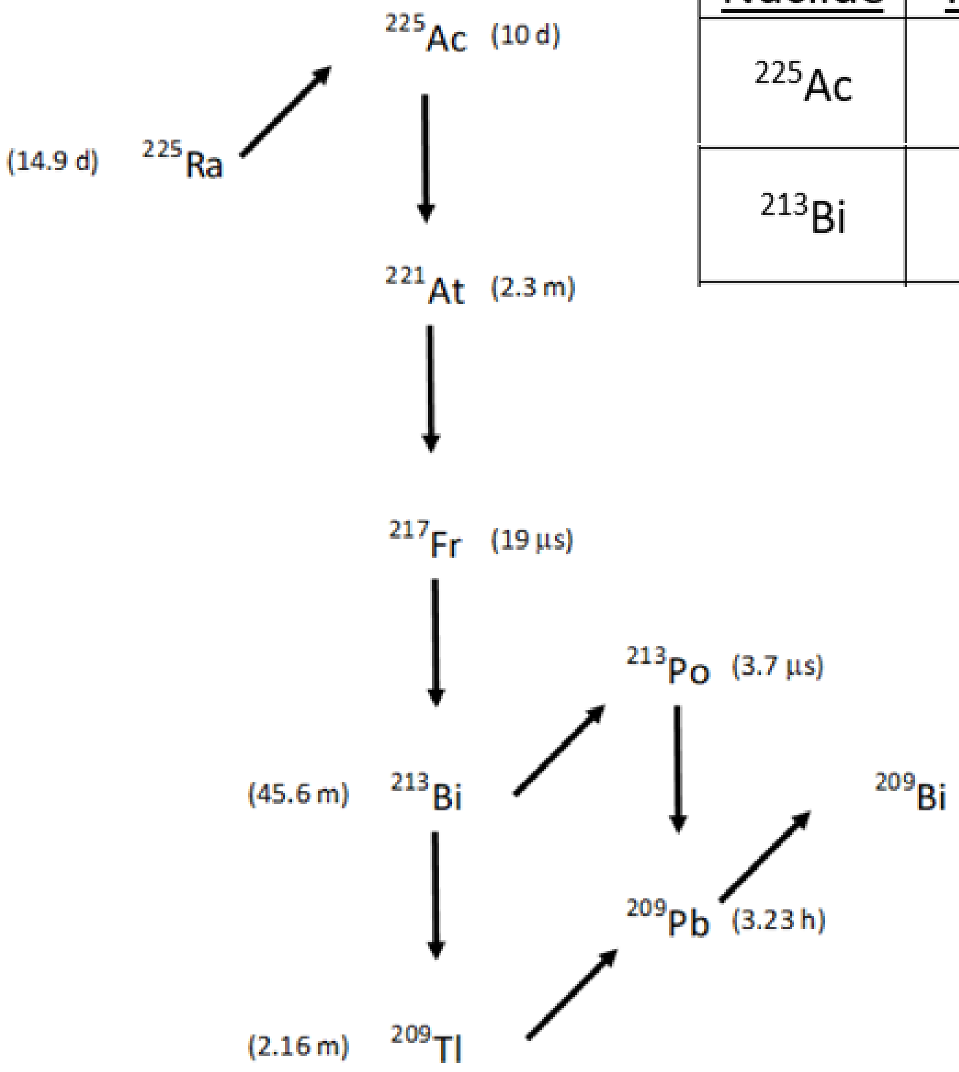
Dunin, A.V., Nerozin, N.A., Togaeva, N.R., Khamyanov, S.V., Shapovalov, V.V. 2014. Extraction of Sr-82, Raw Material for Radiopharmaceutical Production. Pharmaceutical Chemistry Journal, 48(6), 395-397.

$^{225}Ac/^{213}Bi$

-Standard Cow Generator

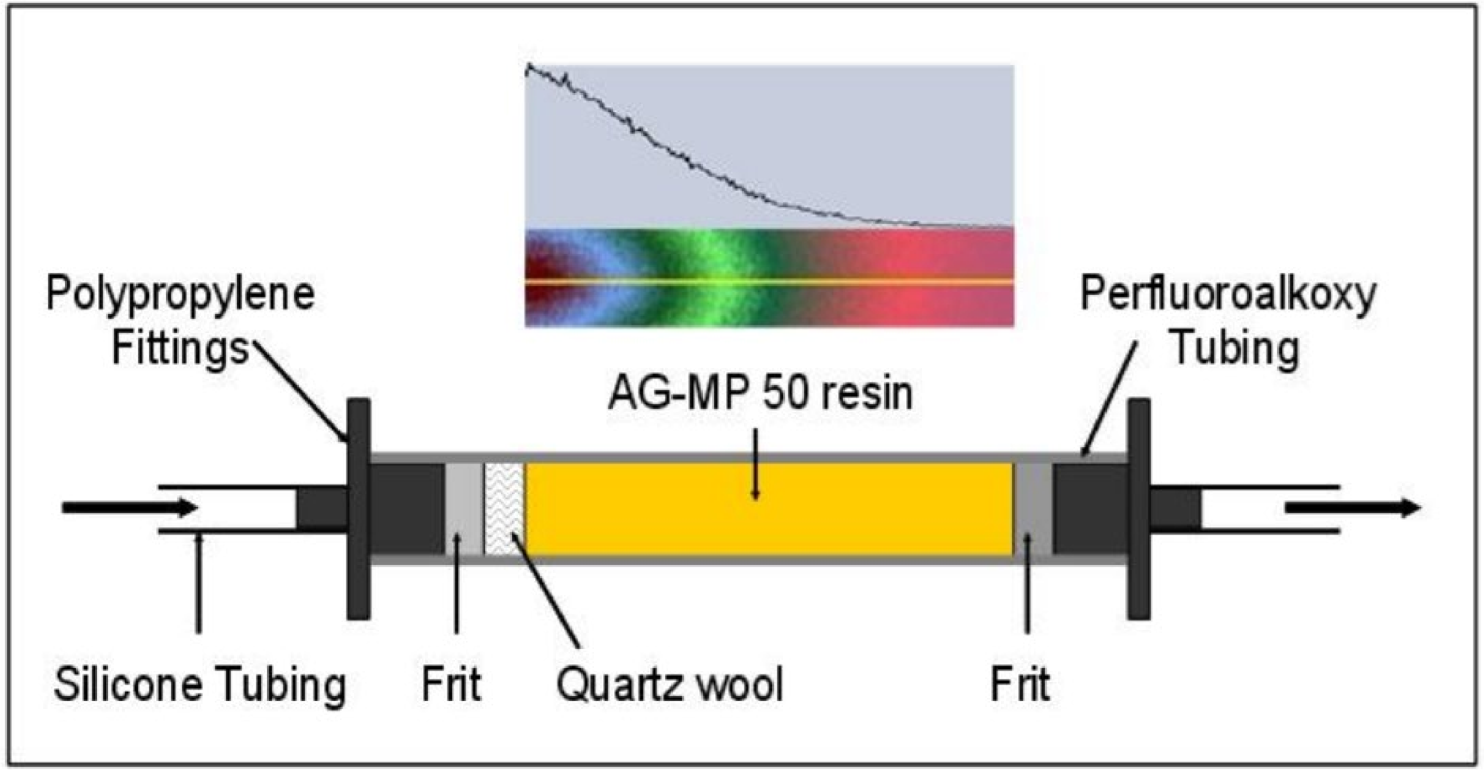
-Multicolumn Selectivity Inversion Generator

$^{225}Ac^{3+}$ / $^{213}Bi^{3+}$



Nuclide	Half Life	Decay	Production
^{225}Ac	10 d	α (5.0 – 5.8 MeV)	Decay ^{229}Th Proton Spallation ^{232}Th
^{213}Bi	45.6 m	α (5.6 – 5.9 MeV), 2.2% β^- (1423 keV), 97.8%	Decay ^{225}Ac

Bi-213 Generators (Standard Cow)



Scheme of Ac-225/Bi-213 generator with Ac-225 distribution profile

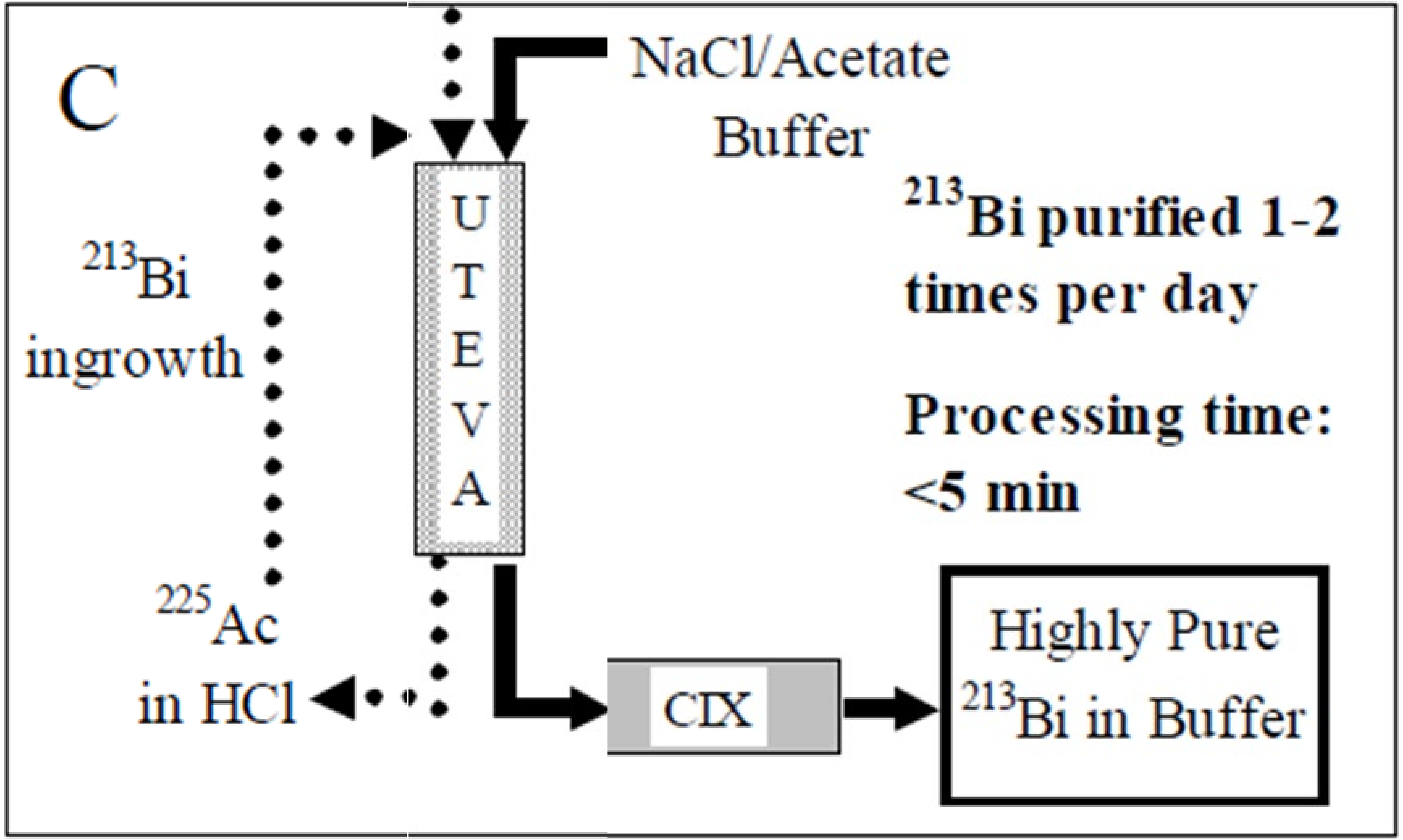
Elution with 0.1M HCl/NaI

30-40 mCi Ac-225:
- 75±10% Yield of Bi-213
- <0.0002% Ac-225 impurity

Application to clinical levels of ^{225}Ac could require multiple small generators or different technique.

http://www.iaea.org/inis/collection/NCLCollectionStore/_Public/42/022/42022139.pdf

Multi-Column Selectivity Inversion Generators (MSIG)



Store ^{225}Ac in solution

Improved radiation resistance.

Disposable columns

Likely requires automation to reduce operator dose.

D. R. McAlister and E. P. Horwitz, "Automated two column generator systems for medical radionuclides," *Applied Radiation and Isotopes*, 67, 1985-1991, (2009).

Bi-213 Generators (Summary Table)

Generator	Resins	Yield	Ac impurity	Matrix
Cow	MP50	76%	<2 E-5 %	0.6 mL 0.1M HCl/HI
MSIG	UTEVA 50Wx8 Prefilter	87%	<1 E-7%	2.0 mL 0.5M NaOAc 0.75M NaCl, pH 4.0

A. N. Vasiliev, V. A. Zobnin, Yu. S. Pavlov & V. M. Chudakov (2020) Radiation Stability of Sorbents in Medical ^{225}Ac/^{213}Bi Generators, Solvent Extraction and Ion Exchange, DOI: 10.1080/07366299.2020.1846892

$^{232/229}Th/^{225}Ra/^{225}Ac$ (^{225}Ac Production Methods)

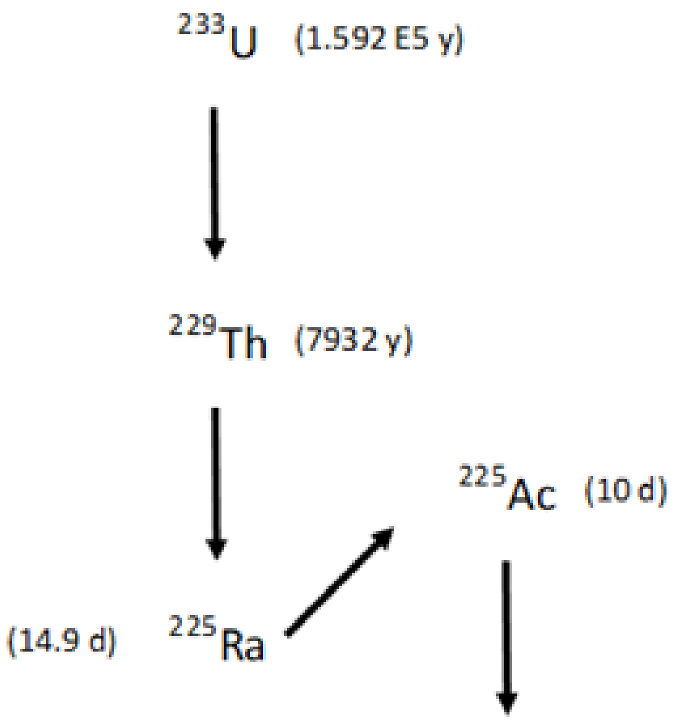
-Solvent Extraction vs Ion Exchange vs EXC

-Importance of Selectivity

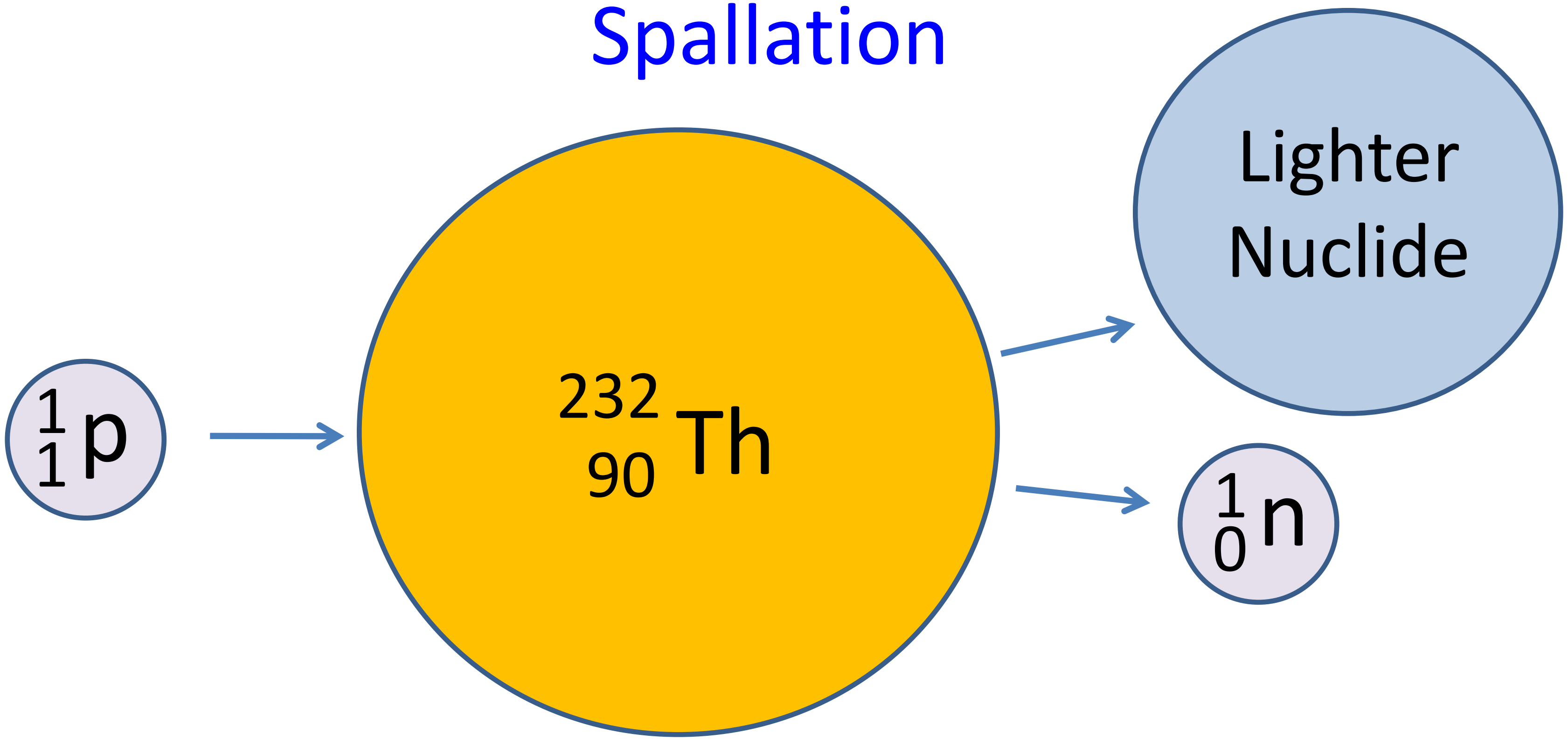
-Large Target Separations

$^{225}Ac^{3+}$ Sources

Nuclide	Half Life	Decay	Production
^{233}U	1.592 E5 y	α (4.5 – 4.8 MeV)	Thermal Breeder Reactors: $^{1}n + ^{232}Th \rightarrow ^{233}Th \rightarrow ^{233}Pa \rightarrow ^{233}U$
^{229}Th	7932 y	α (4.5 – 5.1 MeV)	Decay ^{233}U
^{225}Ac	10 d	α (5.0 – 5.8 MeV)	Decay ^{229}Th Proton Spallation ^{232}Th
^{225}Ra	14.9 d	β^- (356 keV)	Decay ^{229}Th Proton Spallation ^{232}Th
^{213}Bi	45.6 m	α (5.6 – 5.9 MeV), 2.2% β^- (1423 keV), 97.8%	Decay ^{225}Ac
^{227}Ac	21.77 y	α (4.4 – 5.0 MeV), 1.38% β^- (44.8 keV), 98.62%	Decay ^{235}U Proton Spallation ^{232}Th



Spallation



High energy protons strip neutrons and fragments from thorium forming lighter nuclides.

Fragments can also combine with thorium to form heavier nuclides.

Ac-225 Separation Schemes

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

$^{232}Th(p,x)^{225}Ra$ (β-)^{225}Ac

Primary Separation: SX (DA[AP]) – HNO_3

(Th Removal) Anion Exchange (MP1 or 1x8) - HNO_3

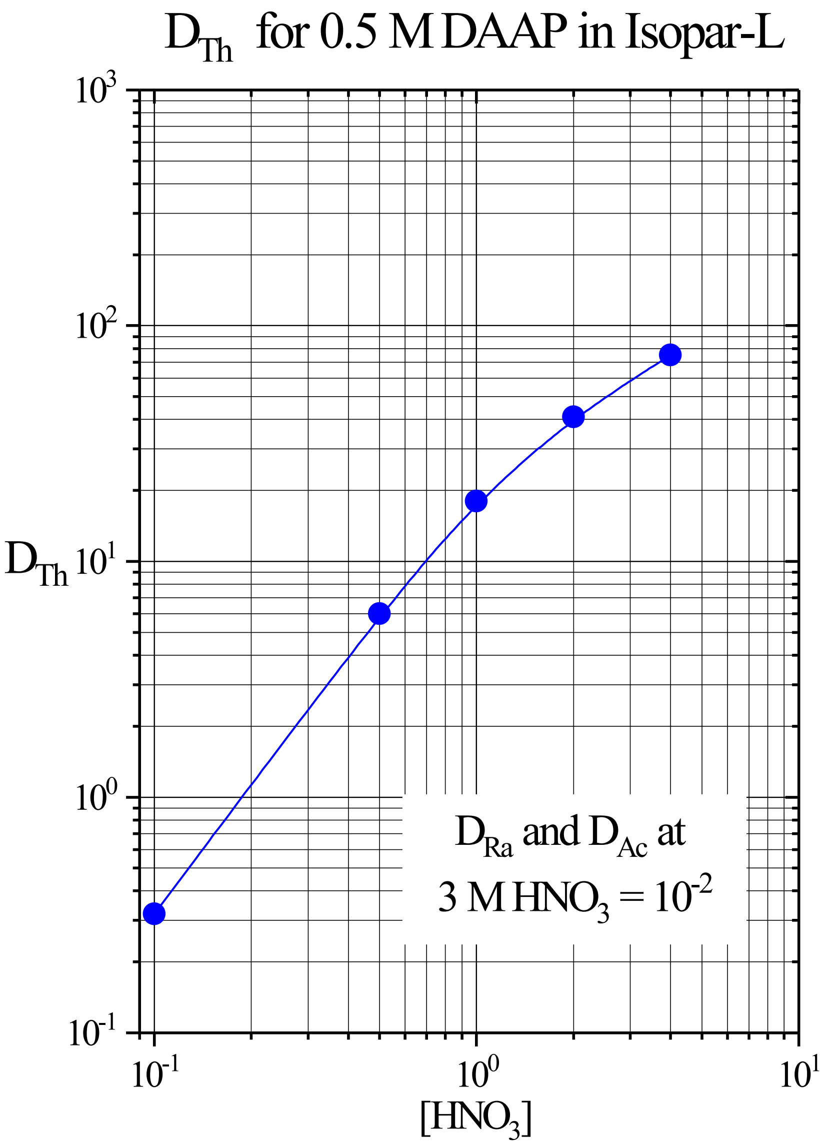
Cation Exchange (50Wx8) -H_2SO_4 or Citrate

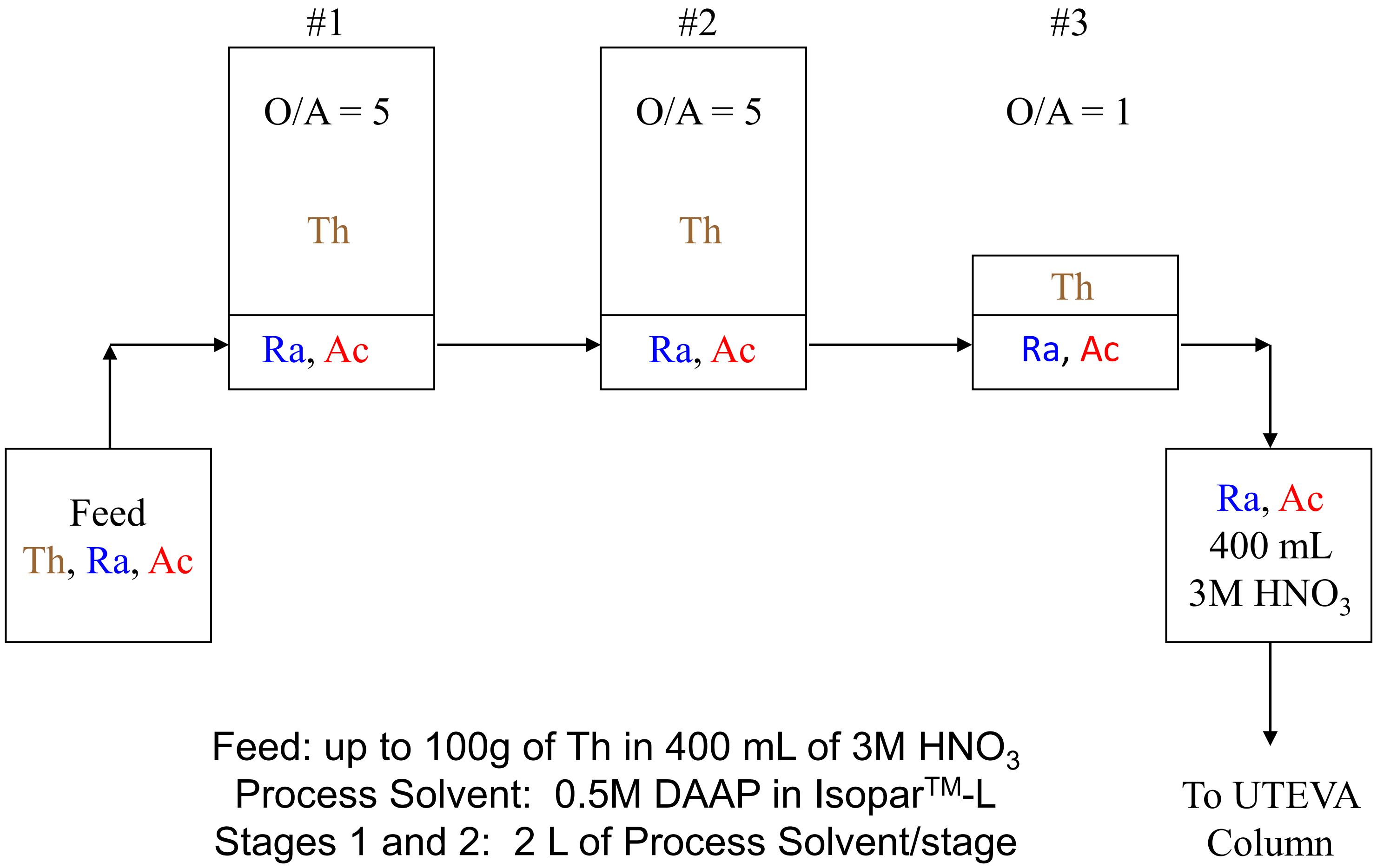
Secondary Columns: UTEVA/DGA, cation exchange

- Remove remaining Th and spallation byproducts
- Separate Ac/Ra
- Remove key byproducts/impurities: ^{230}U, $^{231/233}Pa$, Ca, Fe, ^{140}La, ^{227}Ac???

SX with DA[AP]

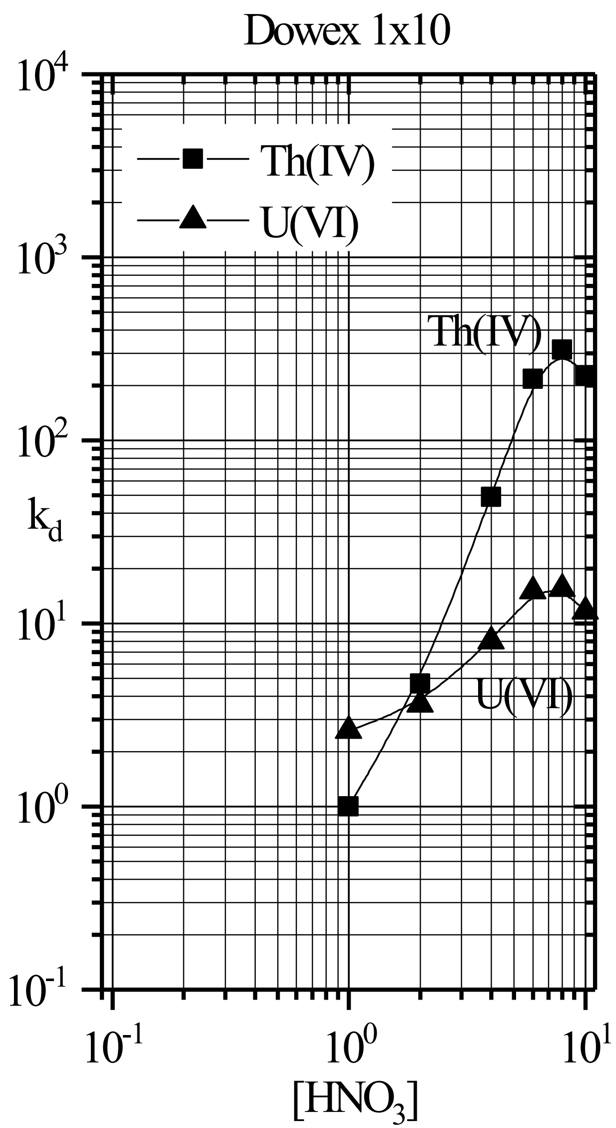
J. Harvey, J. A. Nolen, T. Kroc, I. Gomes, E. P. Horwitz, D. R. McAlister, "Production of Ac-225 via high energy proton induced spallation of Th-232," Proceedings of Application of high energy proton accelerators, Fermilab, Chicago, IL, October 19-21, eds. Rajendran Raja and Shekhar Mishra, pp. 321-326 (2010).

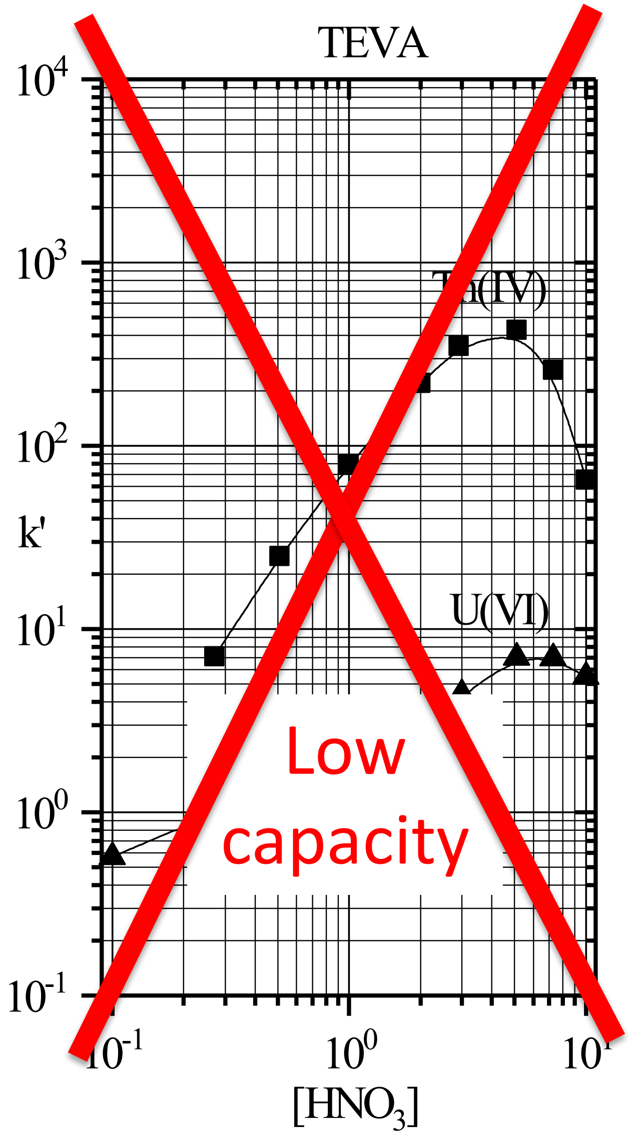




Feed: up to 100g of Th in 400 mL of 3M HNO_3
Process Solvent: 0.5M DAAP in Isopar™-L
Stages 1 and 2: 2 L of Process Solvent/stage
Stage 3: 400 mL of Process Solvent
Mixing Time: 2 minutes/stage

Th Selective Separations



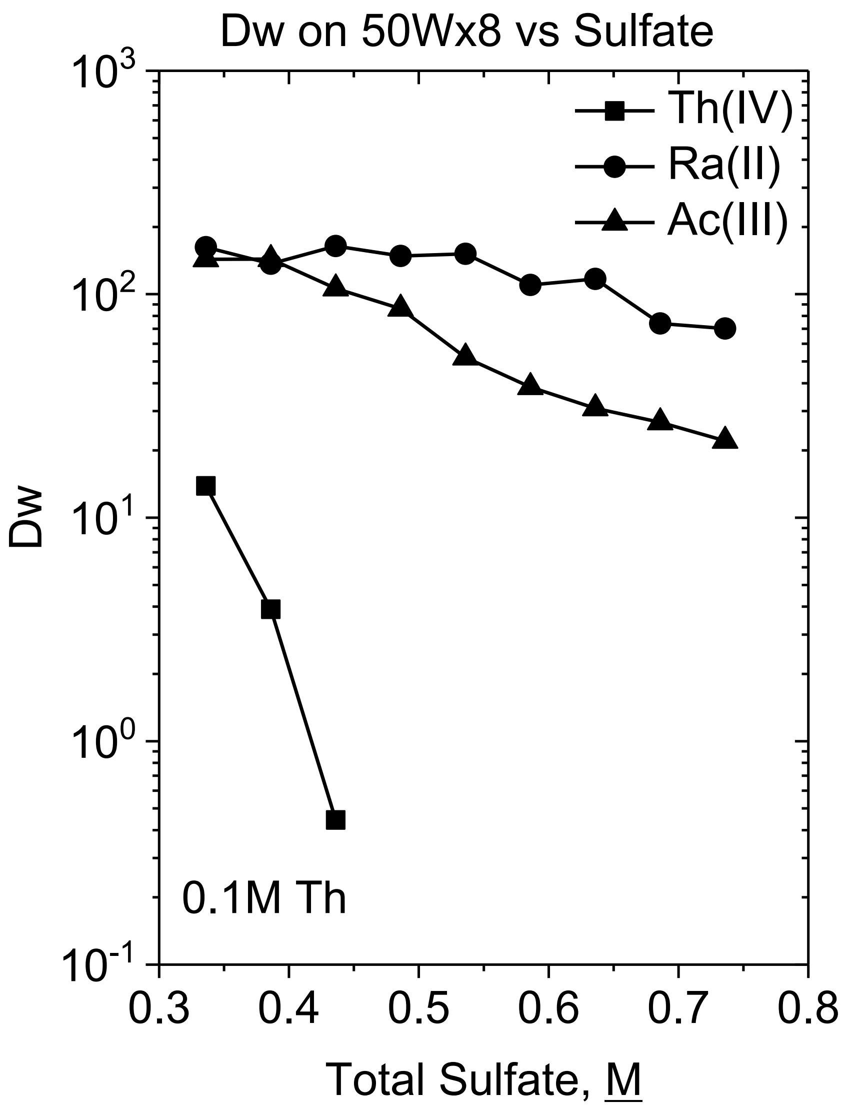


Extracting Th (10-50g) from HNO_3 requires very large columns (1-2 L) of 1x8 or MP-1).

High acid concentration and volume may require evaporation prior to next steps.

Harvey, J.H., Nolen, J., Vandergrift, G., Kroc, T., Gomes, I., McAlister D.R., Horwitz, E.P. 2011. Production of Actinium-225 via High Energy Proton Induced Spallation on Thorium-232. Final Technical Report DE-SC0003602. https://www.osti.gov/scitech/servlets/purl/1032445/

Ac Selective Separations



Reverses selectivity

- Rejects anionic Th
- Retains Ac/Ra

Allows for smaller columns.

Ac/Ra recovered in 5M HNO_3.

No evaporate required prior to next steps.

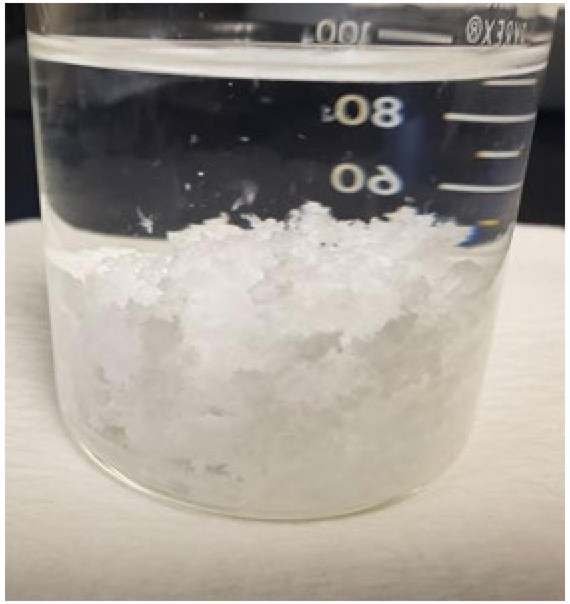
Dissolving Th metal in H_2SO_4?

A.H. Bond, E.P. Horwitz and D.R. McAlister, "A Multicolumn Selectivity Inversion Generator for the Production of High Purity Actinium-225 for Use in Therapeutic Nuclear Medicine," August 8, 2006, United States patent number 7,087,206.

D.R. McAlister, E.P. Horwitz, "Selective Separation of Radium and Actinium from Bulk Thorium Target Material on Strong Acid Cation Exchange Resin from Sulfate Media," *Applied Radiation and Isotopes*, 140, 18-23 (2018).

Mastren, T., Radchenko, V., Owens, A., Copping, R., Boll, R., Griswold, J.R., Mirzadeh, S., Wyant, L.E., Brugh, M., Engle, J.W., Nortier, F.M., Birnbaum, E.R, John, K.D., Fassbender, M.E. 2017. Simultaneous Separation of Actinium and Radium Isotopes from a Proton Irradiated Thorium Matrix. Nature Scientific Reports, 7, 8216. doi:10.1038/s41598-017-08506-9

Dissolution of Th in H_2SO_4/HF

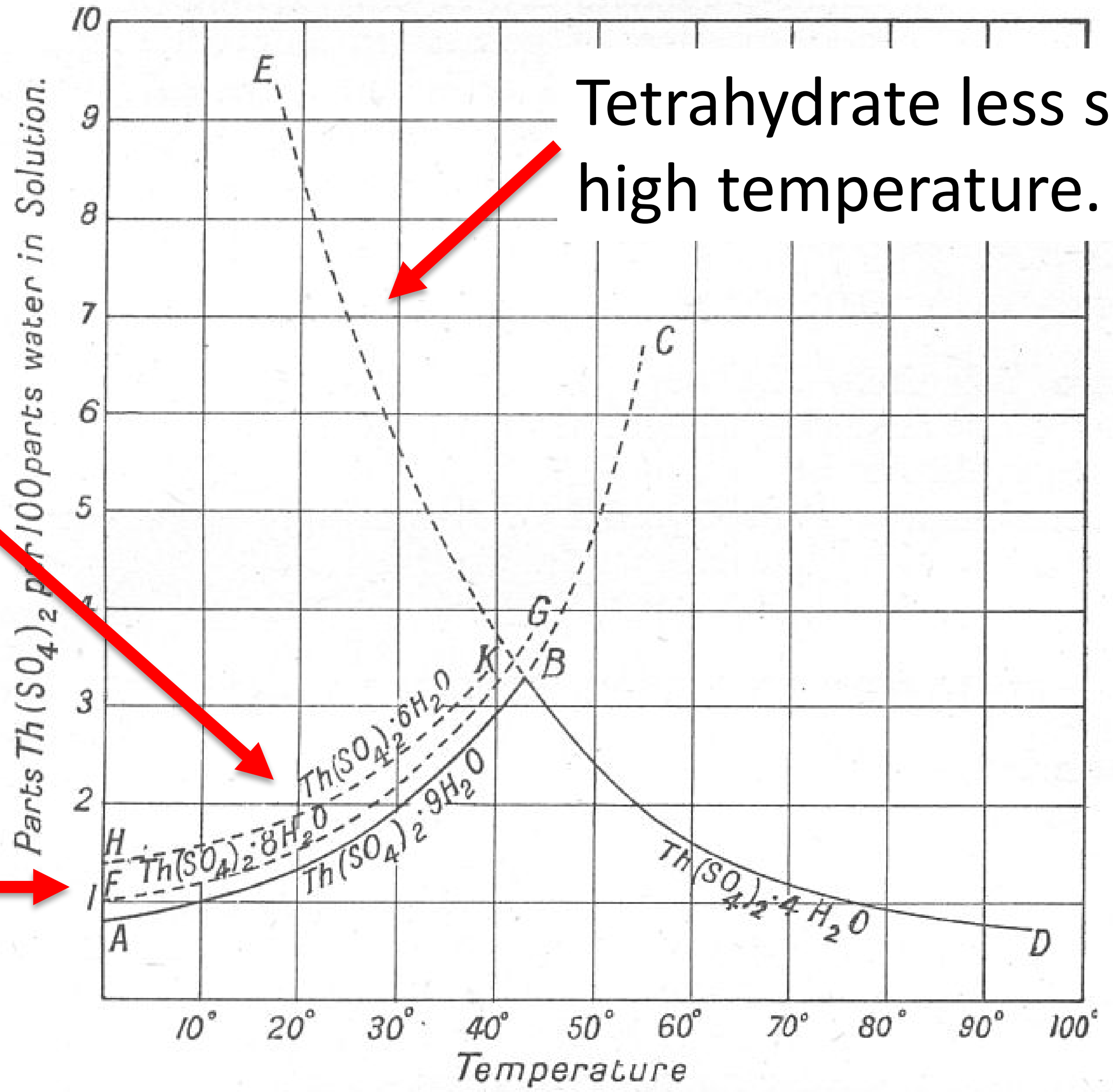


H_2SO_4
HF
H_20

Heat
H_20
Low Solubility??!!

"Selective Separation of Radium and Actinium from Bulk Thorium Target Material," D.R. McAlister, E.P. Horwitz, R. Perron, D. Gendron, P. Causey, J.T. Harvey, 11th International Symposium on Targeted Alpha Therapy, Ottawa, Ontario, Canada, April 1-4, 2019.

Solubility curves of the hydrates of thorium sulphate.



Tetrahydrate less soluble at high temperature.

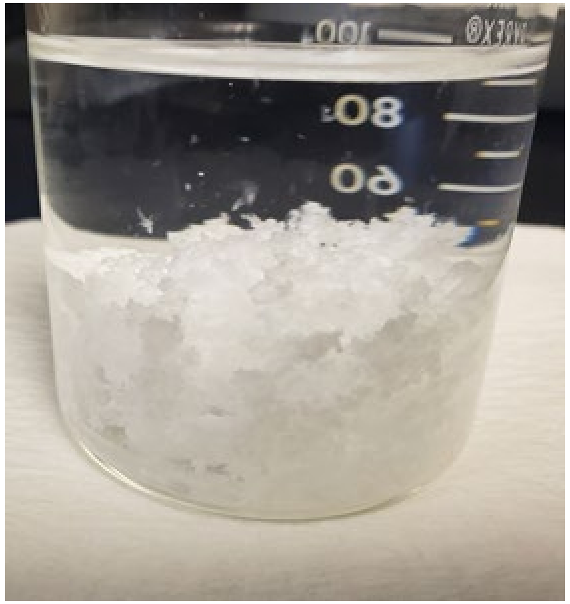
Th-sulfate solubility limit ~0.15 moles/L at 20C.

Hexa-, Octa-, Nona-, hydrates more soluble at high temperature.

https://www.osti.gov/servlets/purl/4844188-dg5S4r/

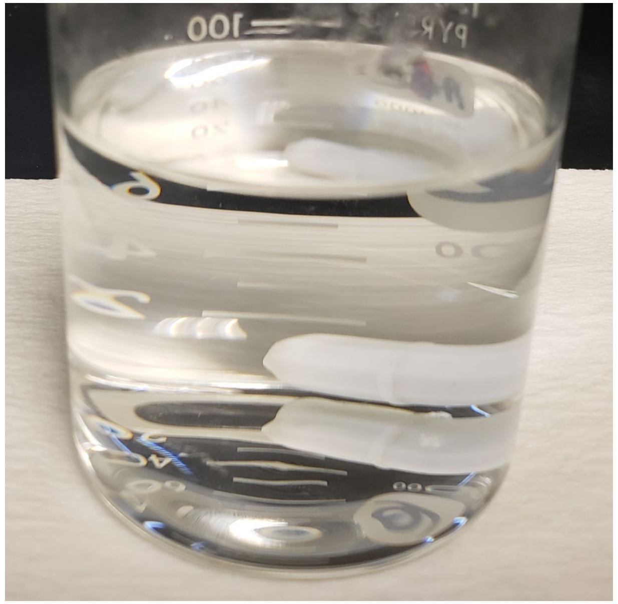
Dissolution of Th in H_2SO_4/HF

H_2SO_4
HF
H_2O

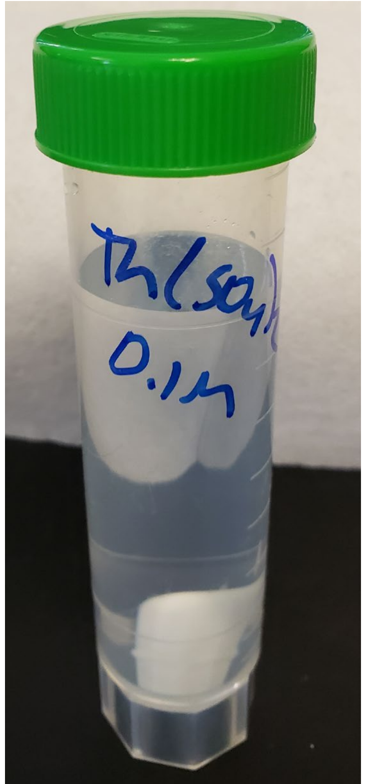


Heat
H_2O
Low Solubility??!!

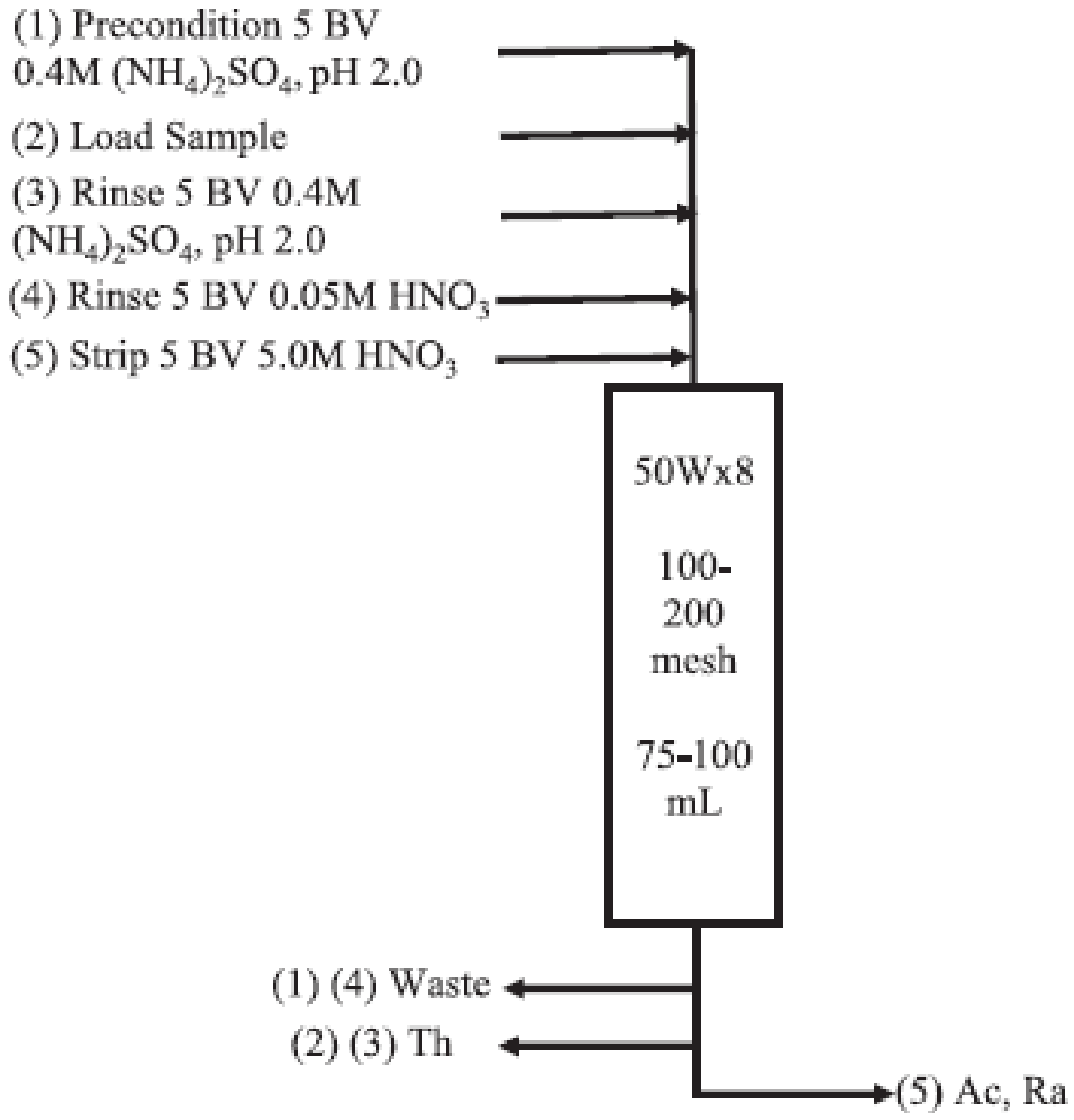
Cool. Mix.



0.6M H_2SO_4
0.03 M HF
0.1 M Th
pH 0.8 – 1.0



Th, Ac, Ra separation from H_2SO_4



75 – 100 mL cation exchange column

1-2 L of feed for (25-50 grams Th target)

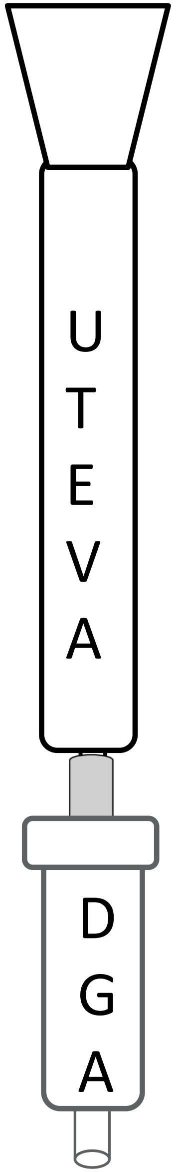
Recover Ac/Ra in 400-500 mL 5M HNO3

No evaporation required for further processing.

D.R. McAlister, E.P. Horwitz, "Sulfate based system for the separation of Actinium and Radium from irradiated Thorium Target," *Applied Radiation and Isotopes*, 140, 18-23 (2018).

Ac Polishing Steps

3-6M HNO_3

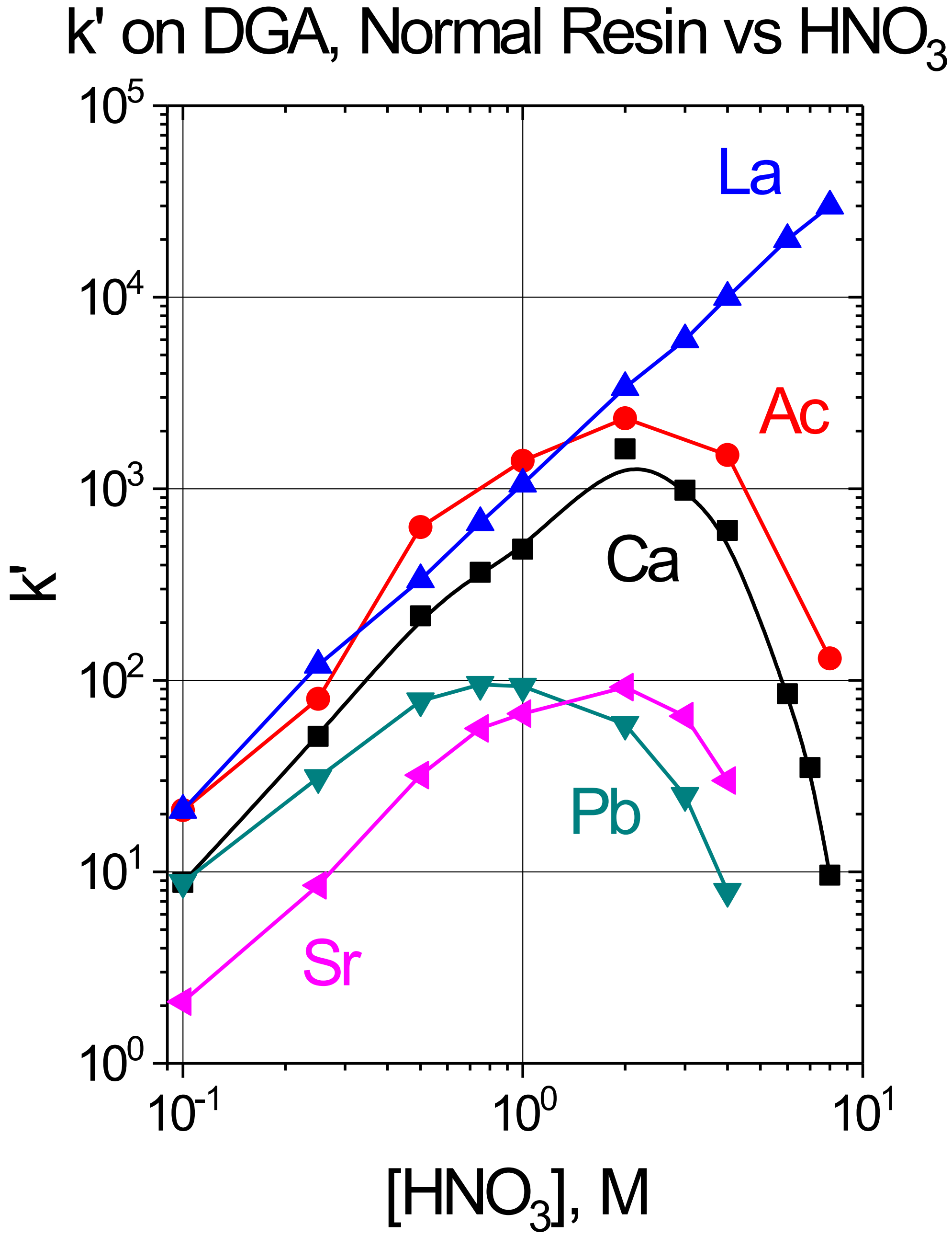


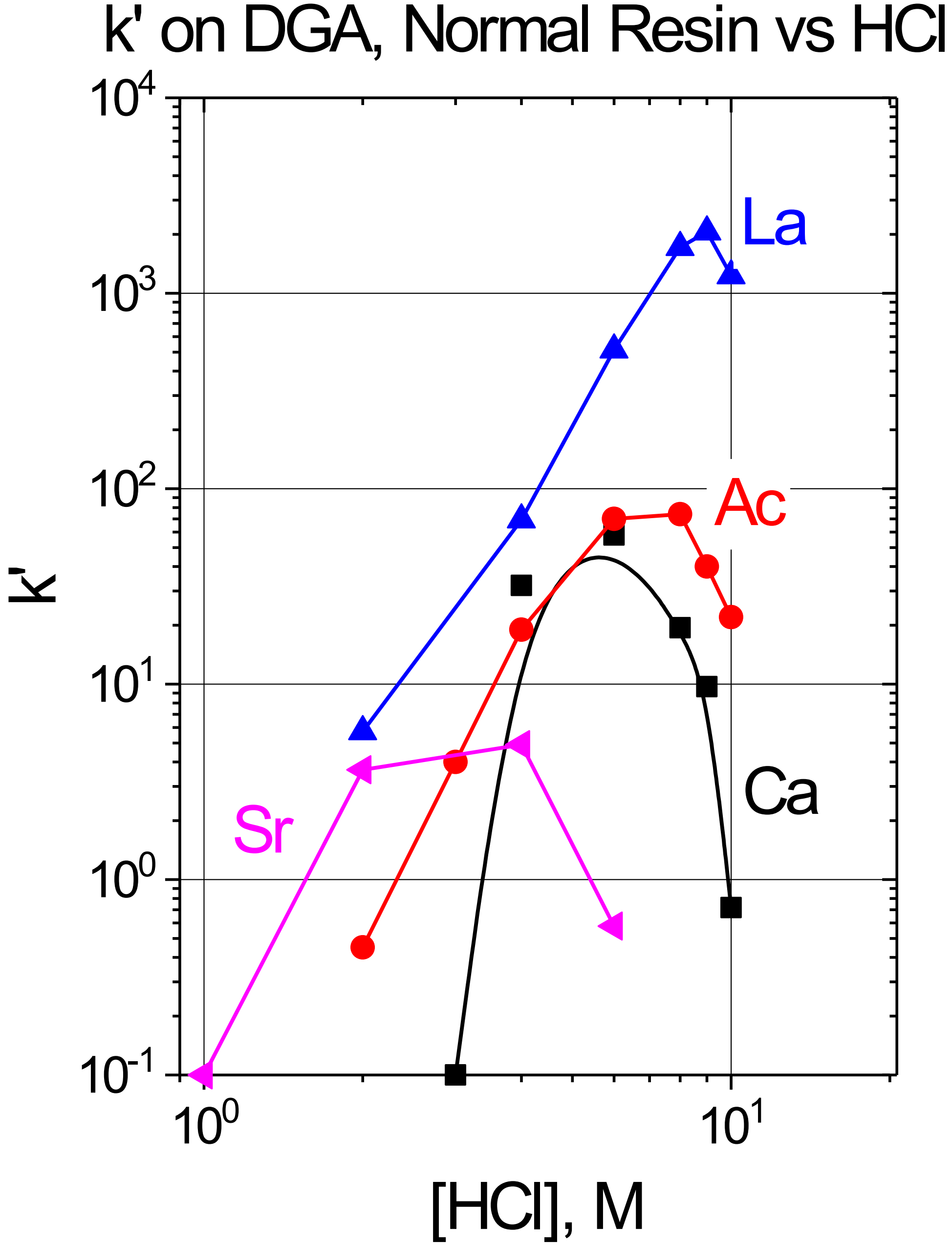
- UTEVA (Phosphonate)
  - removes remaining Th, Pa, U

- DGA
  - retains Ac^{3+}, rare earths, **Ca**

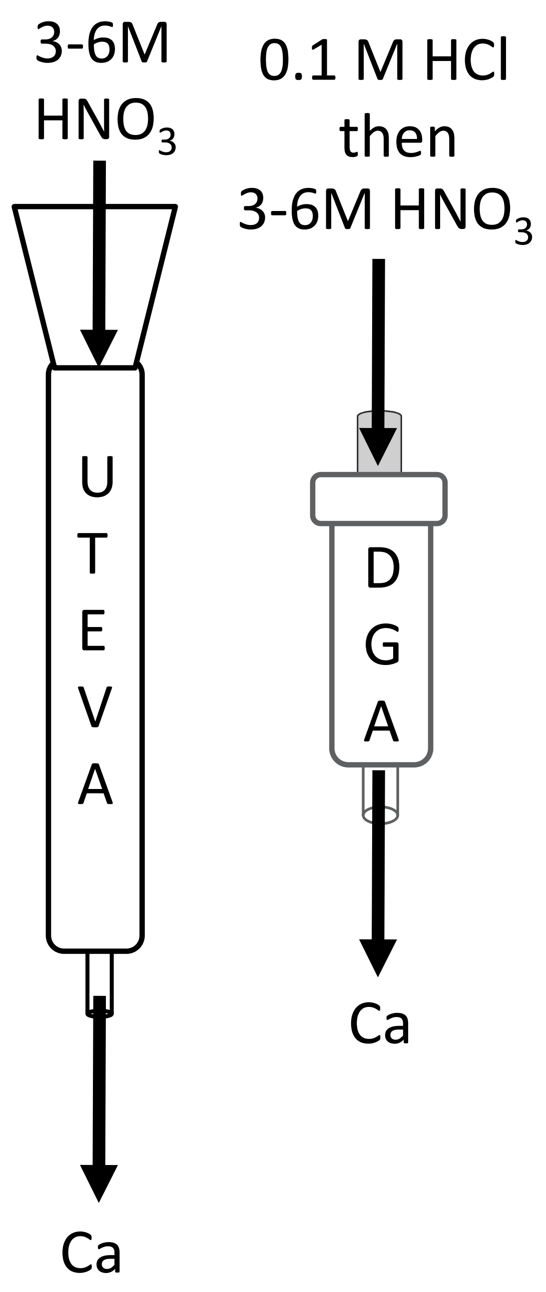
- Ra^{2+} passes both columns (Fe, Ba, Al, many fission products)

Ac Separation from Calcium and La





Ac Polishing Steps

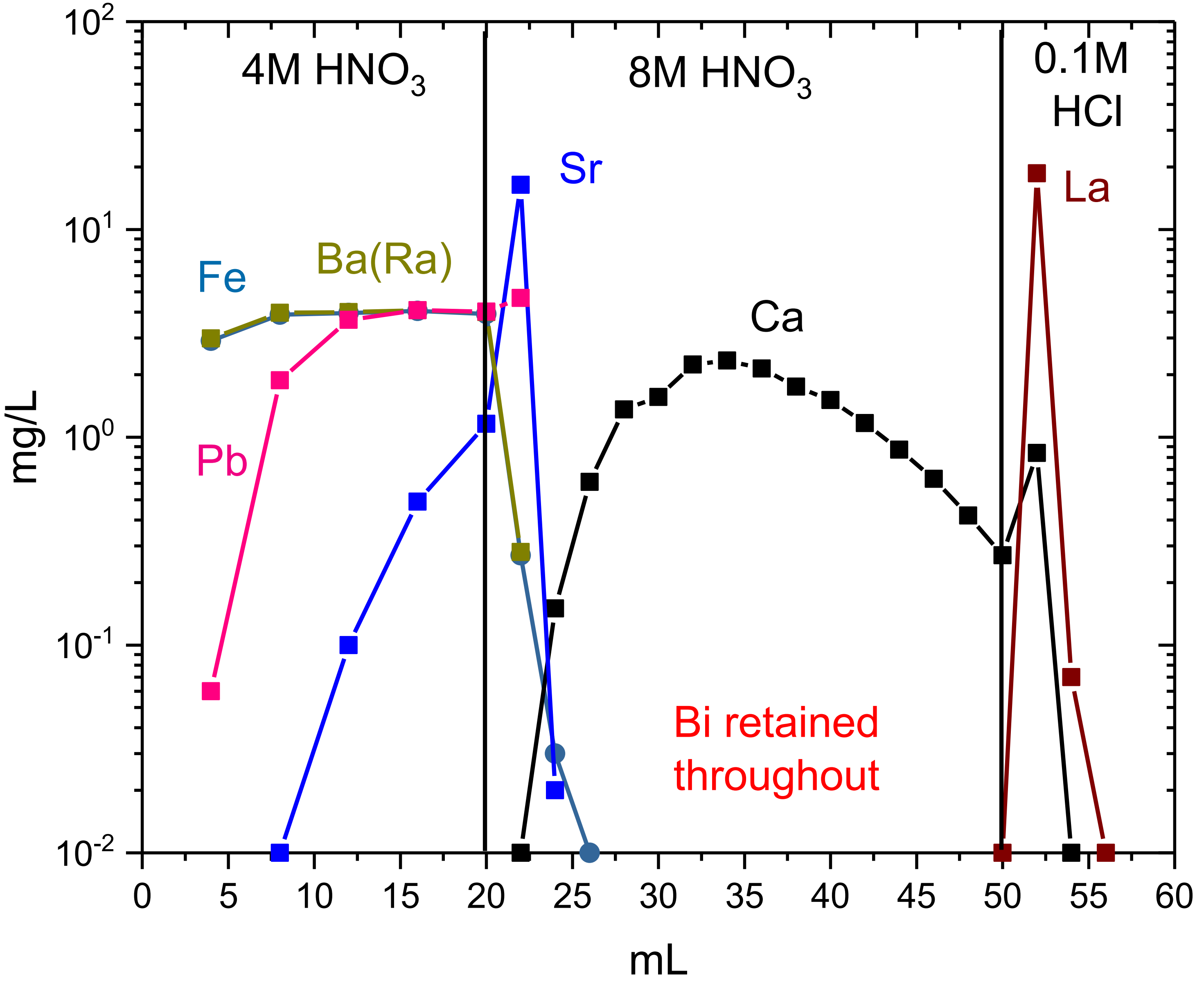


- UTEVA and DGA (and other reagents) can have small traces of Ca impurity precondition separately

- Ac/Ca will coelute from DGA, unless special care is taken to separate them.

- Conditioning UTEVA/DGA separately can eliminate much of the Ca impurity.

^{225}Ac Separation (8M HNO_3)

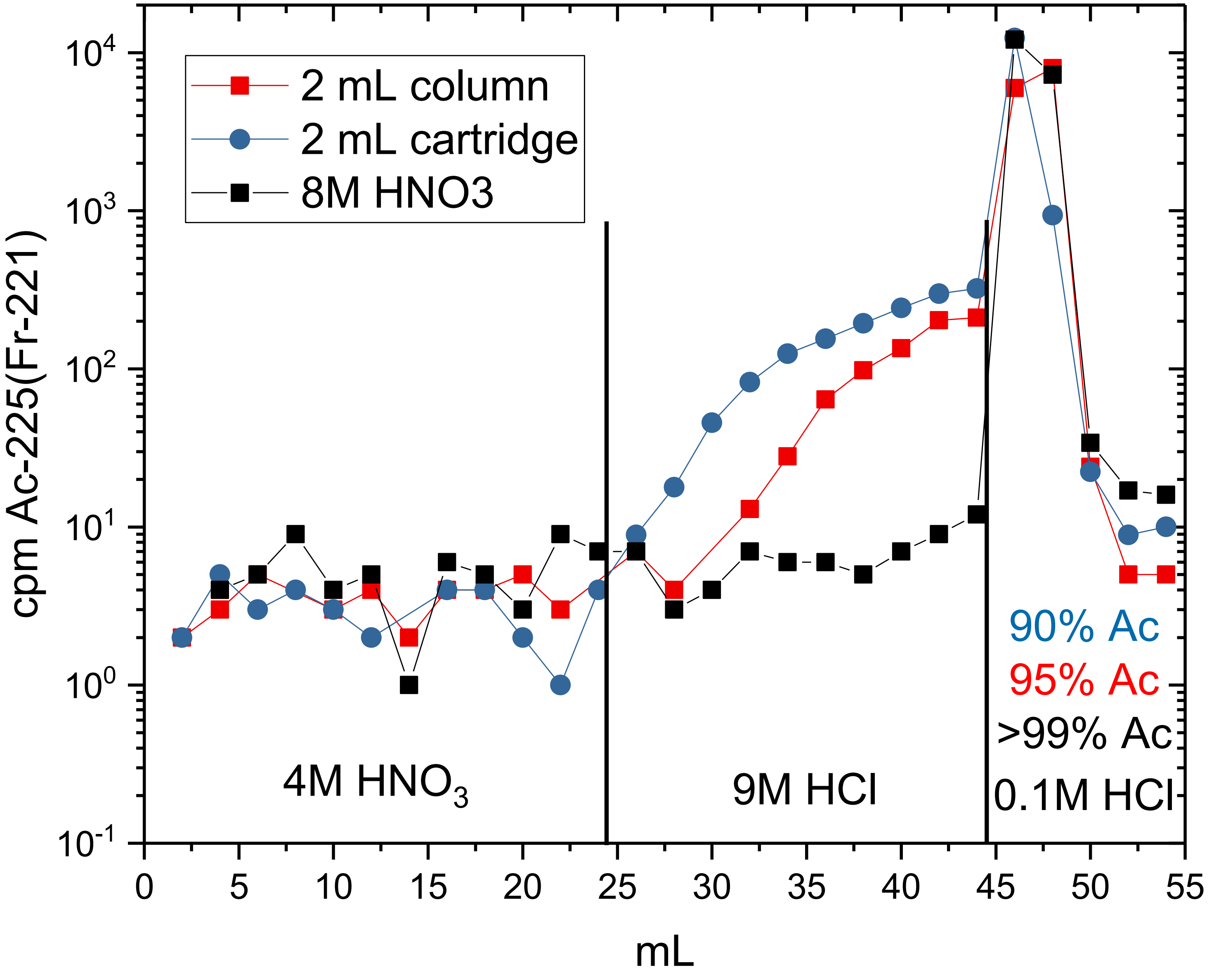


50-100 μm DGA, Normal Resin

Column
4.2 cm length
0.7 cm diameter

- Complete removal of Fe, Ba(Ra), Pb, Sr, Bi
- >95% removal of Ca
- La co-elutes with Ac

^{225}Ac Elution (breakthrough in calcium removal)

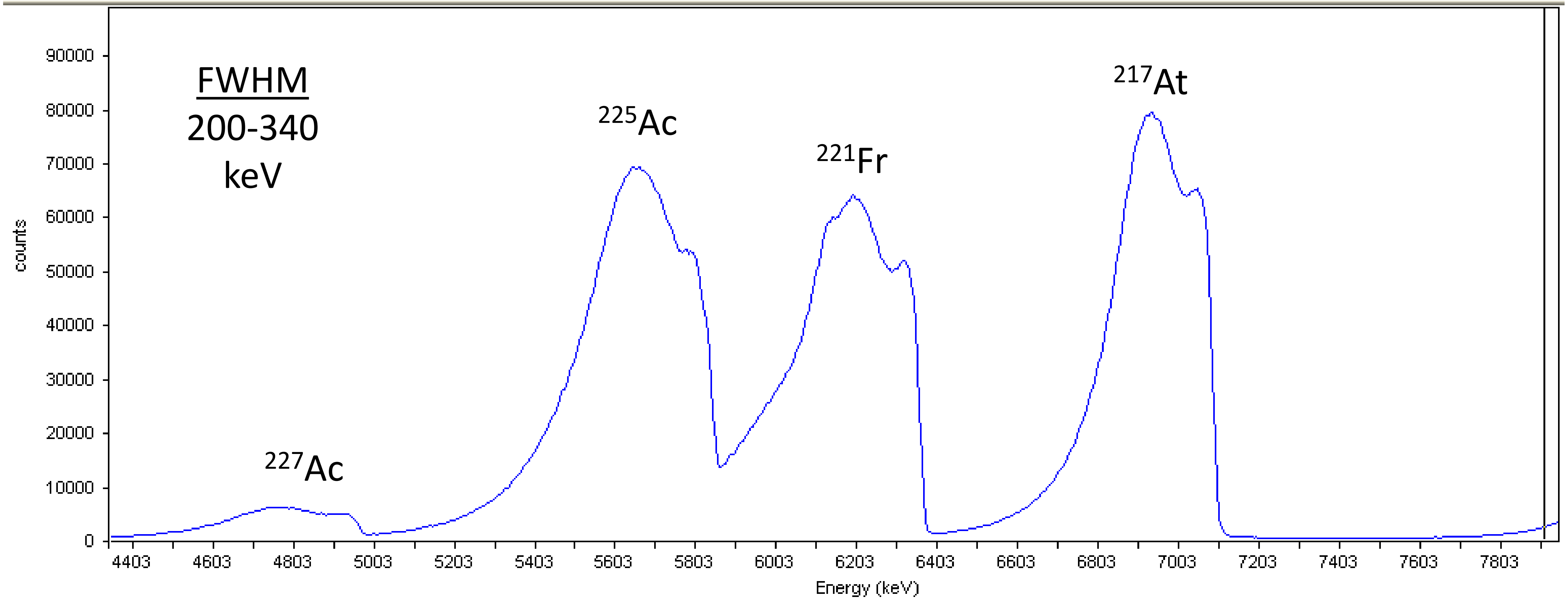


50-100 μm DGA, Normal Resin

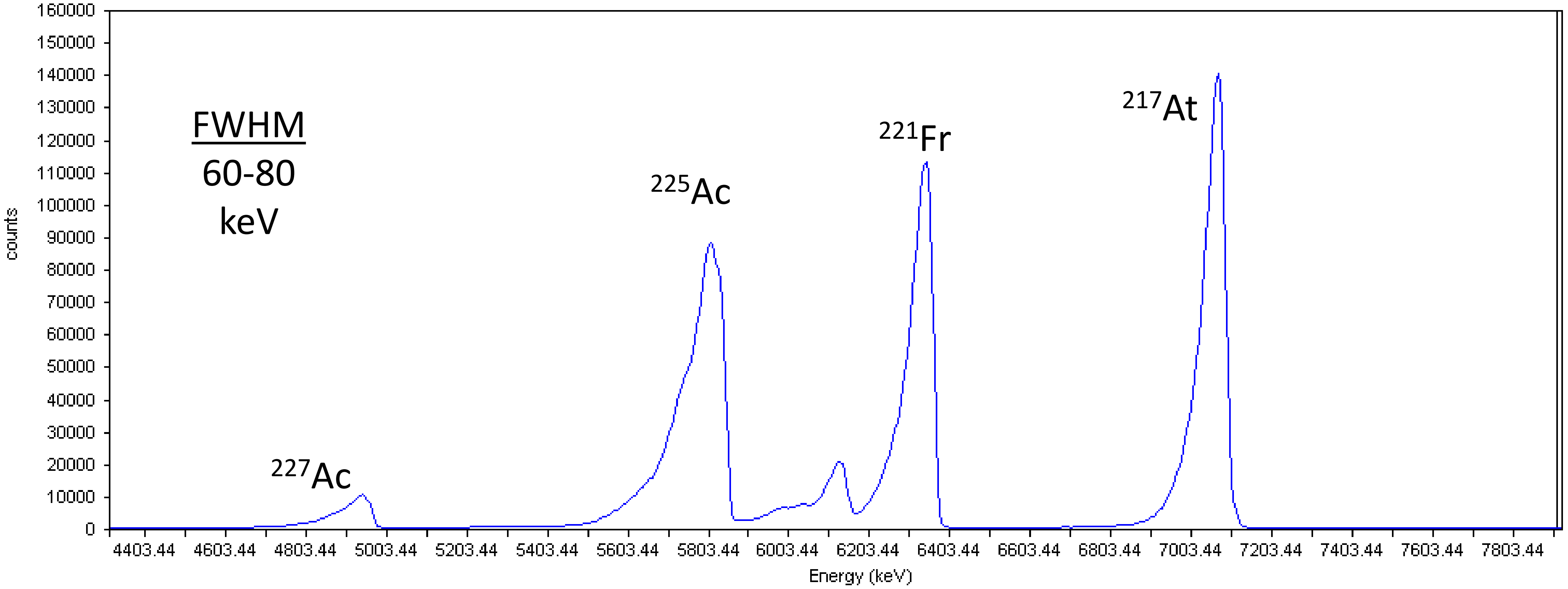
Column
4.2 cm length
0.7 cm diameter

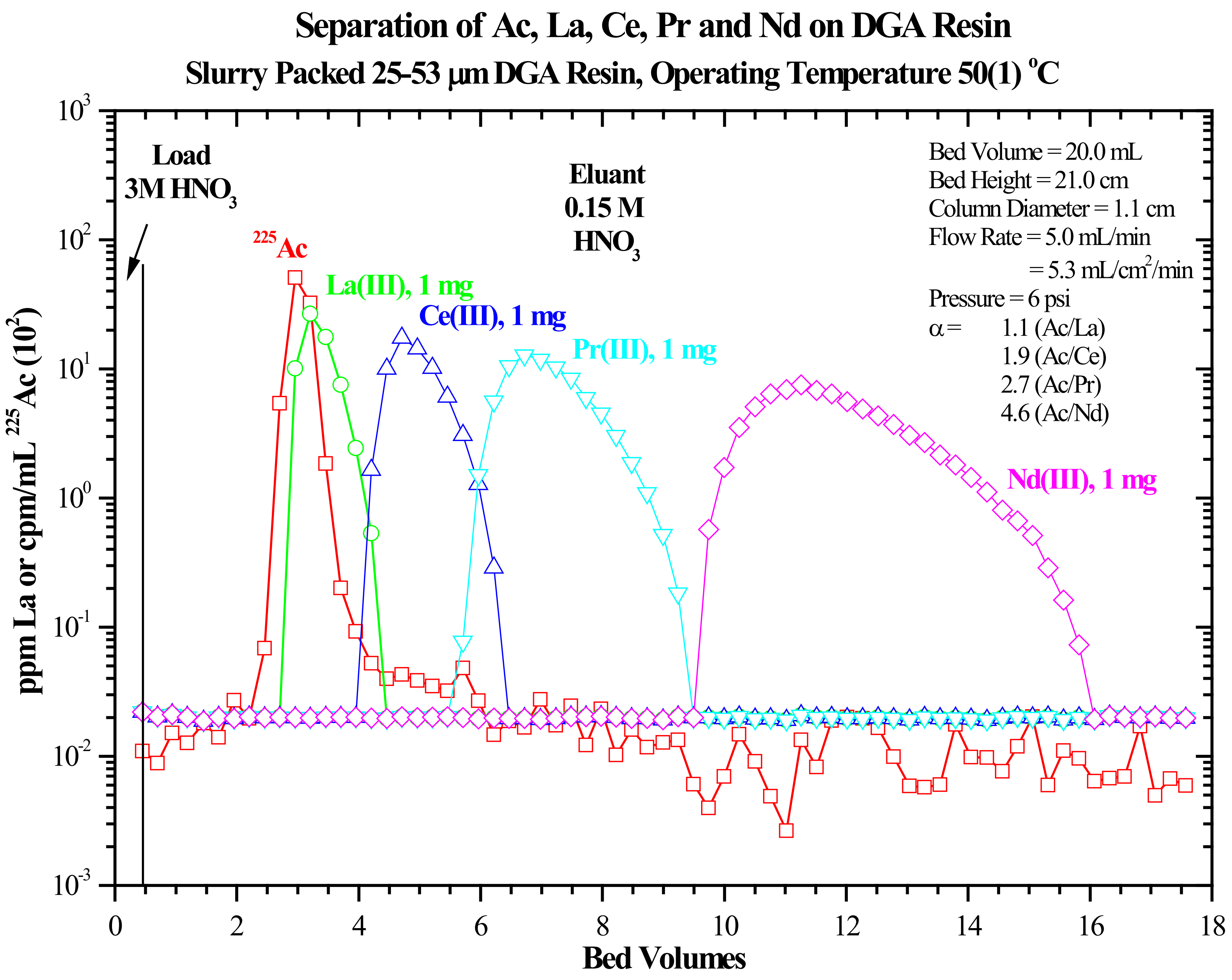
Cartridge
2.7 cm length
0.9 cm diameter

^{225}Ac w/ Ca Impurity

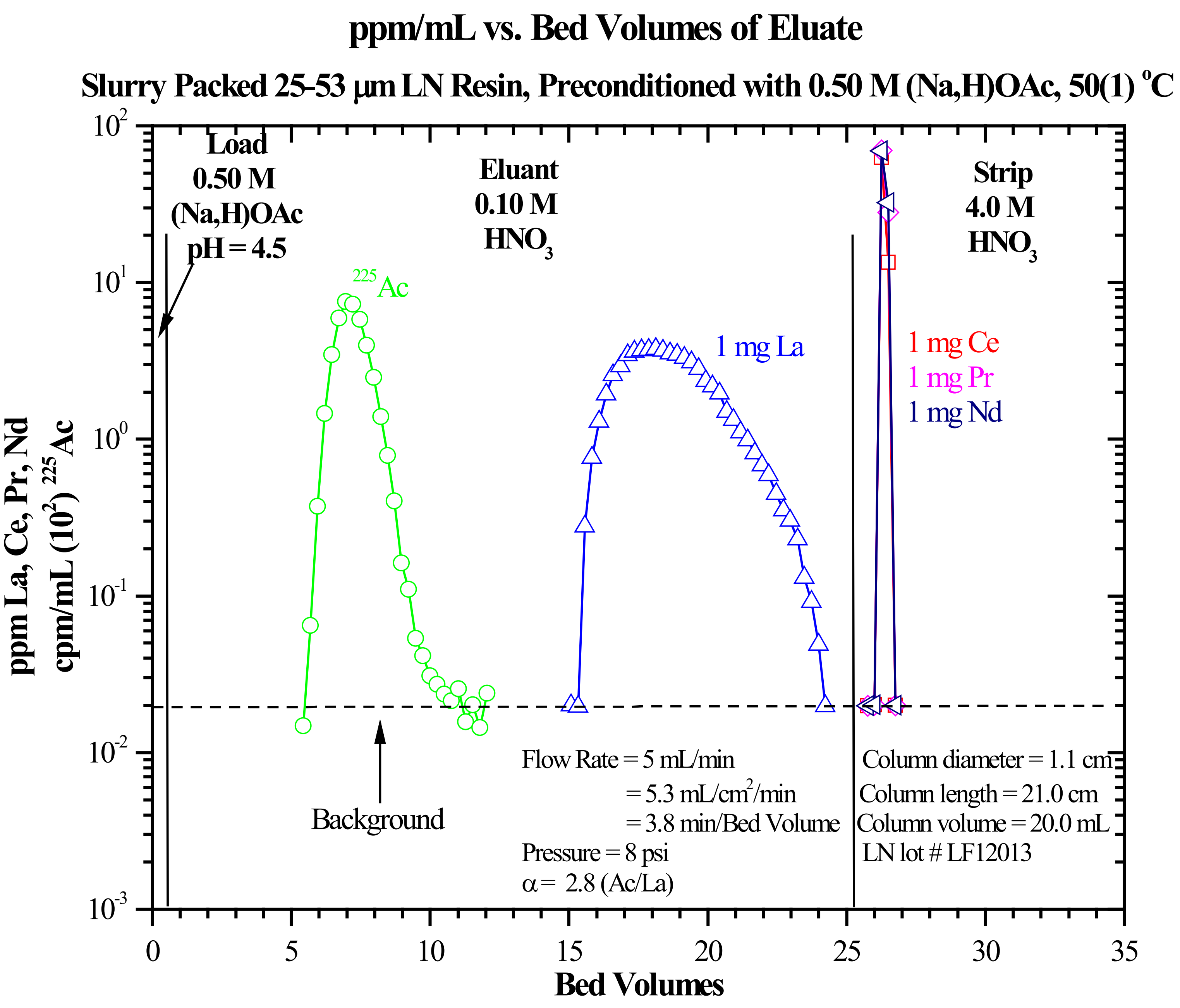


^{225}Ac Purity (Ca Removal)

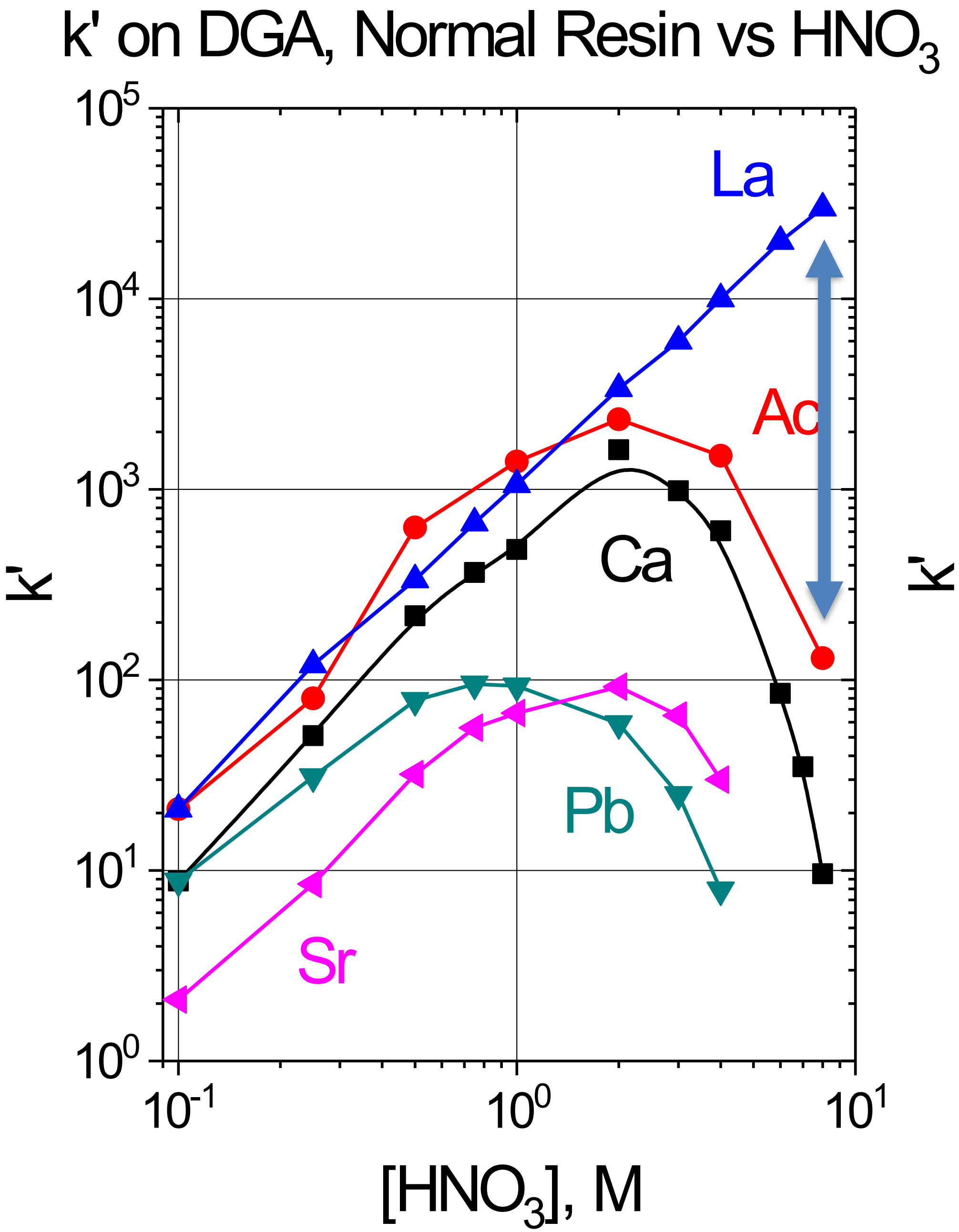


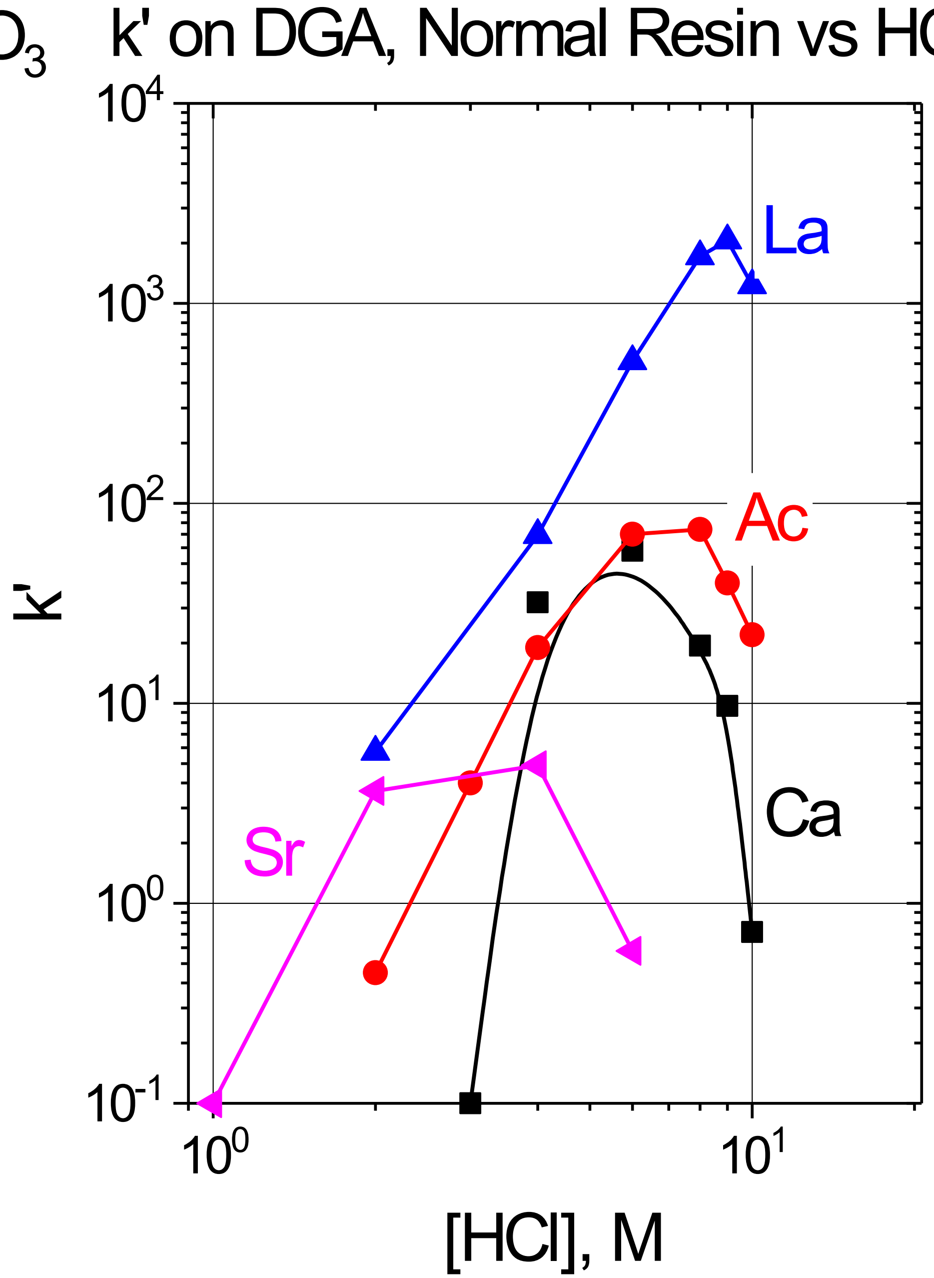


Separation of Ac, La, Ce, Pr and Nd on DGA Resin
Slurry Packed 25-53 μm DGA Resin, Operating Temperature 50(1) °C
Load
3M HNO3
225Ac
La(III), 1 mg
Ce(III), 1 mg
Eluant
0.15 M
HNO3
Pr(III), 1 mg
Nd(III), 1 mg
Bed Volume = 20.0 mL
Bed Height = 21.0 cm
Column Diameter = 1.1 cm
Flow Rate = 5.0 mL/min
= 5.3 mL/cm2/min
Pressure = 6 psi
α = 1.1 (Ac/La)
1.9 (Ac/Ce)
2.7 (Ac/Pr)
4.6 (Ac/Nd)
ppm La or cpm/mL 225Ac (102)
Bed Volumes


ppm/mL vs. Bed Volumes of Eluate
Slurry Packed 25-53 μm LN Resin, Preconditioned with 0.50 M (Na,H)OAc, 50(1) °C
Load
0.50 M
(Na,H)OAc
pH = 4.5
Eluant
0.10 M
HNO3
Strip
4.0 M
HNO3
225Ac
1 mg La
1 mg Ce
1 mg Pr
1 mg Nd
Background
Flow Rate = 5 mL/min
= 5.3 mL/cm2/min
= 3.8 min/Bed Volume
Pressure = 8 psi
α = 2.8 (Ac/La)
Column diameter = 1.1 cm
Column length = 21.0 cm
Column volume = 20.0 mL
LN lot # LF12013
ppm La, Ce, Pr, Nd
cpm/mL (10²) 225Ac
Bed Volumes
10²
10¹
10⁰
10⁻¹
10⁻²
10⁻³
0
5
10
15
20
25
30
35

Ac Separation from La





Mastren, T., Radchenko, V., Owens, A., Copping, R., Boll, R., Griswold, J.R., Mirzadeh, S., Wyant, L.E., Brugh, M., Engle, J.W., Nortier, F.M., Birnbaum, E.R, John, K.D., Fassbender, M.E. 2017. Simultaneous Separation of Actinium and Radium Isotopes from a Proton Irradiated Thorium Matrix. Nature Scientific Reports, 7, 8216. doi:10.1038/s41598-017-08506-9

^{177}Lu and ^{161}Tb

-Rare Earth Separations (low α)

-Effect of Column Loading on Peak Shapes

-Milligrams Target to No-carrier added

177Lu/161Tb

Nuclide	Half Life	β_{max}	β_{avg}	Photons	Production
^{177}Lu	6.7 days	497 keV	130 keV	208 keV (10.4%) 113 keV (6.2%)	$^{176}Yb(n,\gamma)^{177}Yb(\beta^-)^{177}Lu$
^{161}Tb	6.9 days	593 keV	154 keV	45 keV (18%) 49 keV (17%) 75 keV (10.2%)	$^{160}Gd(n,\gamma)^{161}Gd(\beta^-)^{161}Tb$

E. P. Horwitz, D. R. McAlister, A. H. Bond, R. E. Barrans, J. M. Williamson, "A Process for the Separation of ^{177}Lu from Neutron Irradiated ^{176}Yb Targets," *Applied Radiation and Isotopes*, 63, 23-36 (2005).

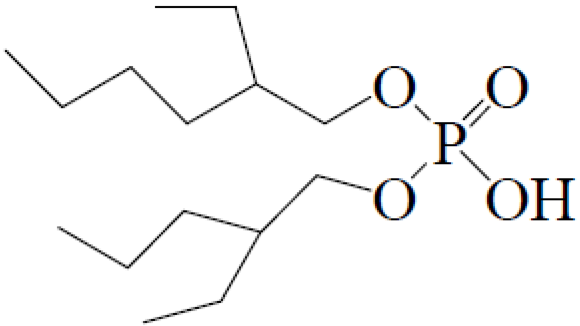
E. P. Horwitz, D. R. McAlister, M. L. Dietz, "Extraction chromatography versus solvent extraction: How similar are they?" *Sep. Sci. and Technol.*, 41(10), 2163-2182 (2006).

D. R. McAlister, E. P. Horwitz, "The Characterization and Novel Applications of Extraction Chromatographic Materials Containing Bis(2-ethyl-1-hexyl)phosphoric Acid, 2-ethyl-1-hexylphosphonic acid, mono 2-ethyl-1-hexyl ester and 2,4,4-trimethyl-1-pentylphosphinic acid," *Solv. Extr. Ion Exch.*, 25(6), 757-769 (2007).

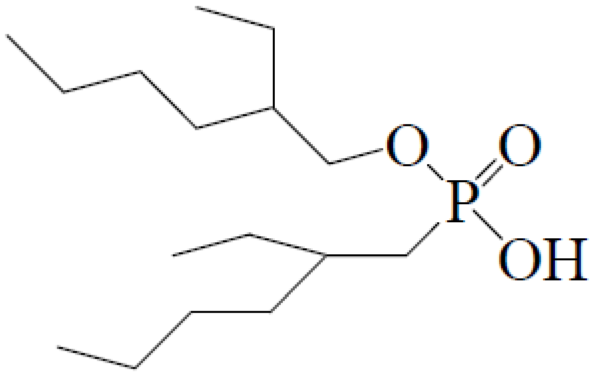
A. Dash, M. Raghavan, A. Pillai, F.F. Knapp Jr., "Production of Lu-177 for targeted therapy: Available options," *Nucl Med Mol Imaging.*, 49, 85-107 (2012).

Acidic Phosphorus Extractants (LN Series)

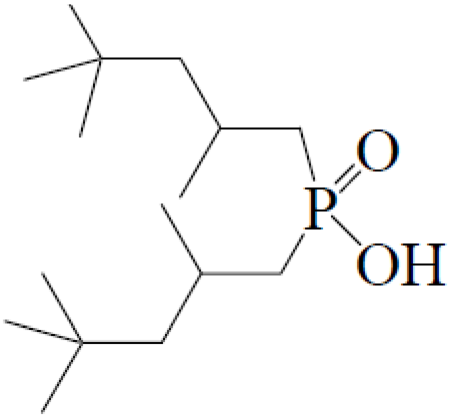
$$M^{3+} + \overline{3(HL)_2} \leftrightarrow \overline{M(HL_2)_3} + 3H^+$$



Phosphoric Acid



Phosphonic Acid

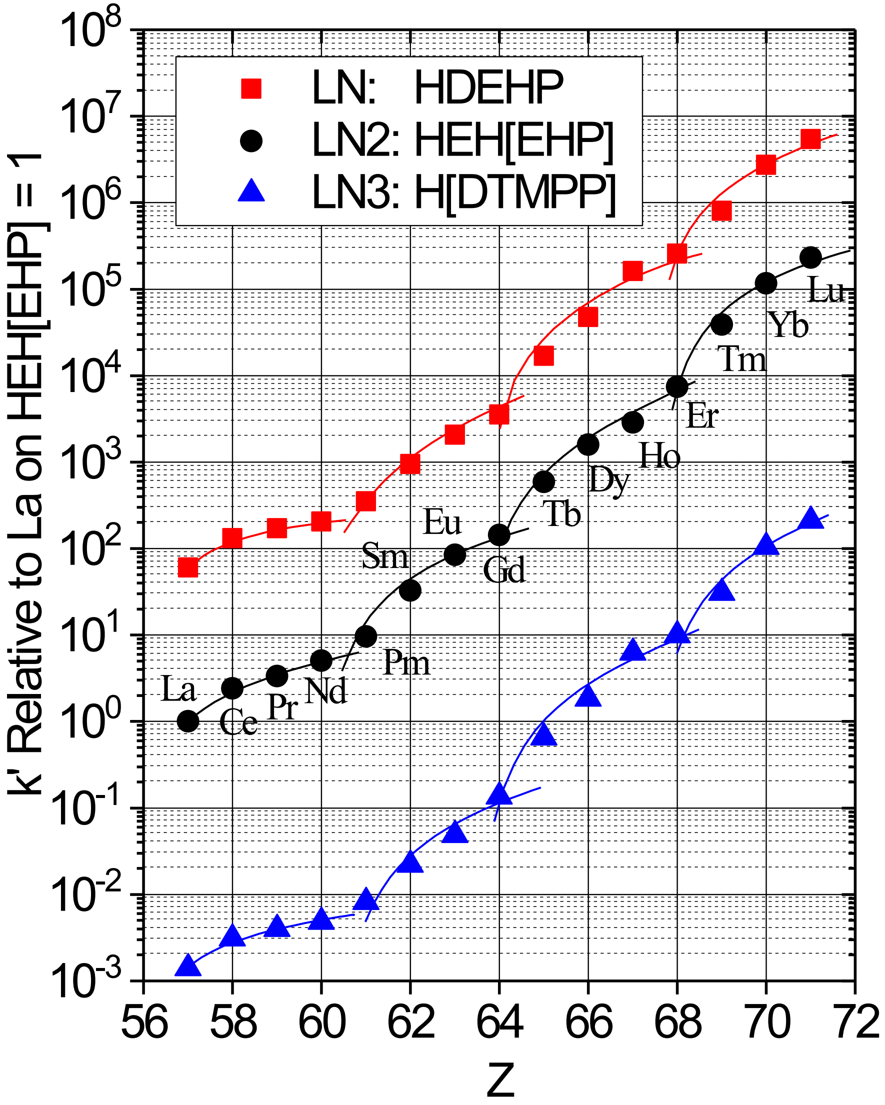


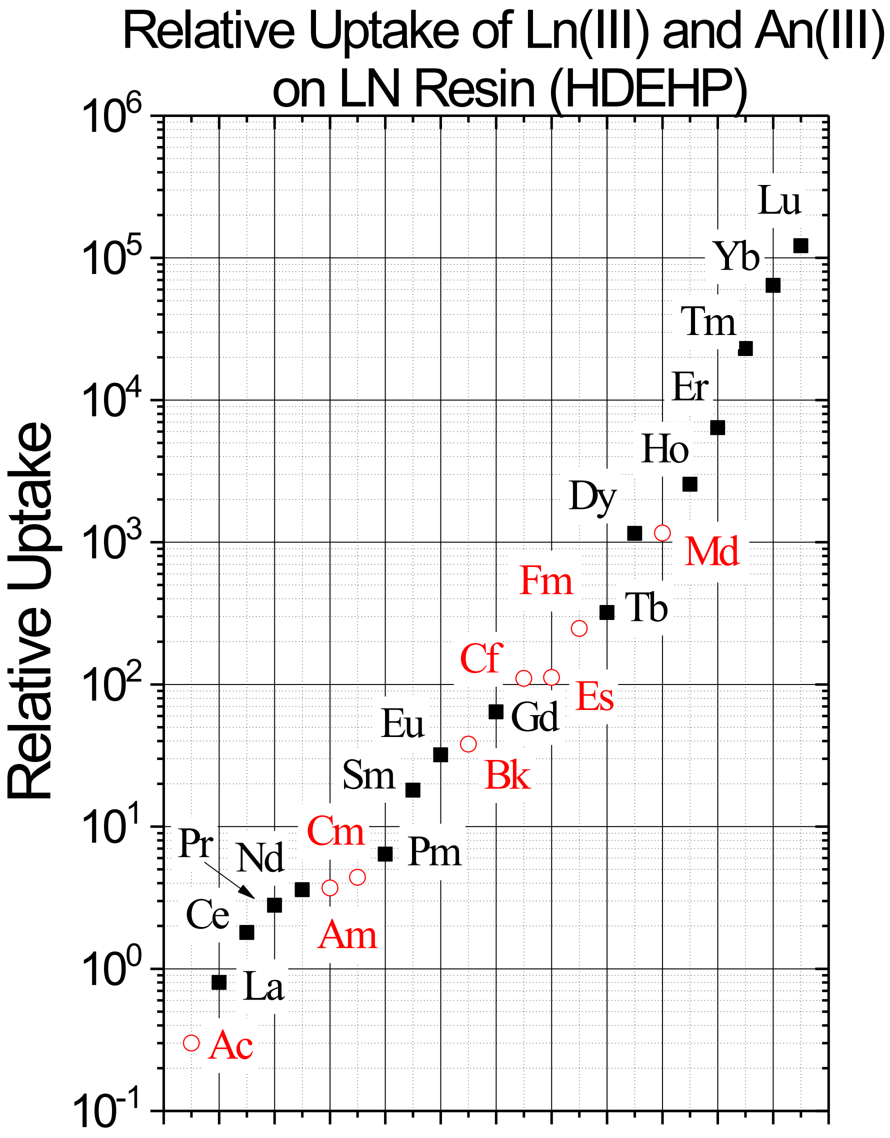
Phosphinic Acid

Basicity of P=O

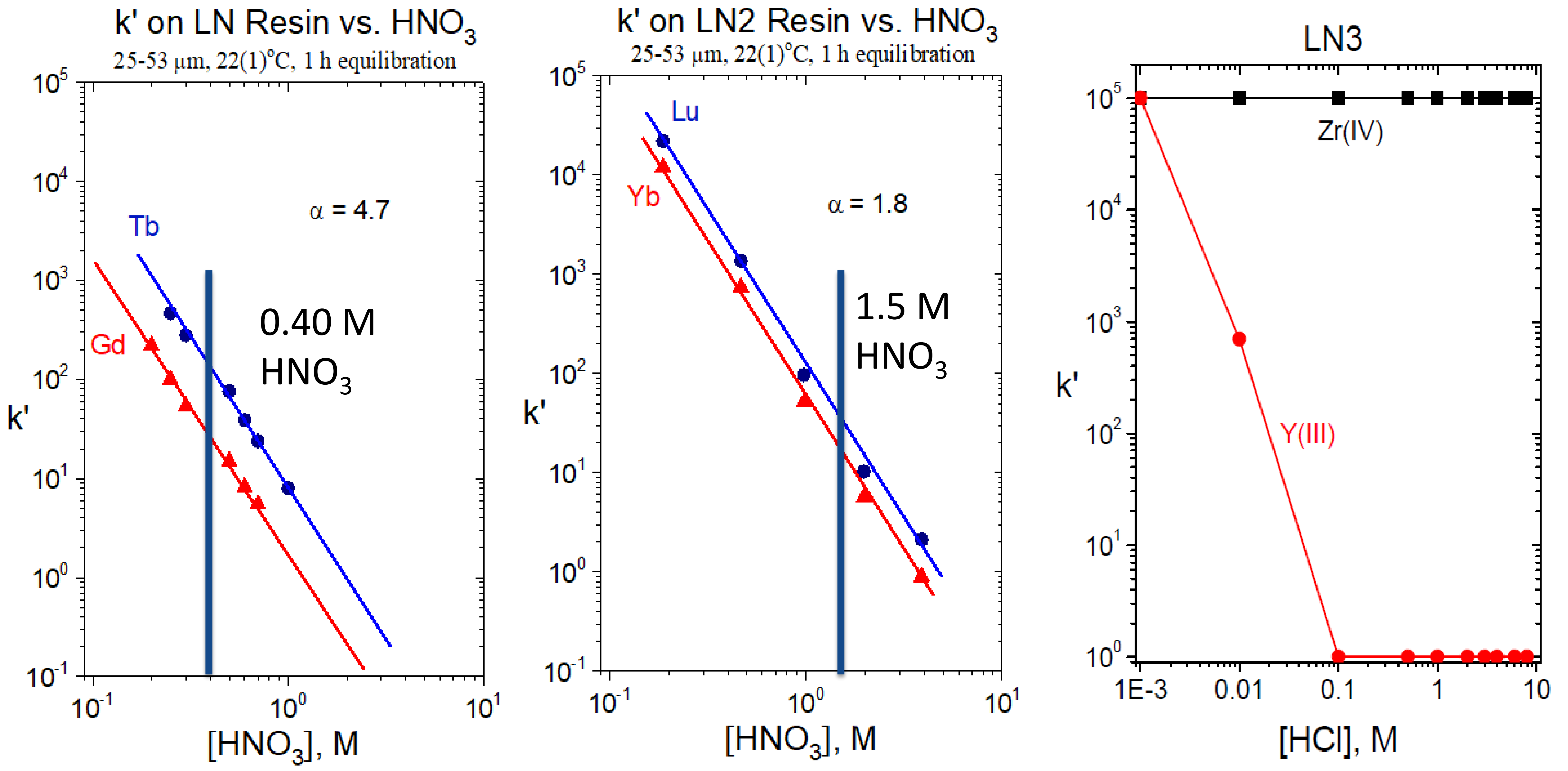
Acidity of P-OH

Separation Factors

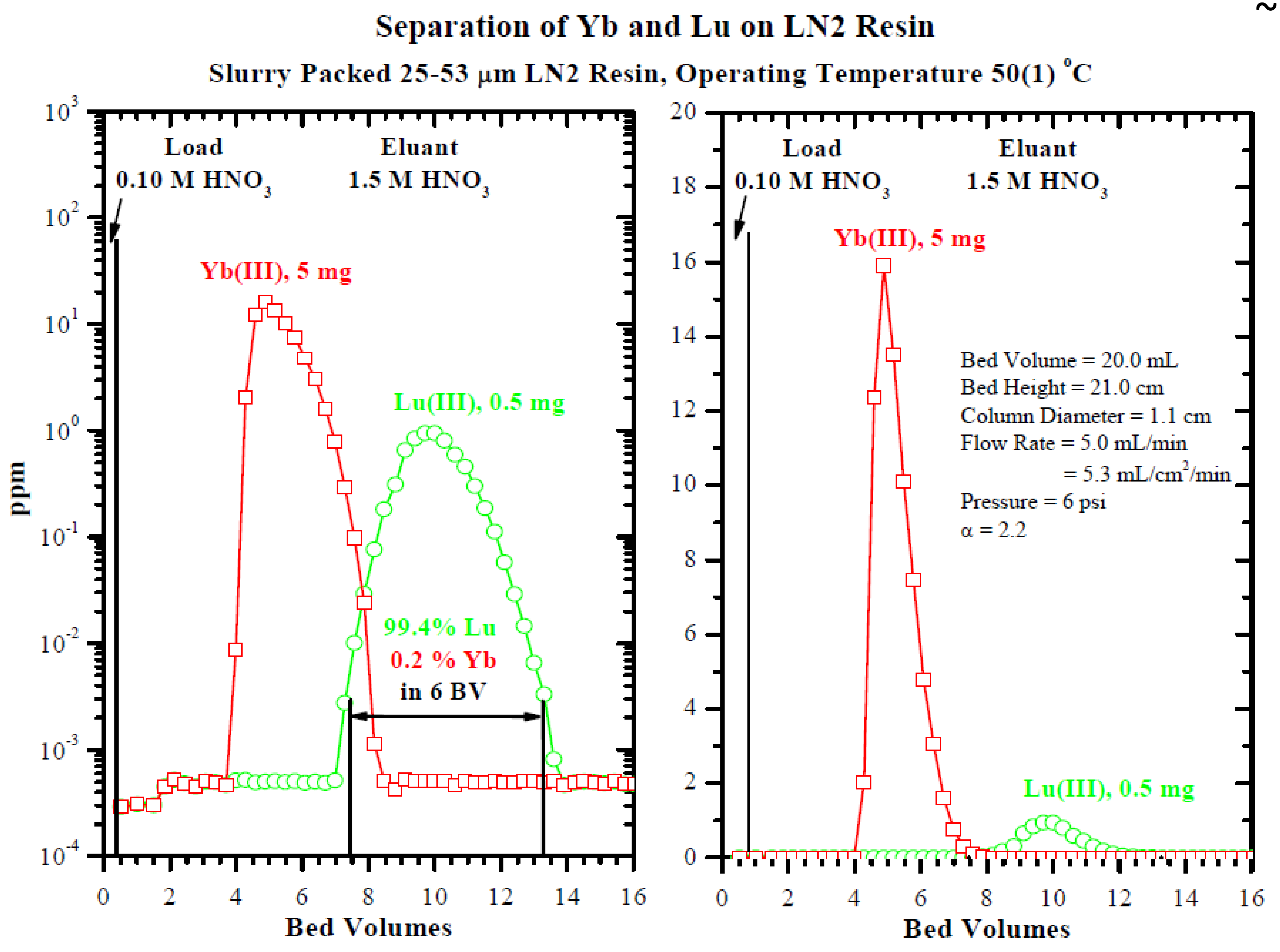


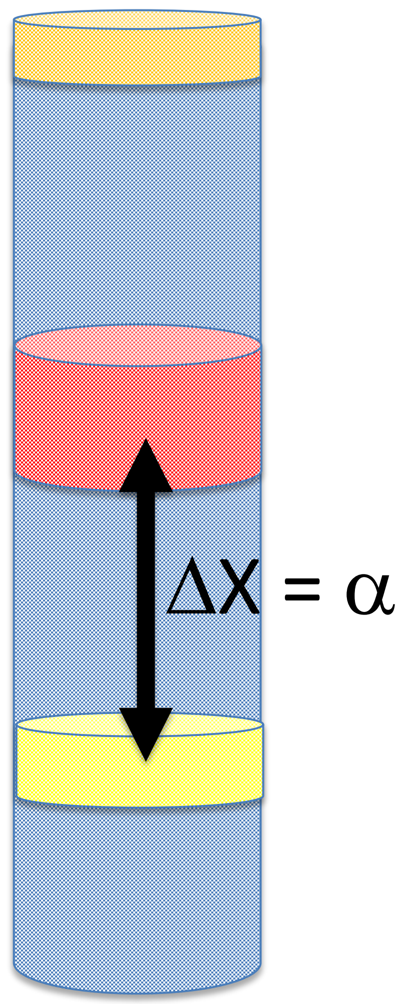


Separation Factors

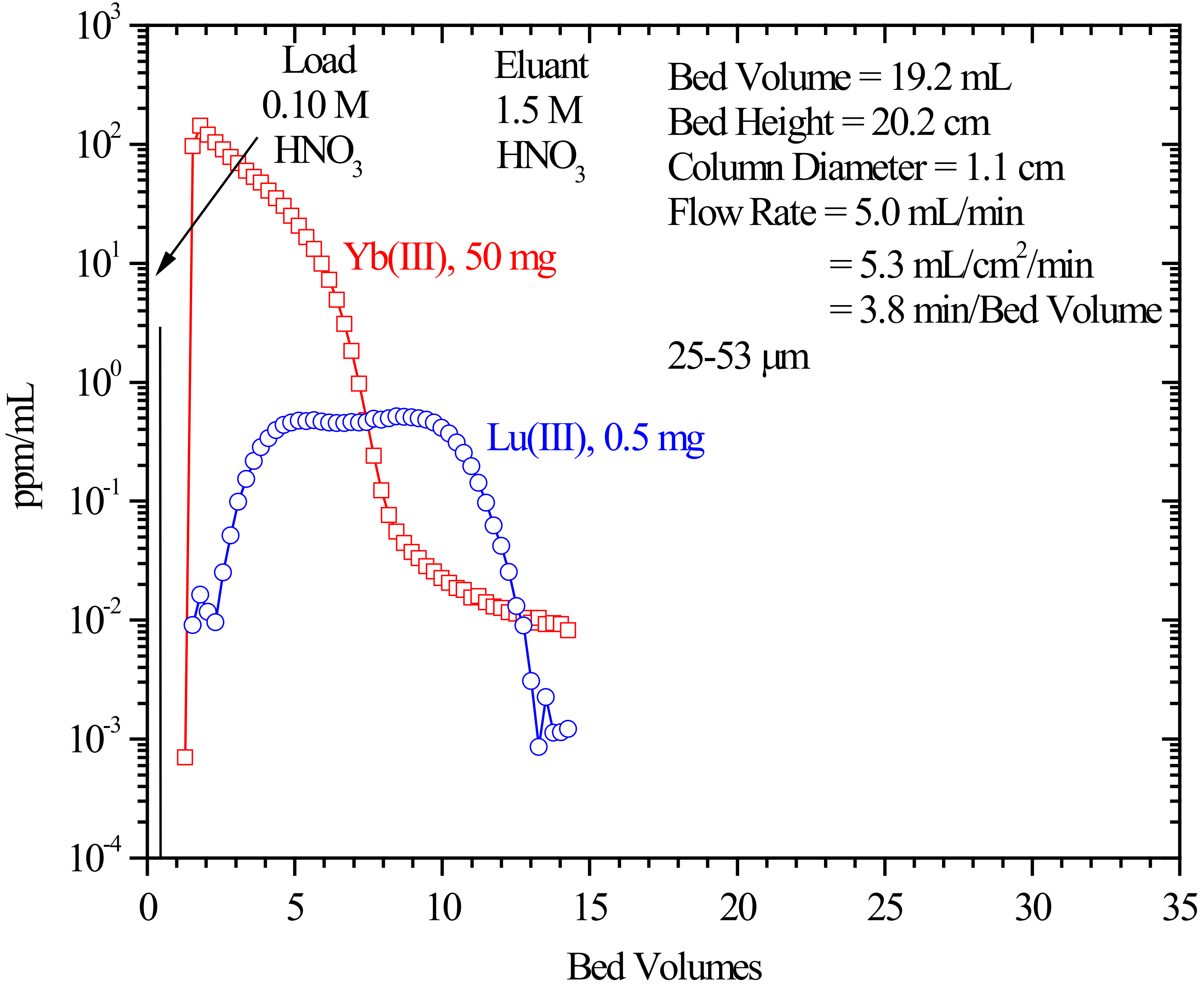


~2% column loading capacity

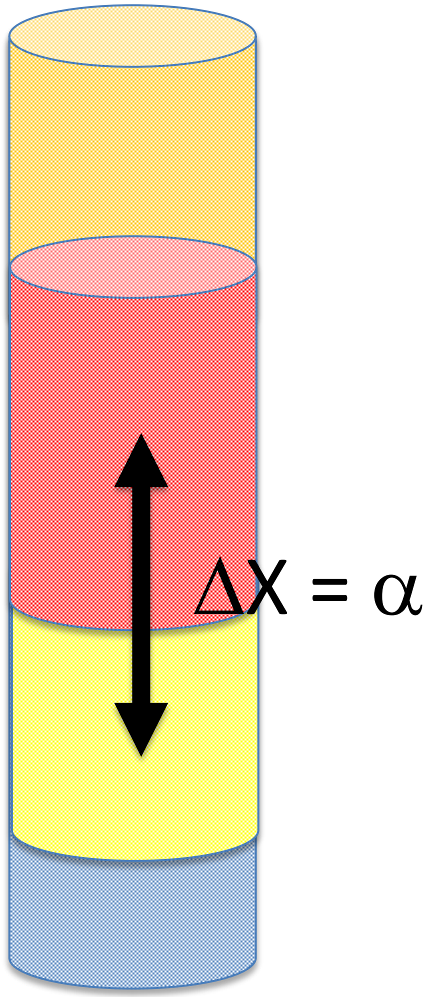




Lu/Yb Separation on LN2 Resin, 50°C, 50 mg Yb

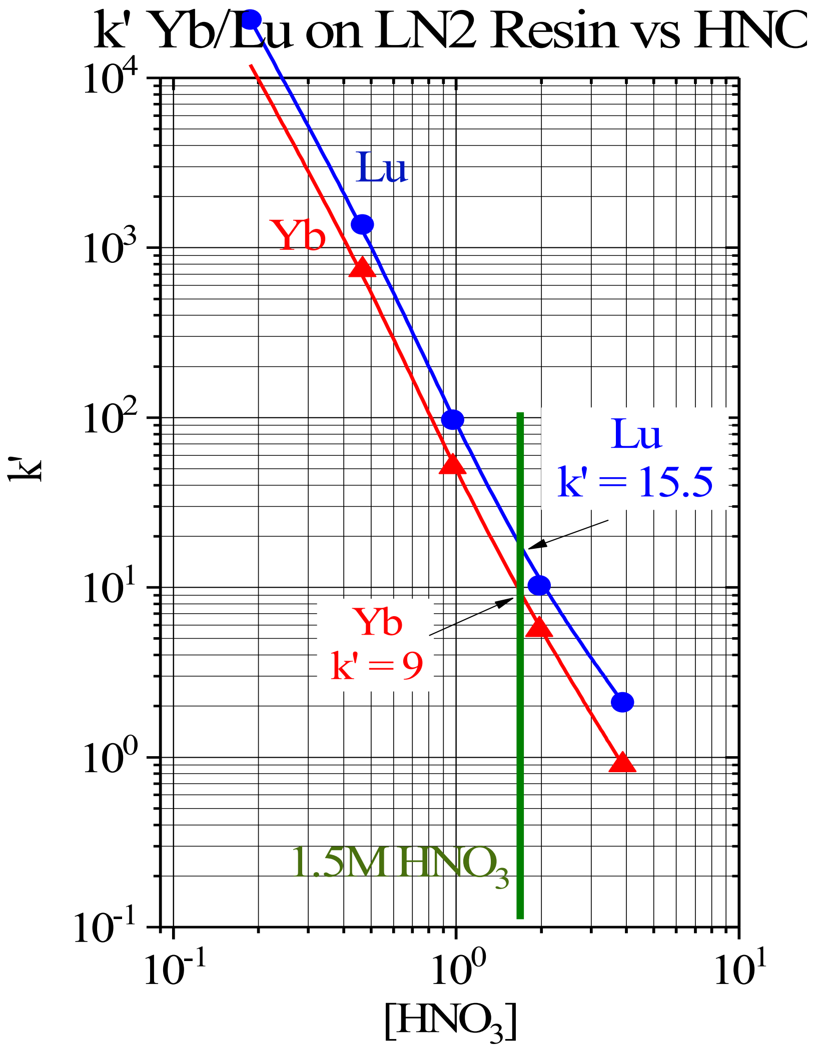


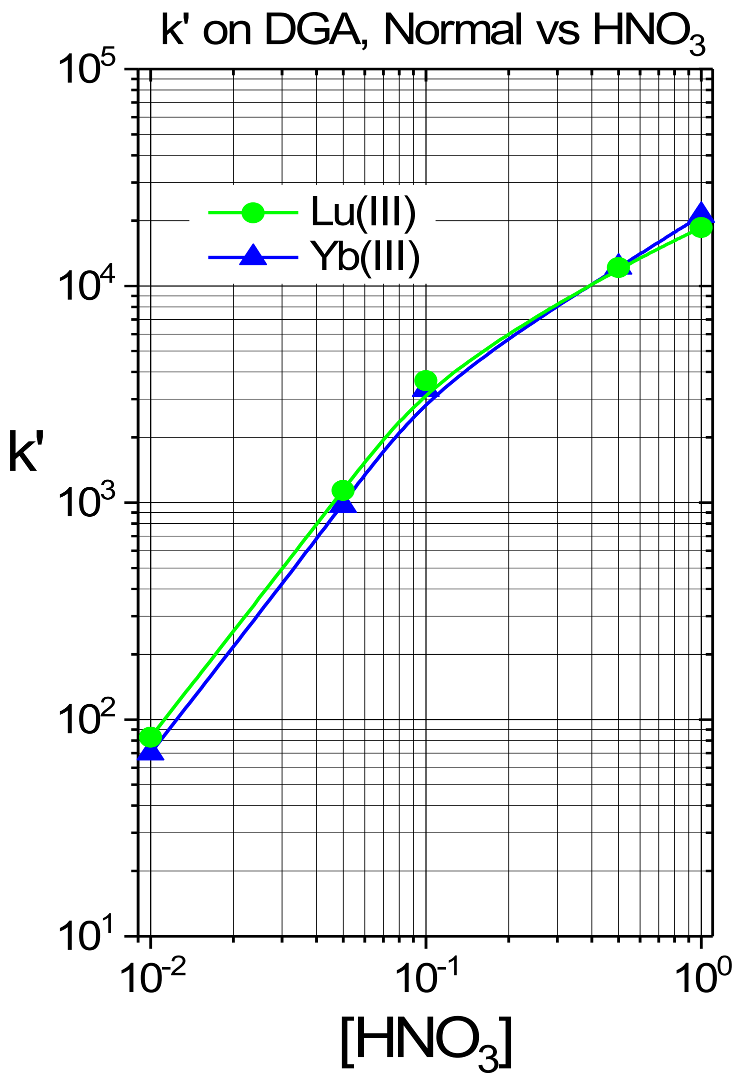
~20% column loading capacity



Scale up to 200 mL column (2%)?

Lu-177 LN2 vs DGA





DGA compliments LN2

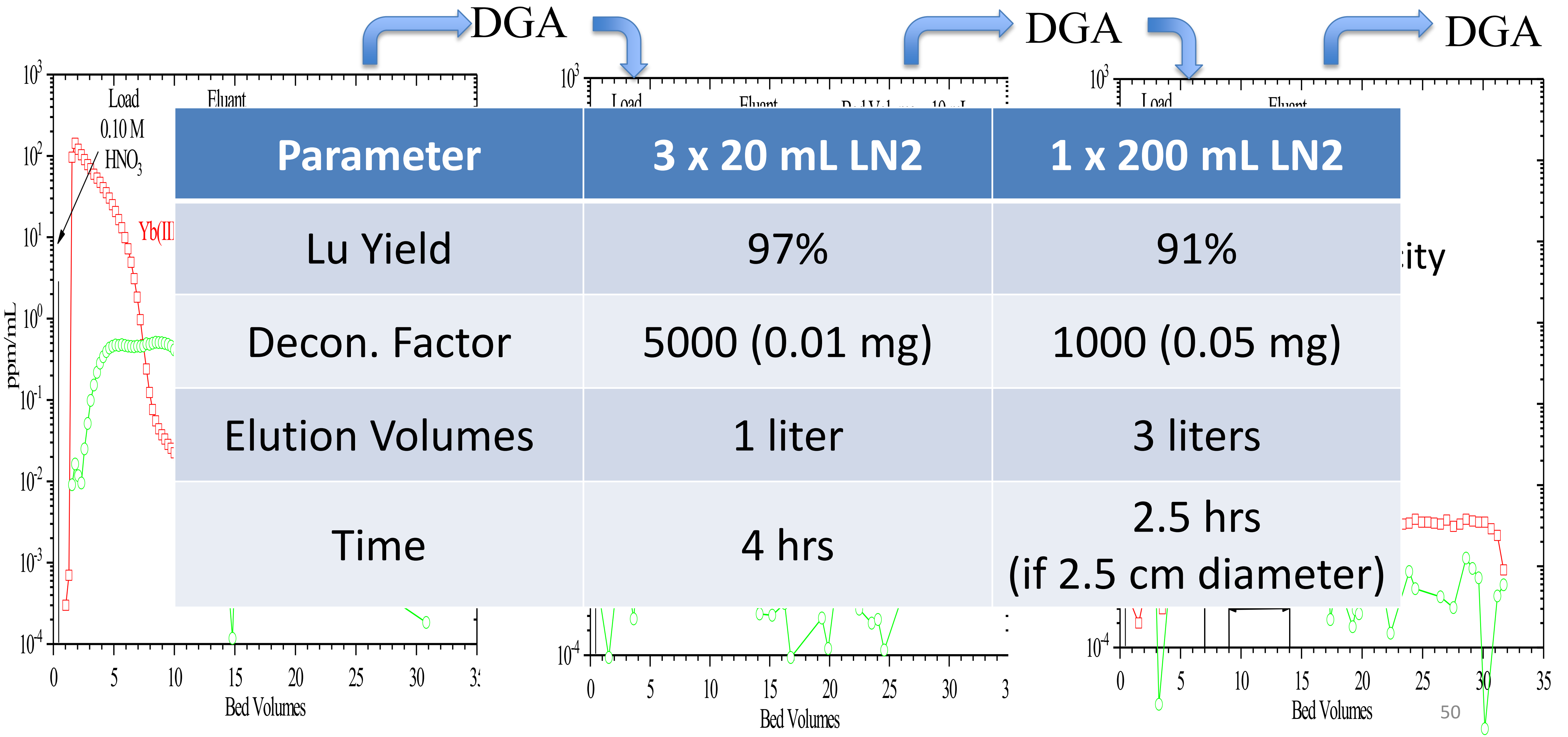
Concentrate Yb/Lu between LN2 columns.

Reduce acidity to avoid evaporations.

Removes common impurities (Ca, Al, Fe, Na, K).

E. P. Horwitz, D. R. McAlister, A. H. Bond, R. E. Barrans, J. M. Williamson, "A Process for the Separation of ^{177}Lu from Neutron Irradiated ^{176}Yb Targets," *Applied Radiation and Isotopes*, 63, 23-36 (2005).

Lu-177 (20 mL LN2 / 2-5 mL DGA)

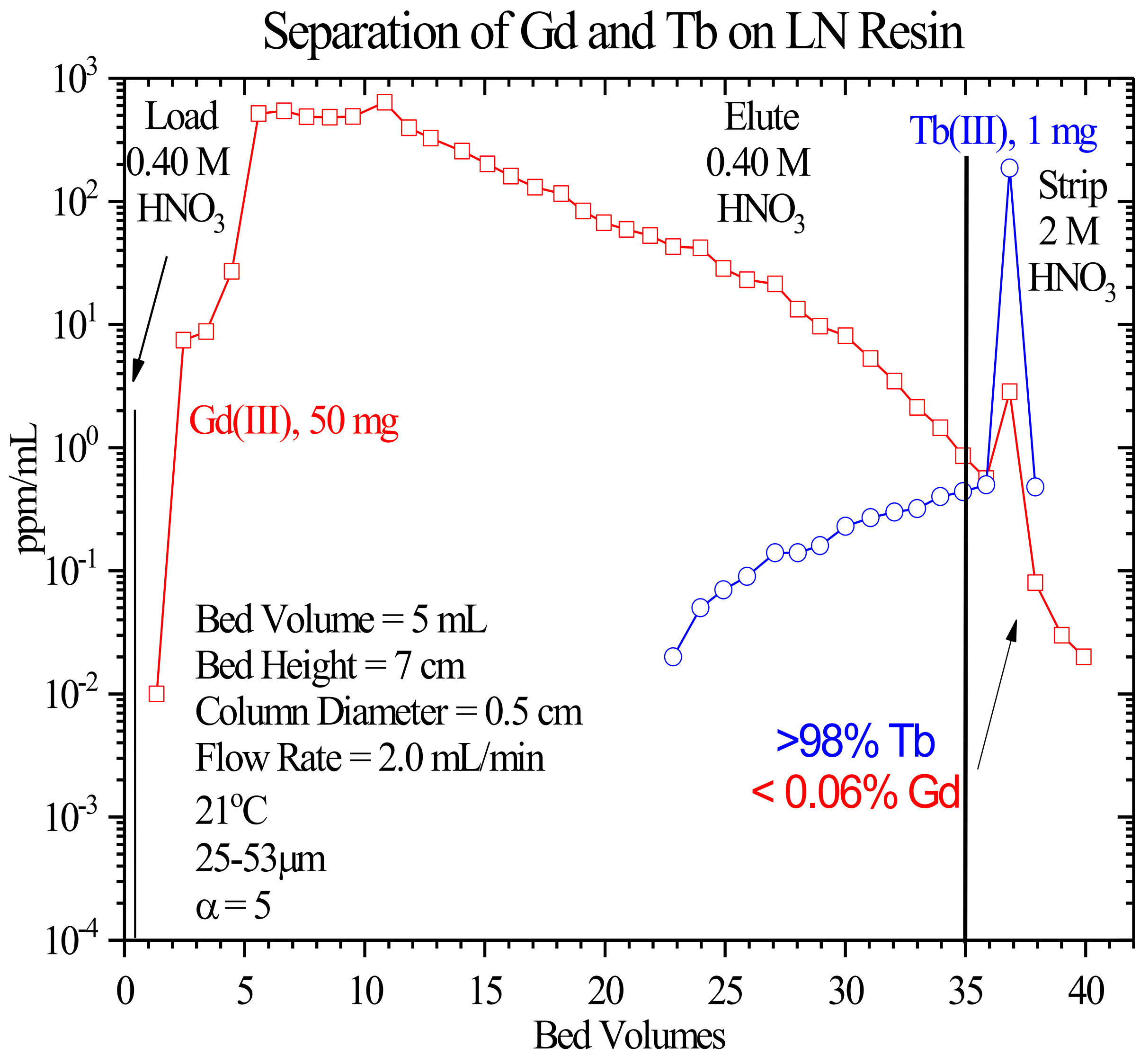


Parameter	3 x 20 mL LN2	1 x 200 mL LN2
Lu Yield	97%	91%
Decon. Factor	5000 (0.01 mg)	1000 (0.05 mg)
Elution Volumes	1 liter	3 liters
Time	4 hrs	2.5 hrs (if 2.5 cm diameter)

Lu/Yb Separation on HEH[EHP] Resin (LN2) vs Yb mass

	Yb				Lu			
Yb mass (mg)	**50 mg**	**25 mg**	**5 mg**	**0.5 mg**	**50 mg**	**25 mg**	**5 mg**	**0.5 mg**
Parameter	**Yb**	**Yb**	**Yb**	**Yb**	**Yb**	**Yb**	**Yb**	**Yb**
Peak	3.00	3.34	5.10	6.38	7.33	8.85	10.13	10.62
Gaussian Width	2.02	1.67	1.30	1.11	6.63	2.99	1.77	1.81
Resolution (Yb/Lu)	1.00	2.36	3.28	2.90				
Number of Plates	35	64	246	529	20	140	524	551
Plate Height (cm)	0.5951	0.3281	0.0853	0.0397	1.0738	0.1498	0.0401	0.0381
% Column Loading	20%	10%	2%	0.2%	20%	10%	2%	0.2%

Tb Isotopes (Tb-161)



Larger separation factor for Tb/Ga (4.7)

Better separation on smaller column (5 mL) with higher loading (75-80%)

>98% Tb

<0.06% Gd

D.F. = 1700 for single column

Purification of ^{68}Ga from SnO_2 generator.

Purification of ^{68}Ga labeled compounds.

(Bonded Silicas)

^{68}Ga Generator

Ge-68 adsorbed on a hydrous stannic oxide column.

Elute Ga-68 ($t_{1/2}$ = 68 min) with 0.1M HCl.

Ga-68 needs to be purified to ensure good labeling and purity.

- Ge-68
- Stable metals Sn, Fe

Recover in a matrix suitable for labeling reaction.

Bonded functional groups to ensure low organic bleed.

Tworowska, I., Ranganathan, D., THamake, S., Delpassand, E., Mojtahedi, A., Schultz, M., Zhernosekov, K., Marx, S., (2016). Radiosynthesis of clinical doses of 68Ga-DOTATATE (GalioMedixTM) and validation of organic-matrix-based 68Ge/68Ge generators, Nuclear Medicine and Biology, 43, 19-26.

^{68}Ga Generator

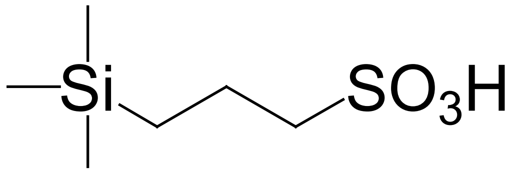
Collect Ga-68 from generator on SCX-silica cartridge in 0.1M HCl.

Recover Ga-68 from SCX with
5M NaCl/0.1M HCl.

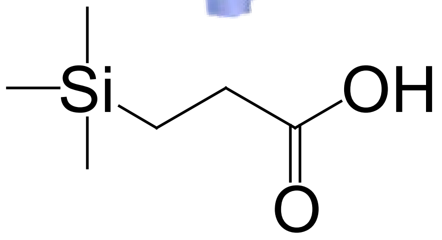
- low acid to allow labeling rxn at pH ~4.5 with addition of acetate or ascorbate buffer

Label Ga-68 to small molecule.

Scavenge free Ga-68 from pH 4-5 buffer with WCX-silica.



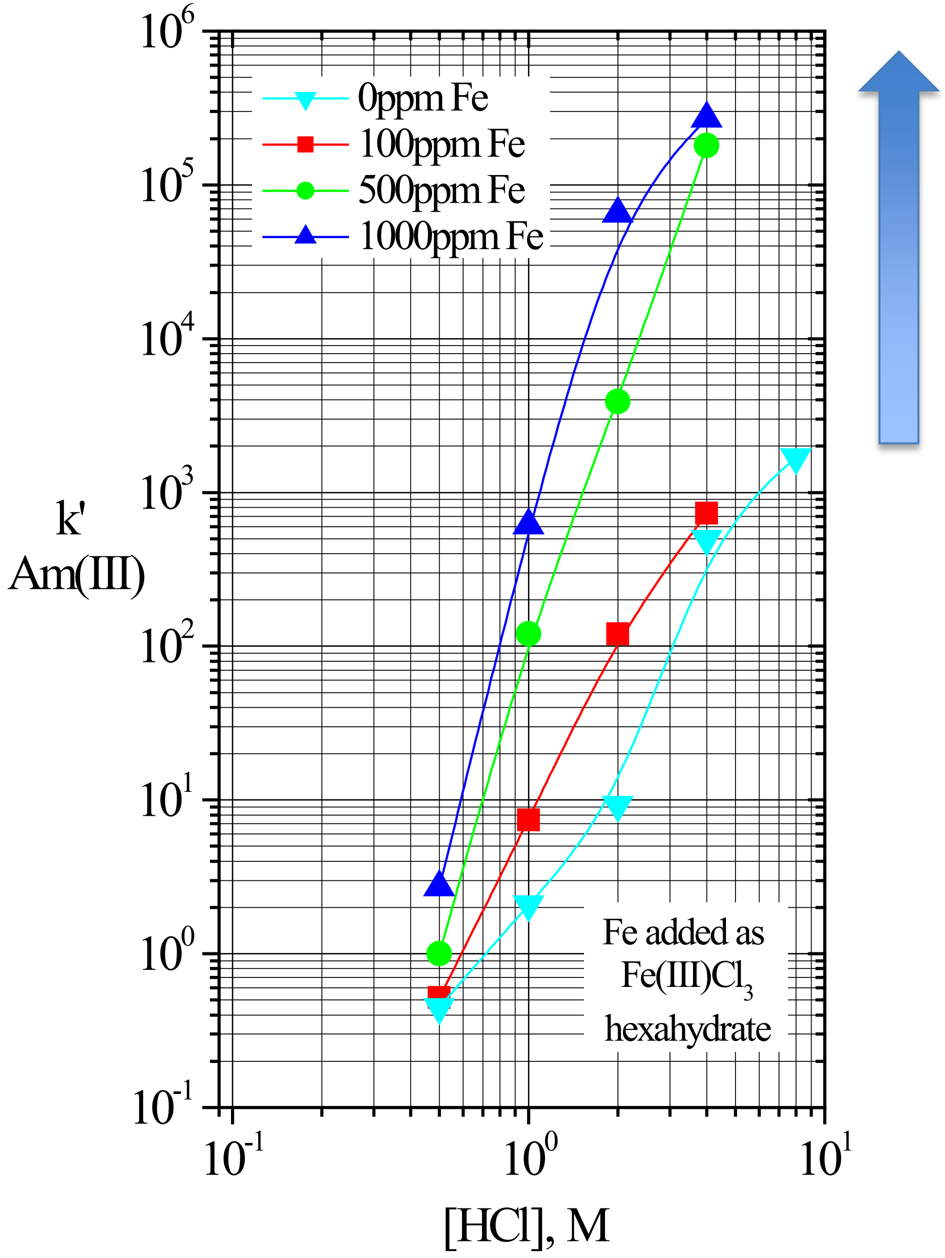
Strong Cation Exchange



Weak Cation Exchange

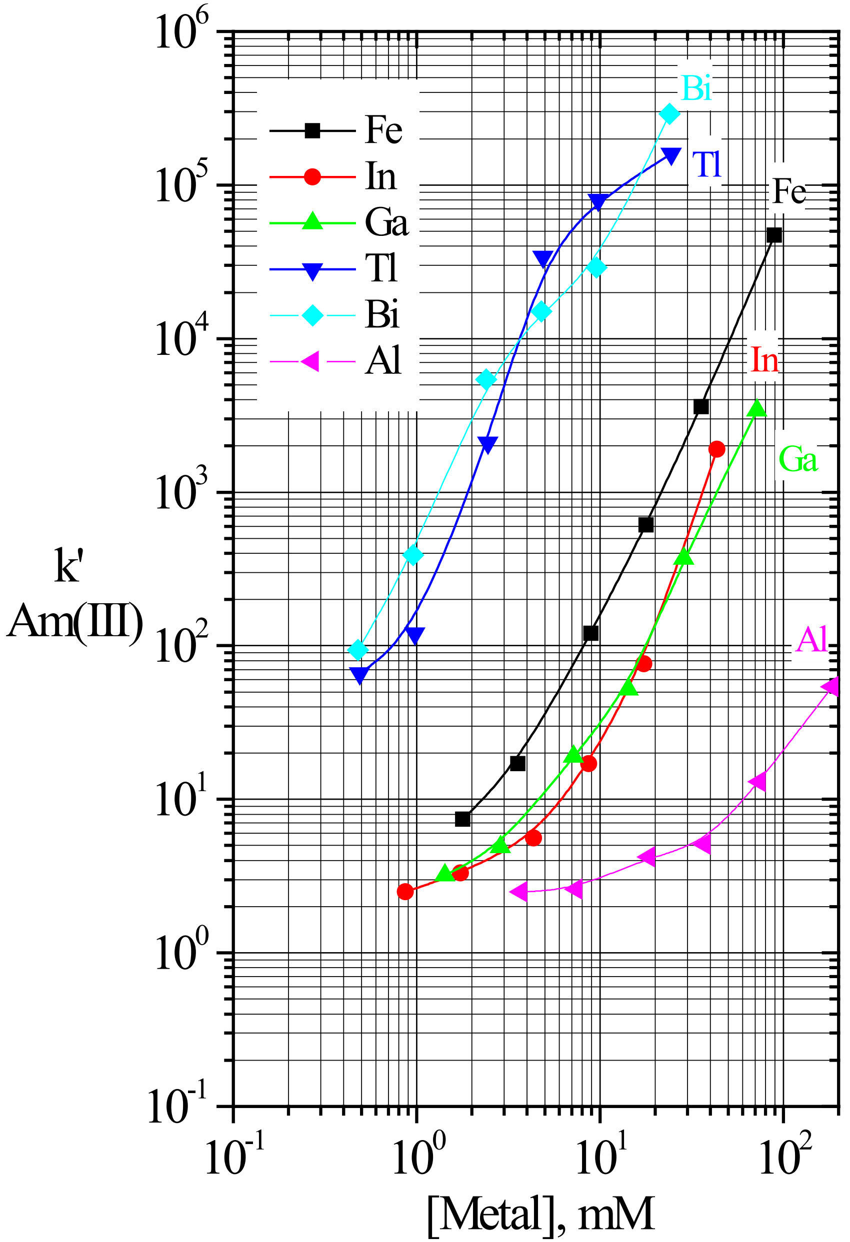
Separation of ^{227}Ac from Ac(Be) neutron sources in stainless steel capsule.

Influence of $FeCl_3$ on the uptake of Am(III) from HCl



$FeCl_3$ increases the uptake of Am(III) more than expected for the additional Cl^-

Influence of Metal Ion on the uptake of Am(III) from 1M HCl



Other metal ions that form anionic chloride complexes show similar effect.

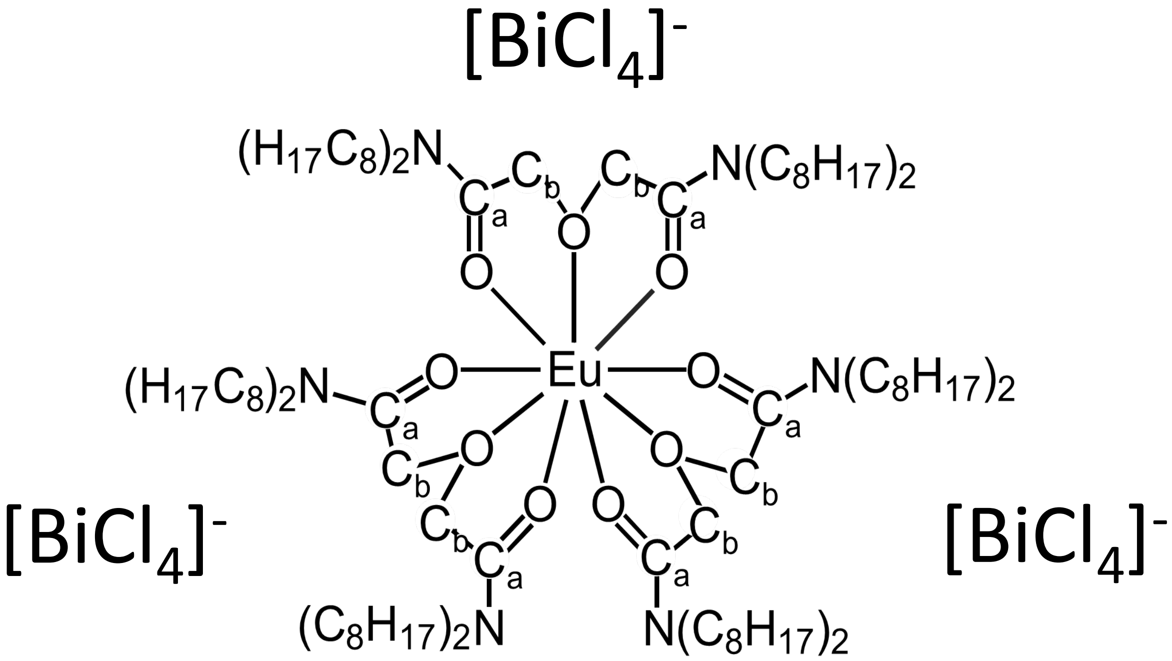
Bi, Tl, Fe, In, Ga.

Al shows only a modest increase due to additional Cl^- from $AlCl_3$.

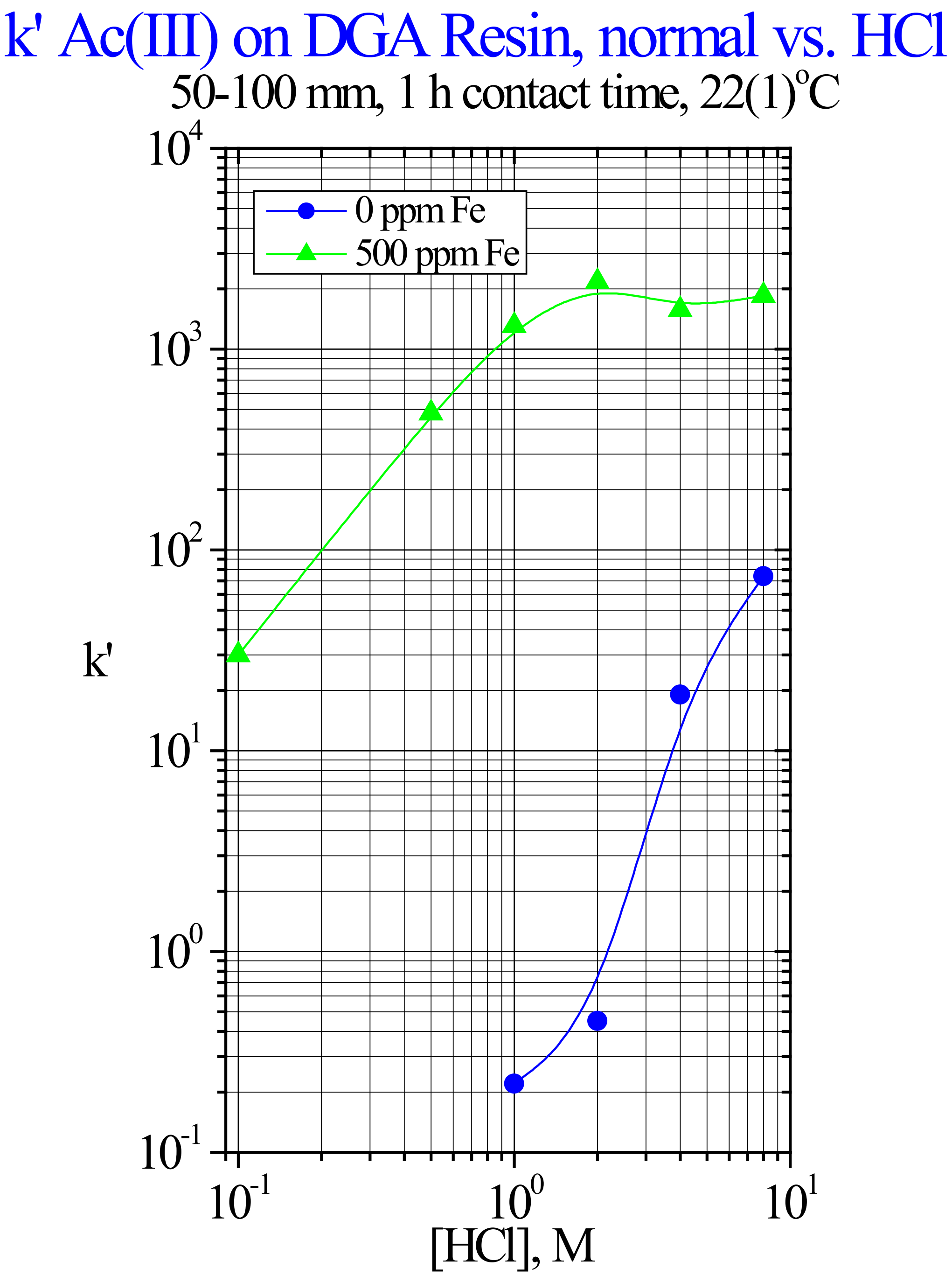
Equilibria for the synergistic extraction of Am(III) from HCl + $FeCl_3$

$$Am^{3+} + 3Cl^{-} + \overline{3DGA} \leftrightarrow \overline{Am(DGA)_3Cl_3} \qquad (1)$$

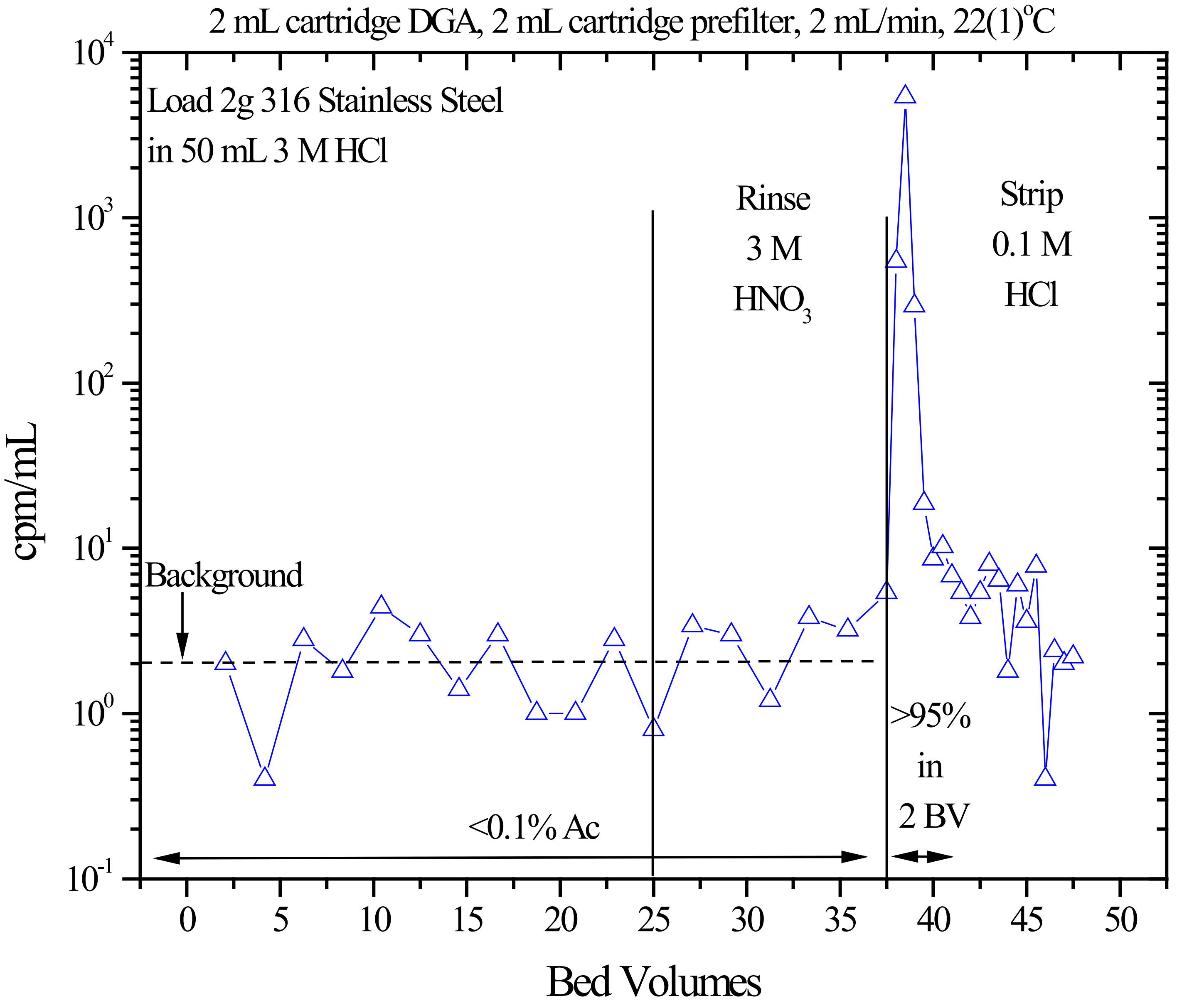
$$Am^{3+} + 3Cl^{-} + 3FeCl_3 + \overline{3DGA} \leftrightarrow \overline{Am(DGA)_3(FeCl_4)_3} \qquad (2)$$



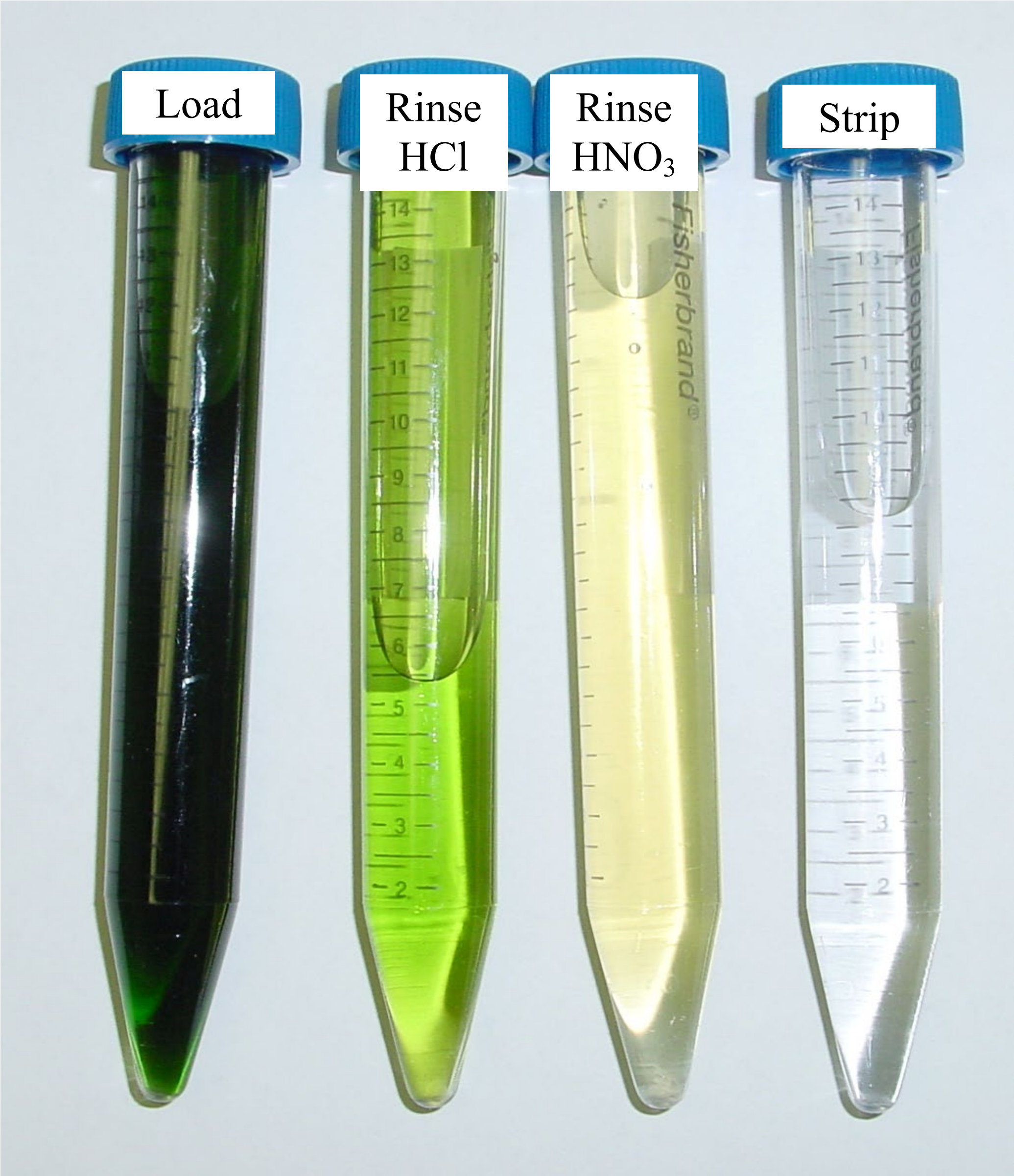
M.A. Antonio, D.R. McAlister, E.P. Horwitz, "Europium(III) Diglycolamide Complex: Insights into the Coordination Chemistry of Lanthanides in Solvent Extraction," *Dalton Transactions*, 44(2), 515-521 (2015).


k' Ac(III) on DGA Resin, normal vs. HCl
50-100 mm, 1 h contact time, 22(1)°C
0 ppm Fe
500 ppm Fe
k'
10^4
10^3
10^2
10^1
10^0
10^-1
10^-1
10^0
10^1
[HCl], M

^{227}Ac from Stainless Steel



^{227}Ac from Stainless Steel



^{227}Ac from Stainless Steel

Before Use | After Load | After Rinse

Prefilter

DGA

1st Separation (DGA + Prefilter, HCl)

Metal Impurities in Ac-227 from 316 Stainless Steel

Fraction	Al (mg)	Cr (mg)	Fe (mg)	Mg (mg)	Mn (mg)	Mo (mg)	Ni (mg)
Load[1]	0.12	225	1100	<0.0005	31	153	170
Rinse[2]	0.07	4	46	<0.0003	0.38	148	3.2
Strip[3]	0.0006	0.006	0.2	<0.0002	0.0004	0.13	0.0016
DF	N/A	24000	2800	N/A	40000	190	70000

[1]2 grams of 316 Stainless Steel, dissolved in HCl/H_2O_2, adjusted to 50 mL 3 M HCl

[2]25 mL of 3 M HNO_3

[3]20 mL of 0.1 M HCl

Polishing Step (DGA, HNO_3)

Metal Impurities in Ac-227 from 316 Stainless Steel

Fraction	Al (mg)	Cr (mg)	Fe (mg)	Mg (mg)	Mn (mg)	Mo (mg)	Ni (mg)
Load[1]	ND	0.0055	0.085	ND	ND	0.0065	ND
Oxalate Rinse[2]	ND	0.003	0.043	0.016	0.0002	0.003	ND
HNO_3 Rinse[3]	ND	ND	ND	ND	ND	ND	ND
Strip[4]	ND	ND	ND	ND	ND	ND	ND
Total DF	N/A	$>10^7$	$>10^7$	N/A	$>10^6$	$>10^6$	$>10^6$

[1] Product from 1st separation acidified to 40 mL 3 M HNO3

[2] 25 mL of 3 M HNO_3 + 0.05 M oxalic acid

[3] 25 mL of 3 M HNO_3

[4] 20 mL of 0.1 M HCl

Conclusions

- The unique selectivity of EXC resins can simplify purification of radionuclides for nuclear medicine applications.
- Organic leaching must be considered when using EXC resins for nuclear medicine applications.
- Combinations of multiple EXC and IX columns are often needed to meet the high purity requirements for nuclear medicine.
- Ion exchange or solvent extraction can compliment EXC when high capacity or low organic impurity levels are required.

References

1) "Separation of Selected Nuclear Medicine Isotopes Using Extraction Chromatography," D.R. McAlister, E.P. Horwitz, 64th Radiobioassay and Radiochemical Measurements Conference, Santa Fe, NM, Oct 27- Nov 1, 2019. http://www.eichrom.com/wp-content/uploads/2019/11/7_McAlister_RRMC-2019_Nuclear-Medicine-Separations.pdf
2) "Selective Separation of Radium and Actinium from Bulk Thorium Target Material," D.R. McAlister, E.P. Horwitz, R. Perron, D. Gendron, P. Causey, J.T. Harvey, 11th International Symposium on Targeted Alpha Therapy, Ottawa, Ontario, Canada, April 1-4, 2019.
3) "Separation and Counting Options for 89/90Sr," D.R. McAlister, 63rd Radiobioassay and Radiochemical Measurements Conference, Portland, ME, May 20-25, 2018.
4) D. R. McAlister and E. P. Horwitz, "Automated two column generator systems for medical radionuclides," Applied Radiation and Isotopes, 67, 1985-1991, (2009).

Conclusion

Thank you

Questions???