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Separation of Selected Nuclear Medicine Isotopes Using Extraction Chromatography

Daniel McAlister and Phil Horwitz

Eichrom Workshop, October 28, 2019

Eichrom Technologies

npo

Radiation shielding and contamination control products: applying our engineering and radiation protection expertise to minimize radiation exposure in commercial nuclear power, nuclear medicine and industrial radiography.

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Ion Exchange, extraction chromatography and solid phase extraction (SPE): applying chemical separation technology to improve efficiency and reduce costs in analytical radiochemistry, isotope geochemistry and nuclear medicine.

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- Application Notes

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Radiochemistry

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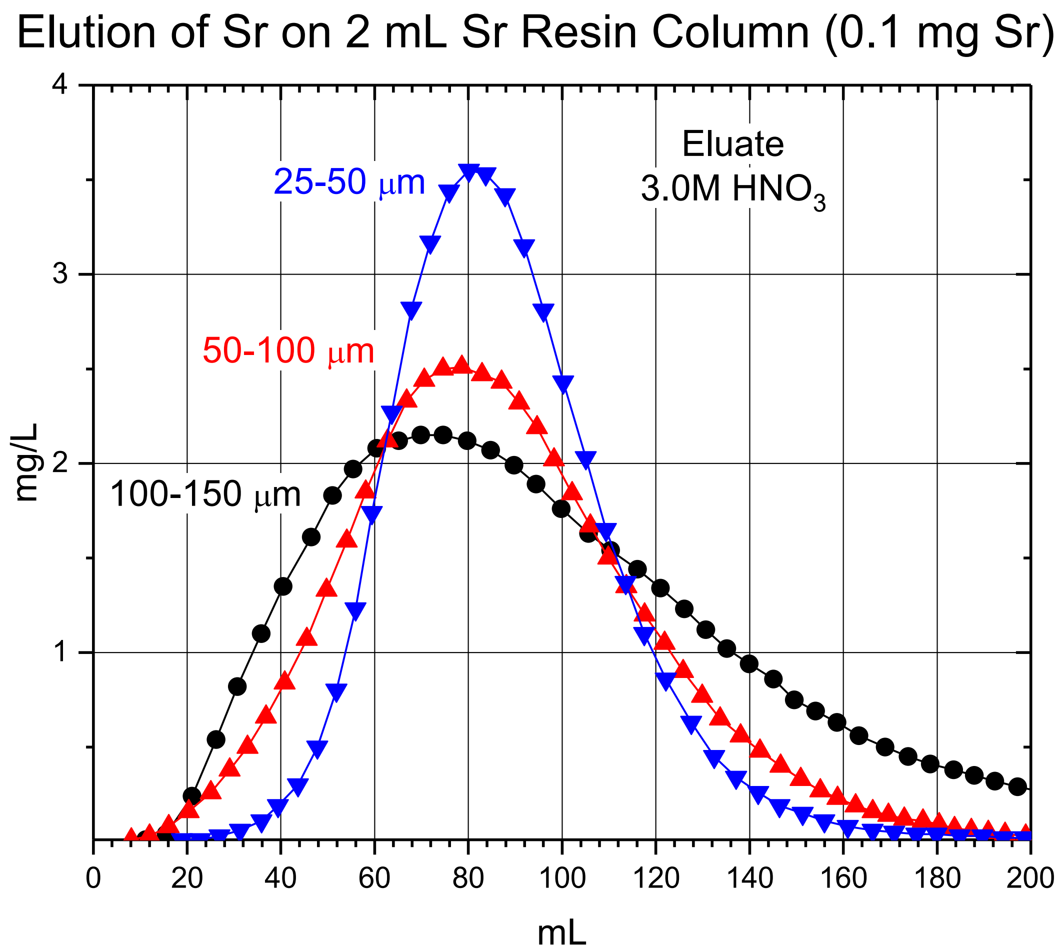
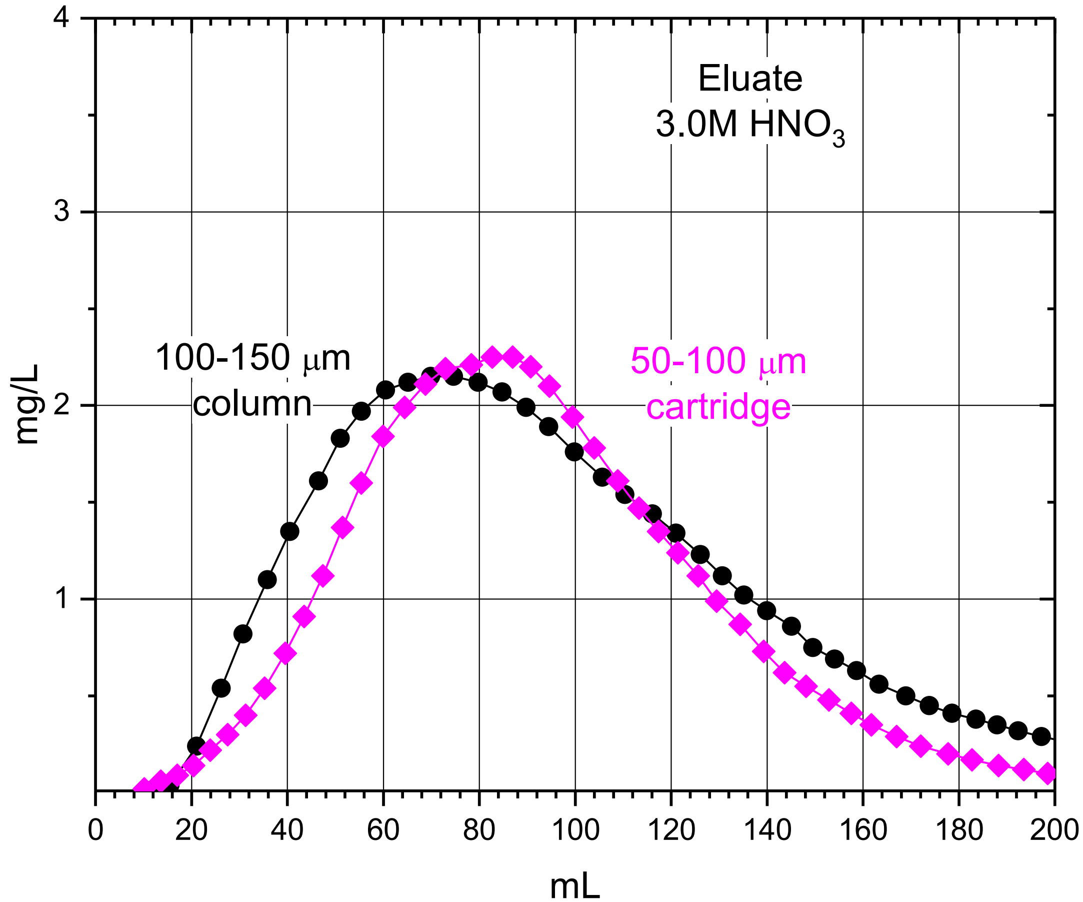


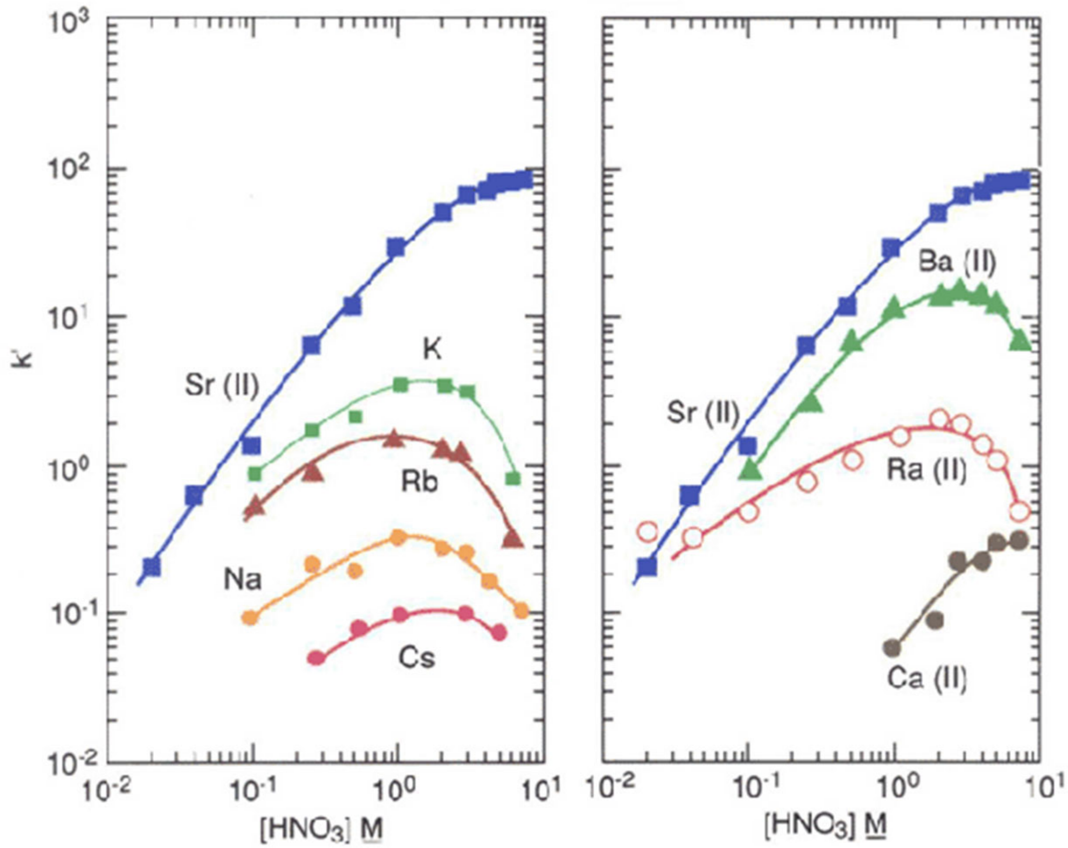
Elution of Sr on 2 mL Sr Resin Column (0.1 mg Sr)
Eluate
3.0M HNO3
25-50 μm
50-100 μm
100-150 μm
mg/L
mL
0
20
40
60
80
100
120
140
160
180
200
1
2
3
4

Elution of Sr on 2 mL Sr Resin Column (0.1 mg Sr)



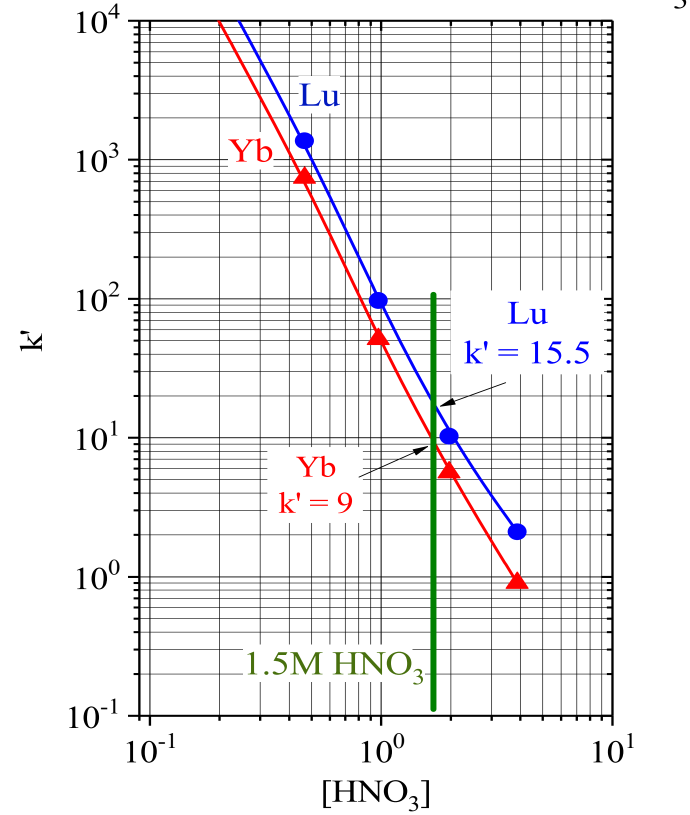
Figures 2 and 3

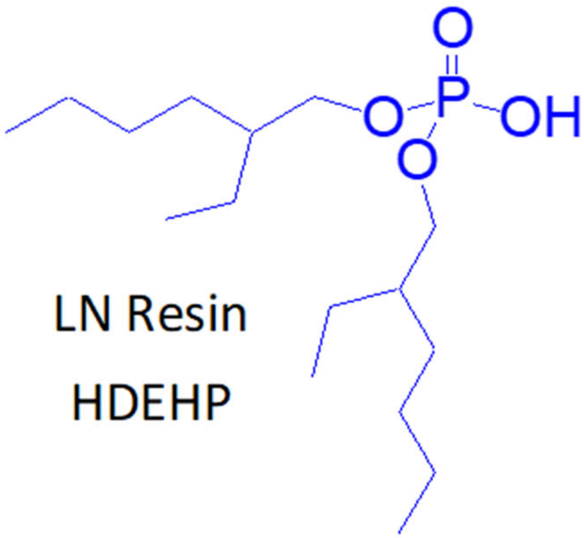
Acid dependency of k' for various ions at 23-25°C.
Sr Resin



Horwitz, et al., (HP292)

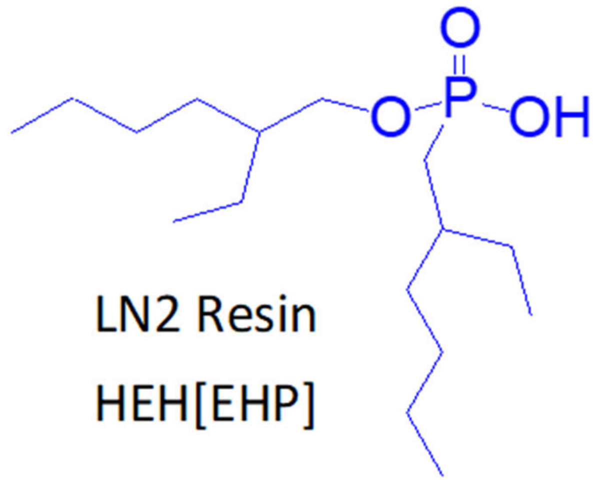
k' Yb/Lu on LN2 Resin vs HNO_3





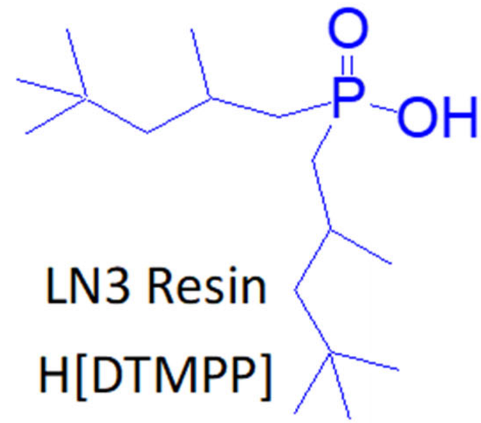
LN Resin

HDEHP



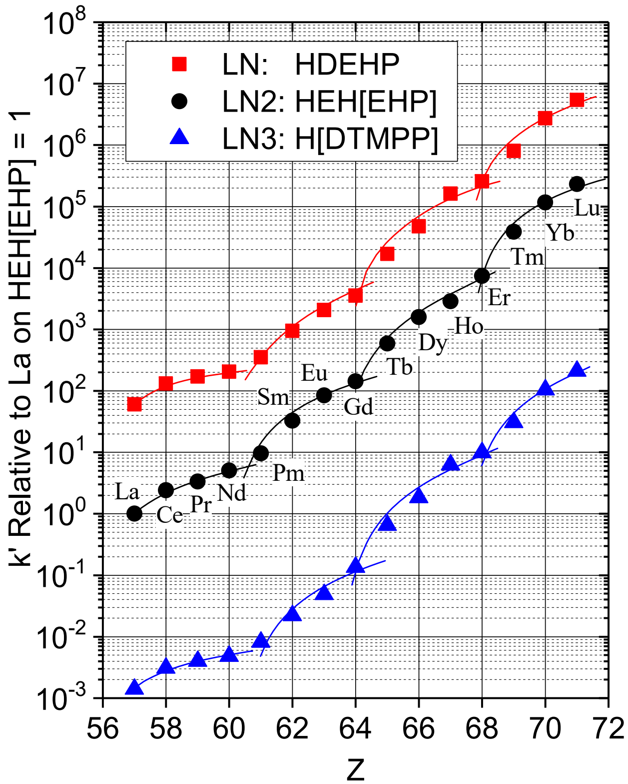
LN2 Resin

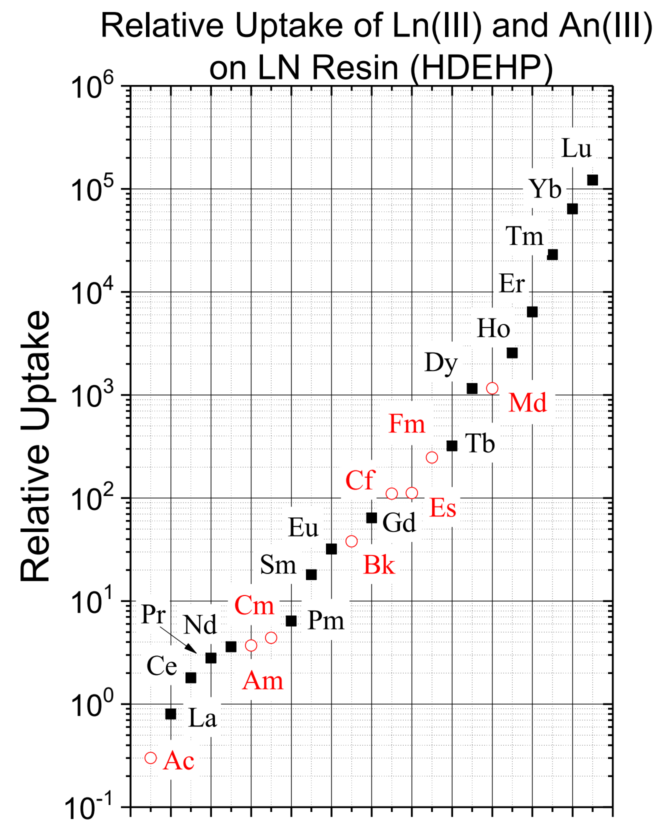
HEH[EHP]



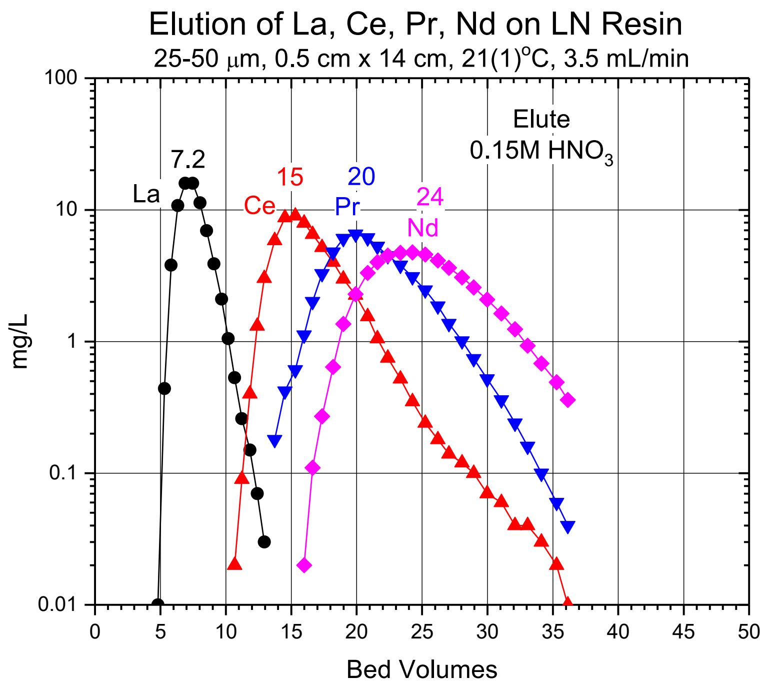
LN3 Resin

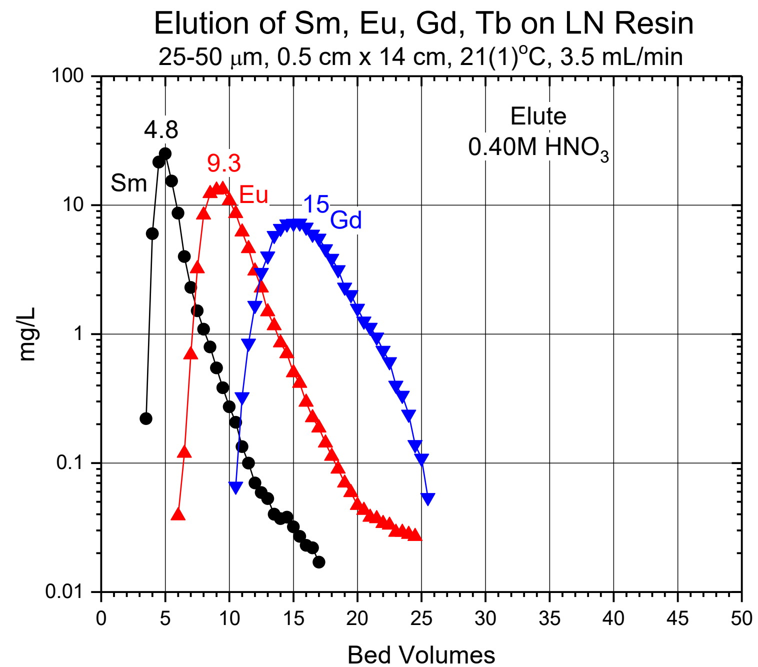
H[DTMPP]


LN: HDEHP
LN2: HEH[EHP]
LN3: H[DTMPP]
k' Relative to La on HEH[EHP] = 1
Z

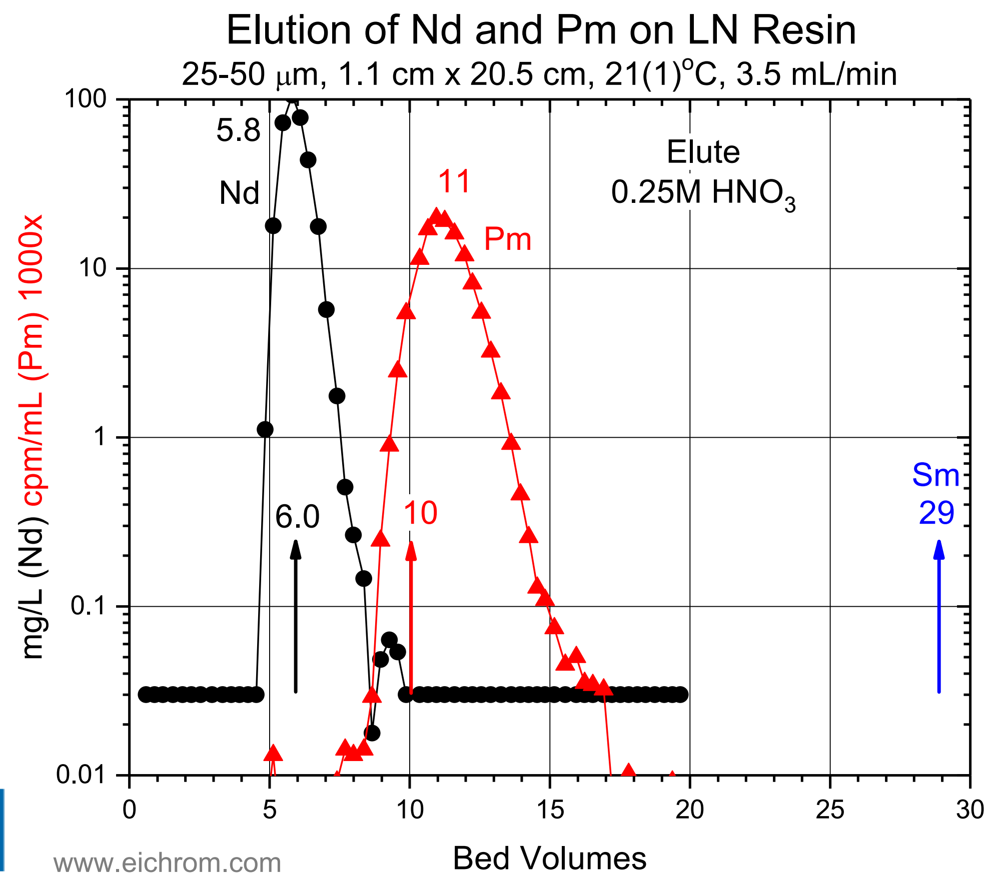

Relative Uptake of Ln(III) and An(III) on LN Resin (HDEHP)
Relative Uptake

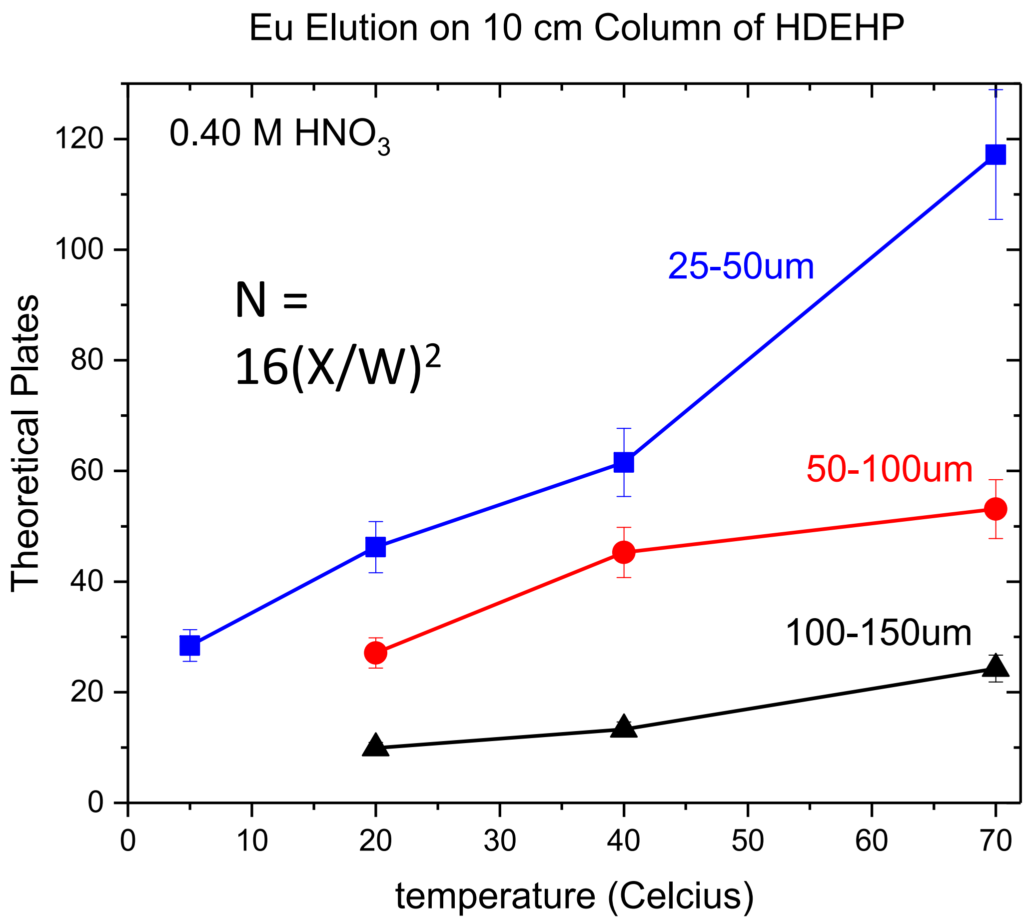
Additional Lanthanide Data





Additional Lanthanide Data




Eu Elution on 10 cm Column of HDEHP
0.40 M HNO_3
$N = 16(X/W)^2$
25-50um
50-100um
100-150um
Theoretical Plates
temperature (Celcius)
0
20
40
60
80
100
120
0
10
20
30
40
50
60
70

Nuclear Medicine

More than 25 years spent developing chromatography products and methods of separation and purification in the field of radiochemistry has created a high level of expertise at Eichrom. Our proprietary products are the global standard for laboratory analysis of actinides and beta-emitting fission products. They are routinely used for environmental monitoring and internal dosimetry programs at nuclear facilities in over 150 countries and on all 7 continents.

We are licensed to work with radioactive materials in our facility in suburban Chicago. All our products are manufactured under a quality management system that has been registered to the ISO 9001 standard since 1995.

As experts in chromatography, column packing and packaging, and radiochemistry, we have long supported the chemical separation and purification needs of organizations involved in radiopharmaceutical R&D and production. We apply our experience base to solve customer problems with both proprietary and commercially available separation media.

View More Info

Nuclear Medicine Radionuclides (partial list)

- Th-227
- Ac-225
- Ra-223
- At-211
- Bi-213
- Pb-212
- Pb-203
- Tl-201
- Re-188

- Re-186
- Lu-177
- Ho-166
- Tb-161
- Sm-153
- Pm-149
- La-135
- La-132
- Sn-117m

- In-111
- Tc-99m
- Y-90
- Zr-89
- Y-88
- Ga-68
- Ga-67
- Cu-67
- Cu-64

- Sc-47
- Sc-44

C. Culter, et al., “Radiometals for combined imaging and therapy,” Chemical Reviews, 113, 858-883 (2013)

Selected Nuclear Medicine Radionuclides Separations

- No carrier added or carrier free radionuclides
- Production route other than fission of HEU
- Diagnostic and therapeutic nuclides

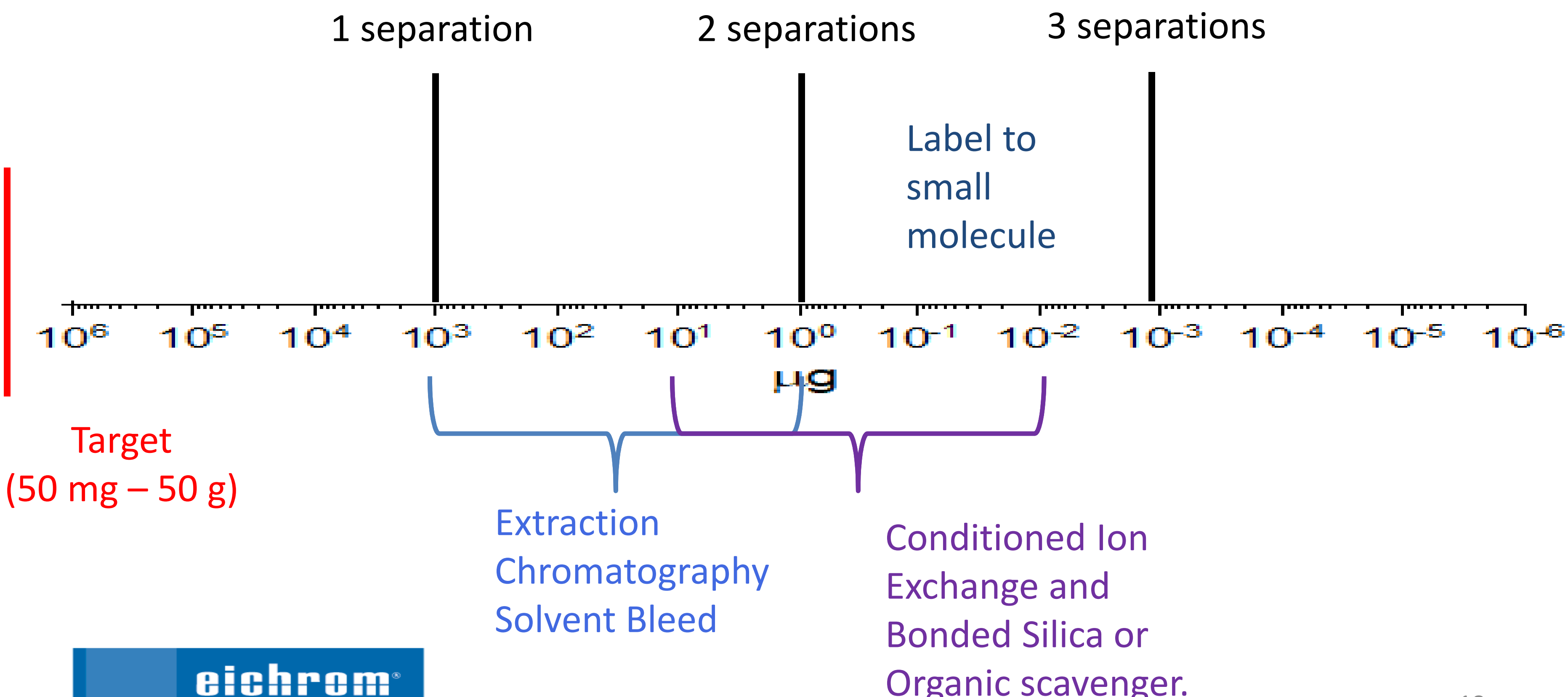
Need for high purity

- Target mass of 50 mg – 50 grams
  - Decontamination factors of 10^6-10^{10}
- Often chelated to targeting molecule
  - Remove Fe and other metals that compete
- Injected to image / treat patients
  - sterile/pyrogen free

General Separation Scheme

- Primary Separation (EXC)
  - Separate radionuclide from bulk target material
- Secondary Separation(s) (EXC, IX)
  - Separate radionuclide from trace impurities (target, Fe, Cu, byproducts)
- Polishing (C18, prefilter, alumina, IX)
  - Separate radionuclide from organic material

Estimated Separation Factors



Relative extractant bleed

High → Low

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

Organic Scavengers / Cleaner Stationary Phases

- Polymeric ion exchangers
  - Stable in highly acidic conditions, Less selective than EXC
- Bonded silica ion exchangers
  - Stable from pH ~ 2-10, Less selective than EXC
- Polymeric scavengers
  - Stable in highly acidic conditions
- Bonded silica scavengers
  - Stable from pH ~2-10
- Alumina / Inorganic ion exchangers
  - Can leach metal ions

Examples

- Pb-203, Pb-201(Tl-201)
- In-111
- Sc-47
- Zr-89
- Ac-225
- Lu-177, Tb-161

^{203}Pb, $^{201}Pb/^{201}Tl$

$^{203}Tl(p,3n)^{201}Pb$ (β-) ^{201}Tl (heart imaging by SPECT)

$^{205}Tl(p,3n)^{203}Pb$ (SPECT imaging, theranostic pair with ^{212}Pb)

Target: Thallium

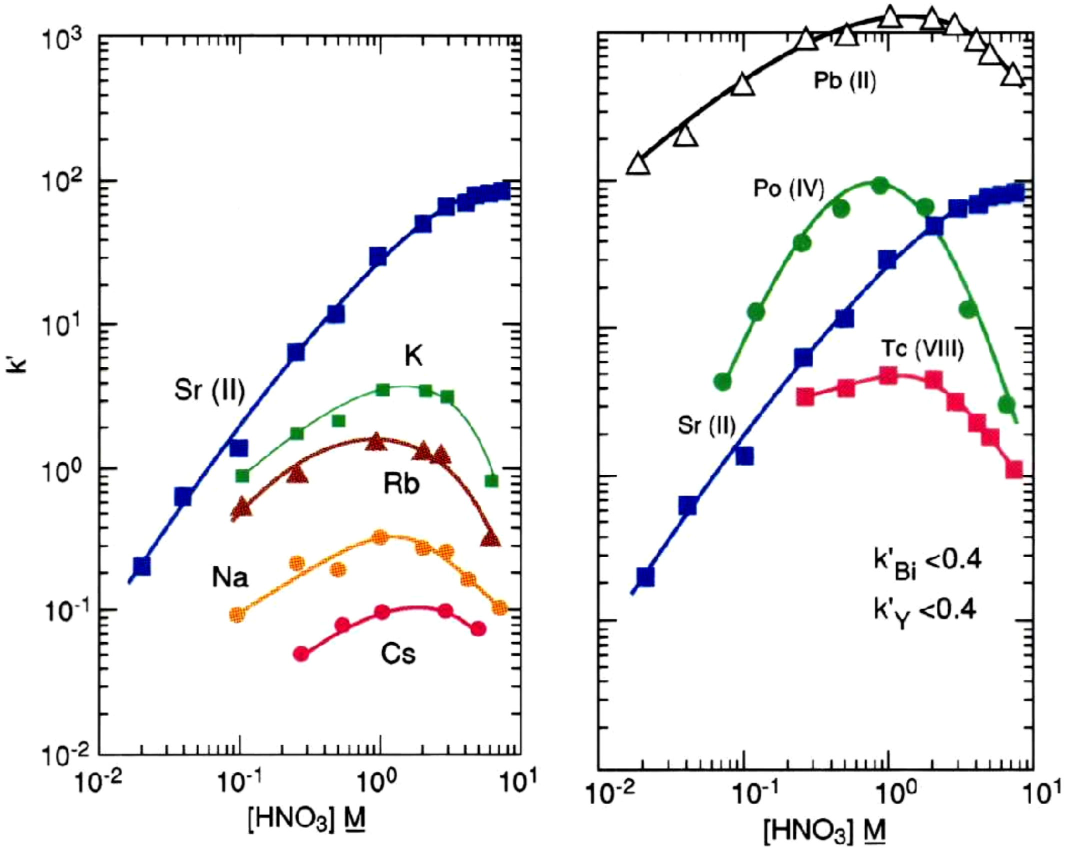
Key Impurities: Copper, Zinc, Cobalt

Primary Column: Sr Resin

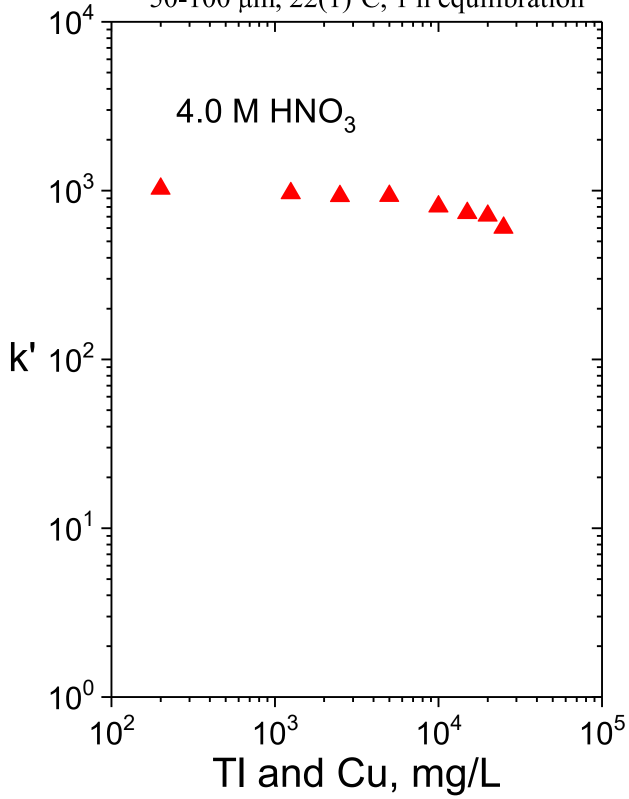
Secondary Columns: UTEVA, Alumina (^{201}Tl)
Weak cation exchange, C18

Pb Isotopes (^{212}Pb, ^{203}Pb, $^{201}Pb/^{201}Tl$)

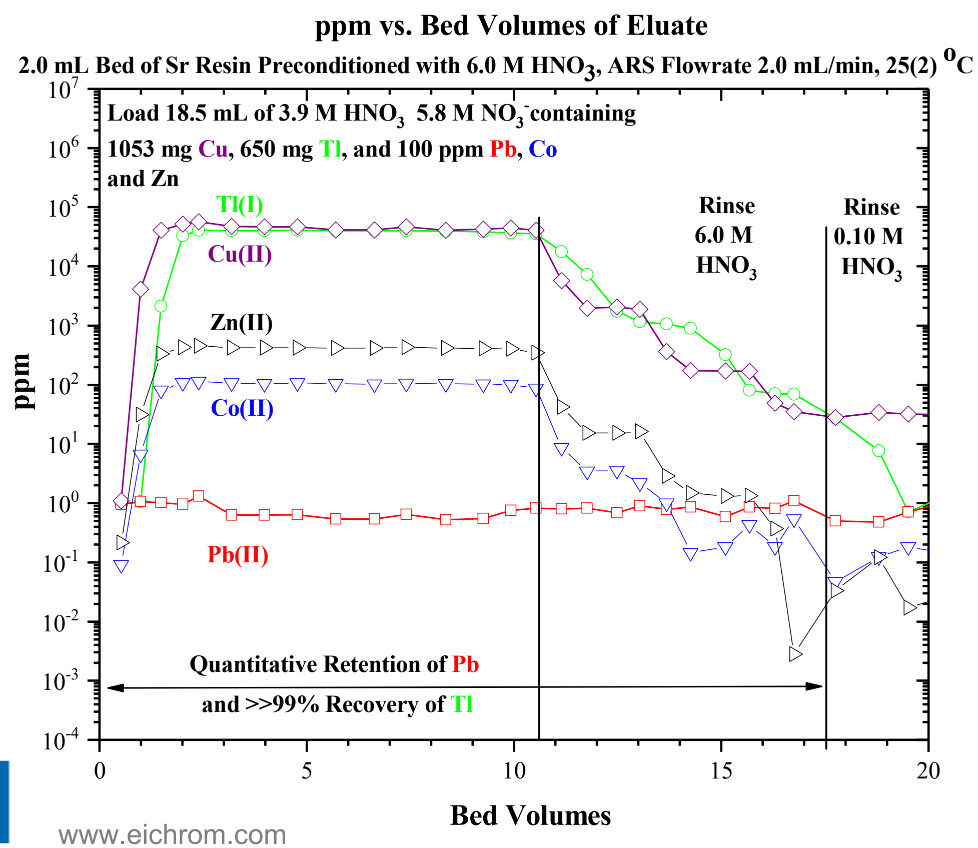
Acid dependency of k' for various ions at 23-25°C.
Sr Resin



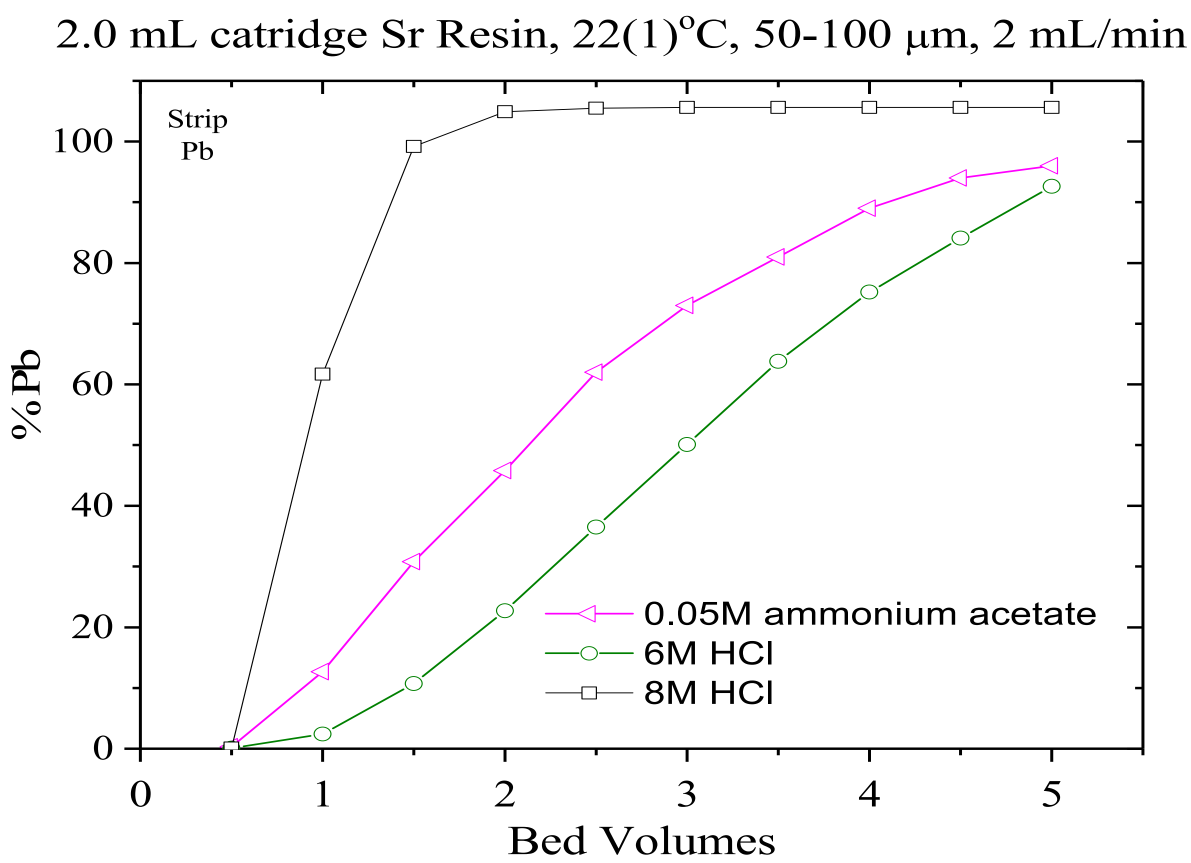
k' on Sr Resin from 4.0M HNO_3
50-100 µm, 22(1)°C, 1 h equilibration



Pb Isotope Separations



Pb Isotope Separations



6-8M HCl for ^{201}Pb.

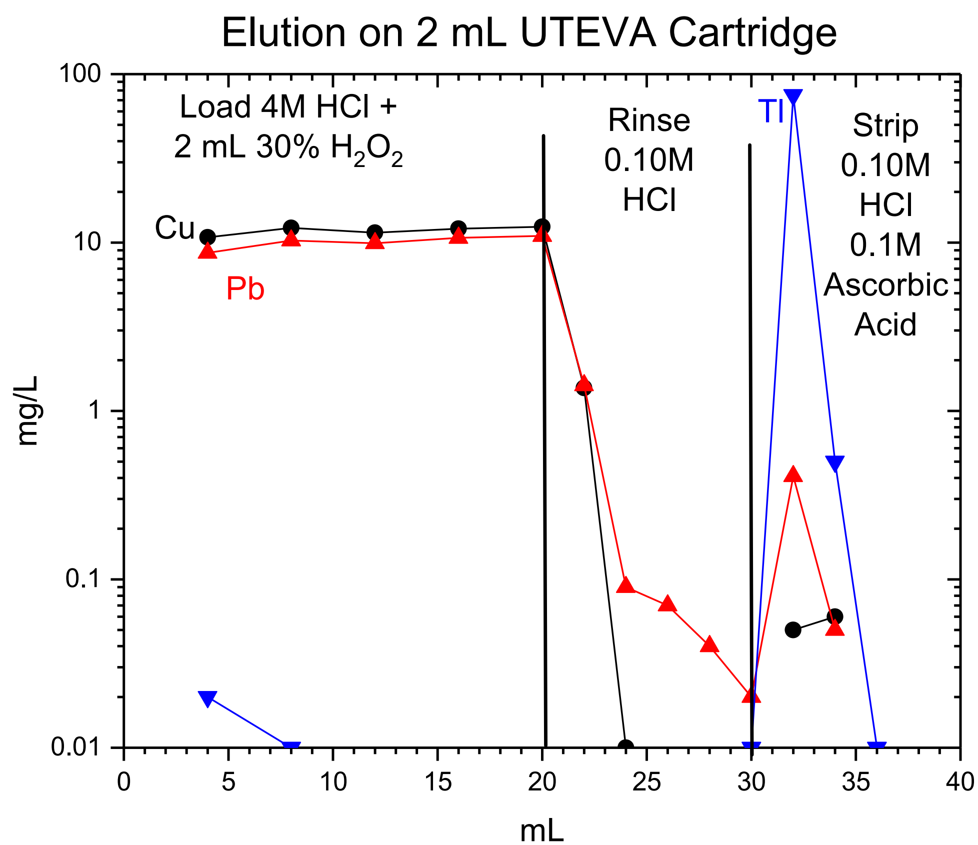
Oxidize Tl(I) to Tl(III).

Separate $^{201}Tl(III)$ on UTEVA or 1x8.

Ammonium acetate for ^{203}Pb or ^{212}Pb. (C-18)

Label ^{203}Pb or ^{212}Pb to small molecule for targeted therapy or imagining.

Tl-201 from Pb-201

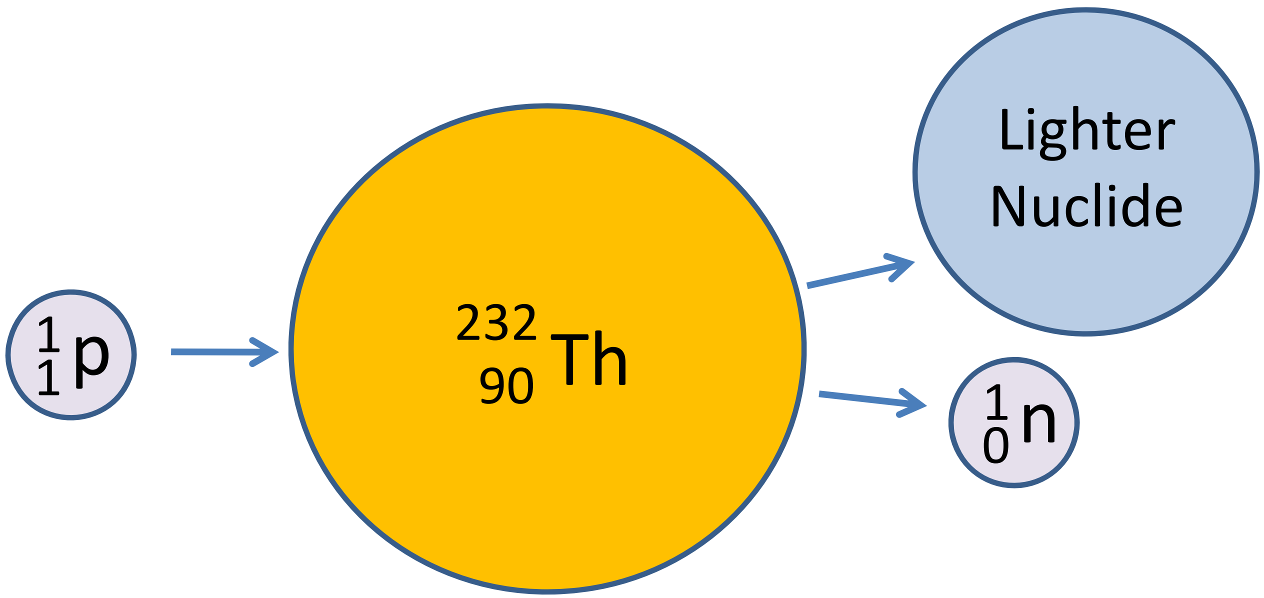


Oxidize Tl(I) to Tl(III)

-HCl + H_2O_2 works well

-Cl_2-H_2O or NaOCl/HCl leads to poor Pb recovery (Sticks to UTEVA)

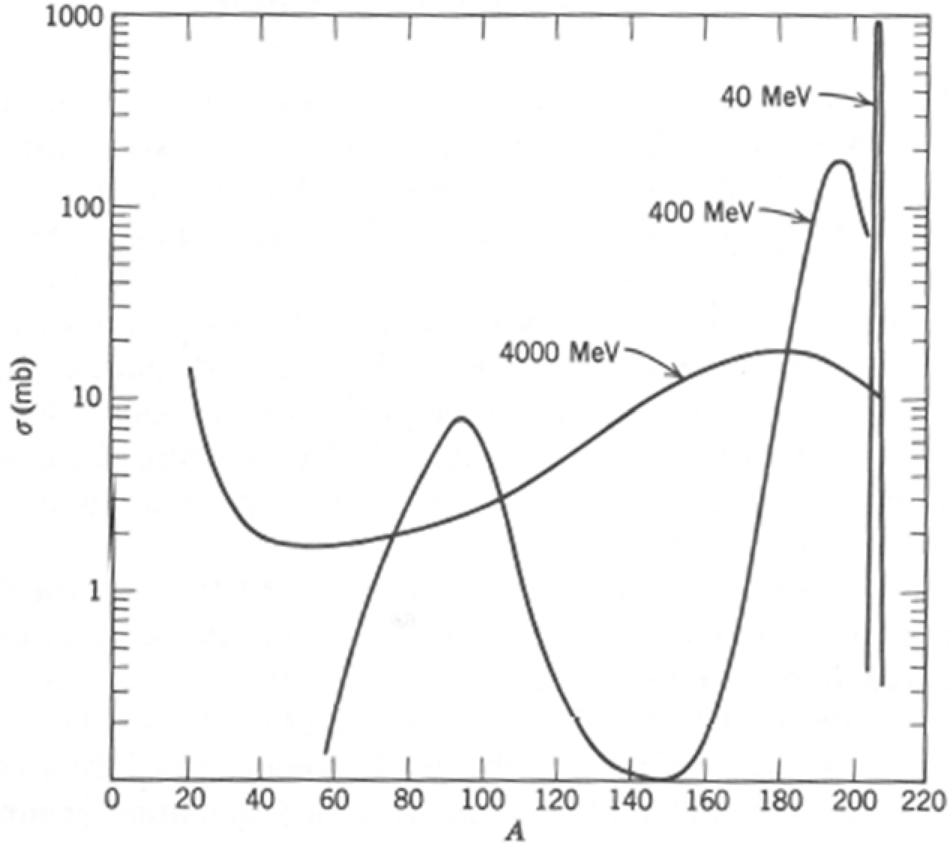
Ac-225 Production via proton Spallation



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

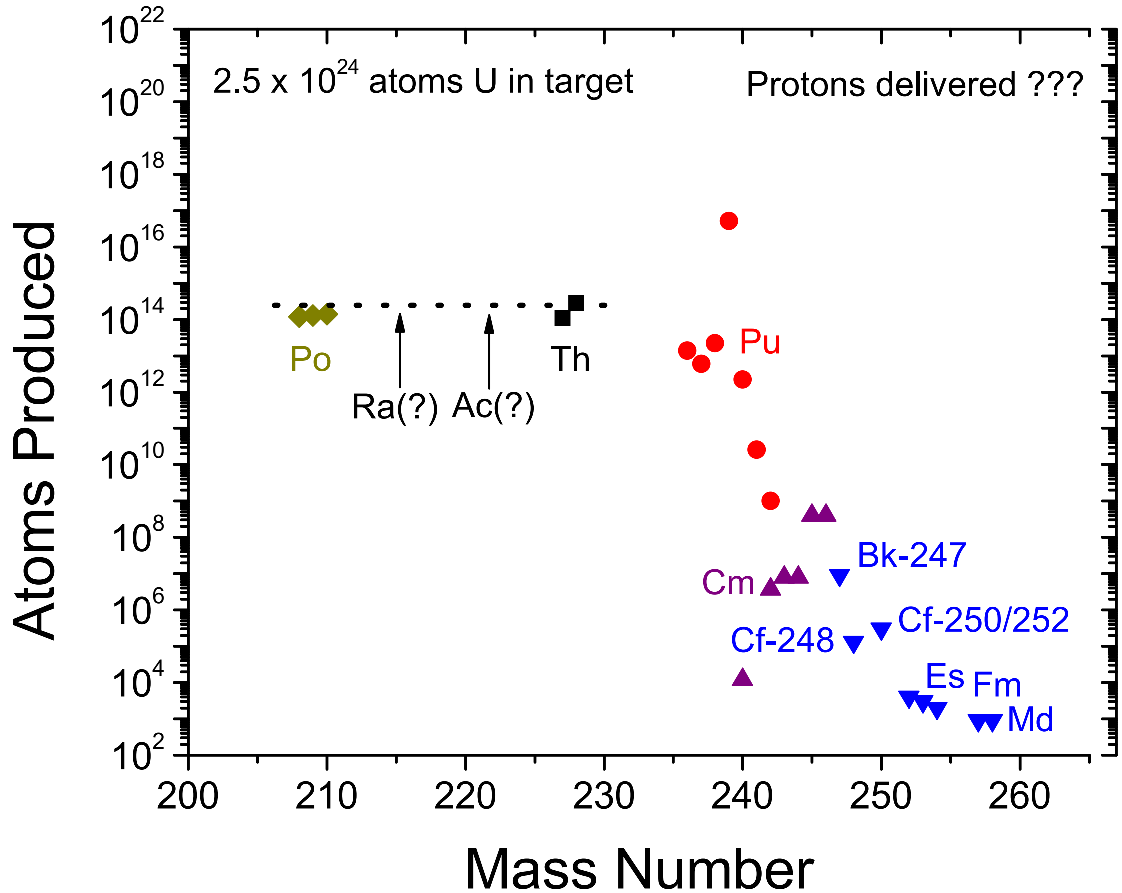
Fragments can also combine with thorium to form heavier nuclides.

Mass Distribution for Reaction of Protons with ^{209}Bi

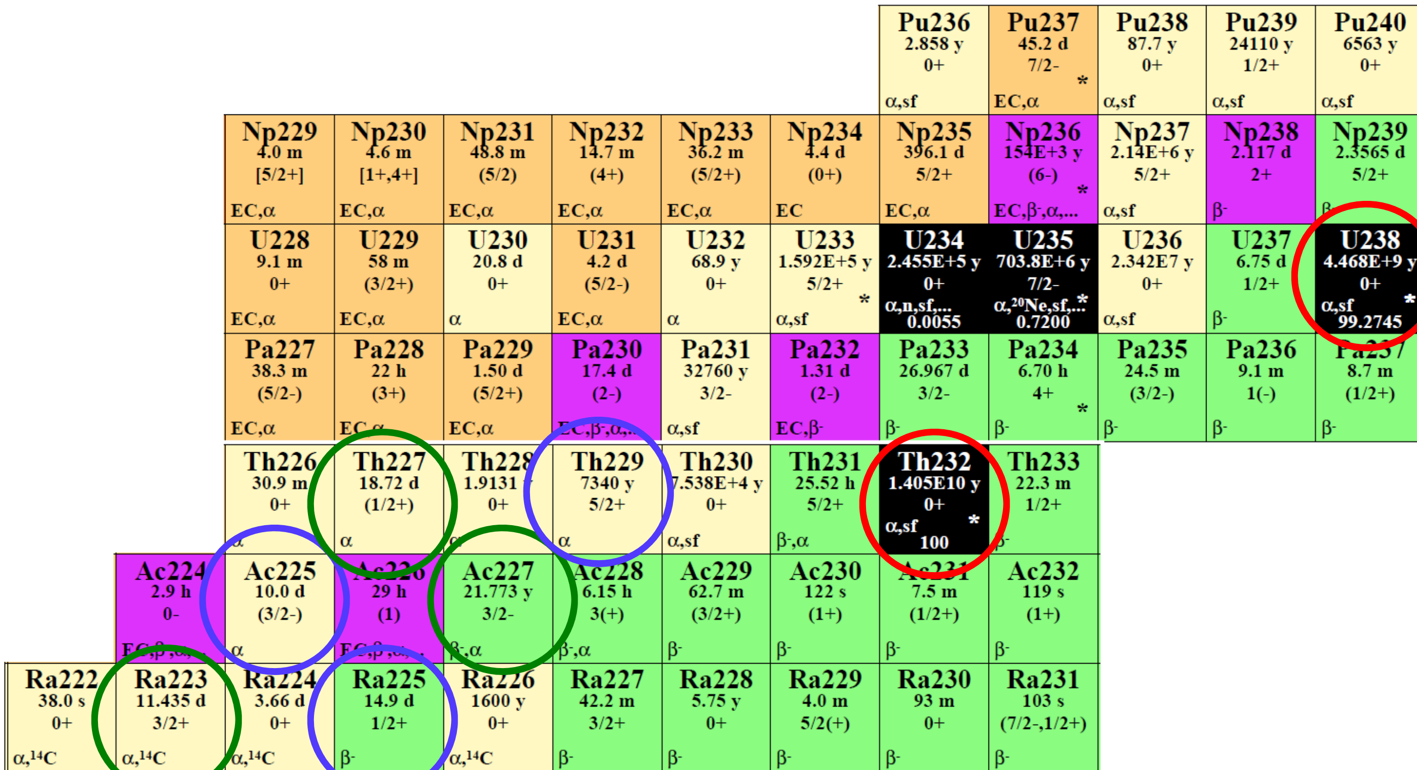


Friedlander, G.; et al. Nuclear and Radiochemistry. 3rd Ed. John Wiley and Sons, New York, 1981, p 172.

U beam-stop from ZG-Synchrotron (ANL), 12 MeV



Unik, J.P.; Horwitz, E.P.; et al.; Production of Actinides and the search for super-heavy elements using secondary reactions induced by GeV protons, Nucl. Phys. A191, 233-244 (1972)



$$^{232}Th(p, 2p\,6n)^{225}Ac \text{ and/or } ^{232}Th(p, \alpha\,4n)^{225}Ac \quad (1)$$

$$^{232}Th(p, p\,7n)^{225}Th\ (T_{1/2} = 8 \text{ min, EC, } 10\%) \rightarrow {}^{225}Ac \quad (2)$$

$$^{232}Th(p,\ 4n)^{229}Pa\ (T_{1/2} = 1.4 \text{ d}, \alpha, 0.48\%) \rightarrow {}^{225}Ac \quad (3)$$

$$^{232}Th(p, 3p\,5n)^{225}Ra\ (T_{1/2} = 14.8 \text{ d}, \beta^-, 100\%) \rightarrow {}^{225}Ac \text{ and/or } ^{232}Th(p, \alpha\,p\,3n)^{225}Ra \rightarrow {}^{225}Ac \quad (4)$$

Zhuikov, B.L.; et al.; Production of 225Ac and 223Ra by Irradiation of Th with Accelerated Protons *Radiochemistry*, *53(1)*, 73-80 (2011).

Ac-225

$^{232}Th(p,x)^{225}Ac$ (targeted alpha therapy, direct or ^{213}Bi)
$^{232}Th(p,x)^{225}Ra\ (\beta\text{-})^{225}Ac$

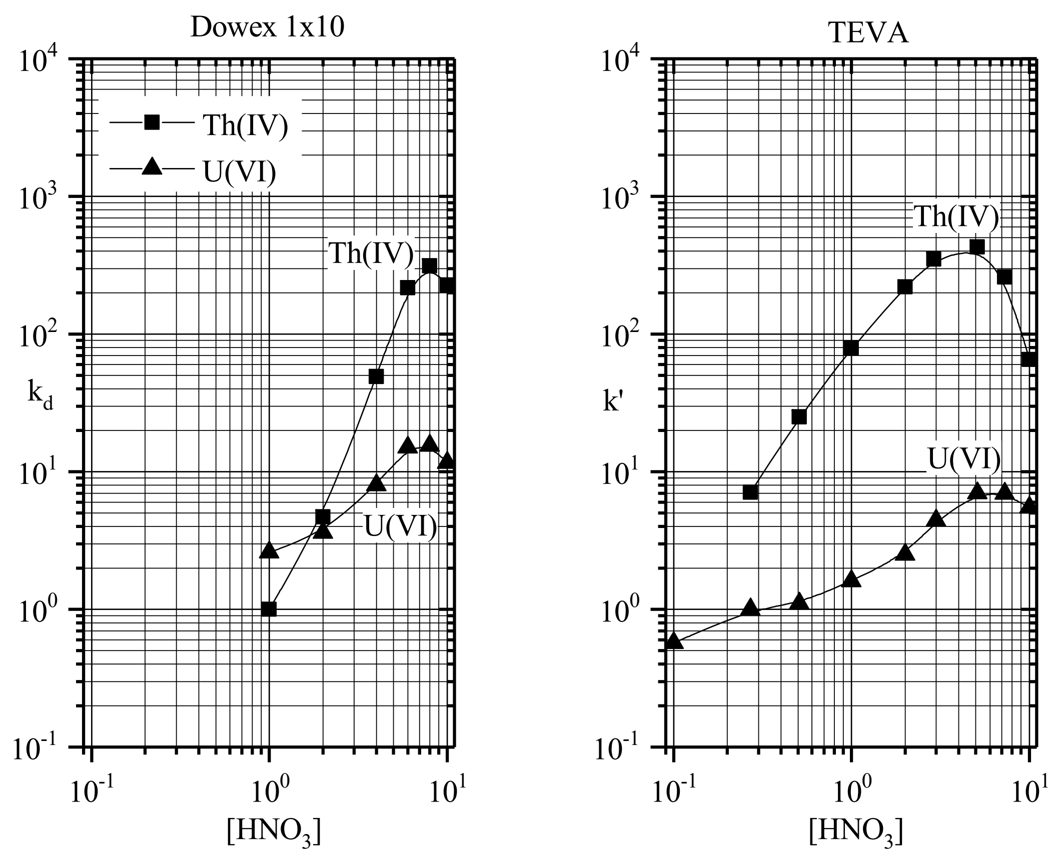
Target: Thorium

Key Impurities: Iron, Ca, spallation byproducts, La-140

Primary Column: Ion Exchange (1x8 – HNO_3, 50Wx8-H_2SO_4)

Secondary Columns: UTEVA/DGA, cation exchange

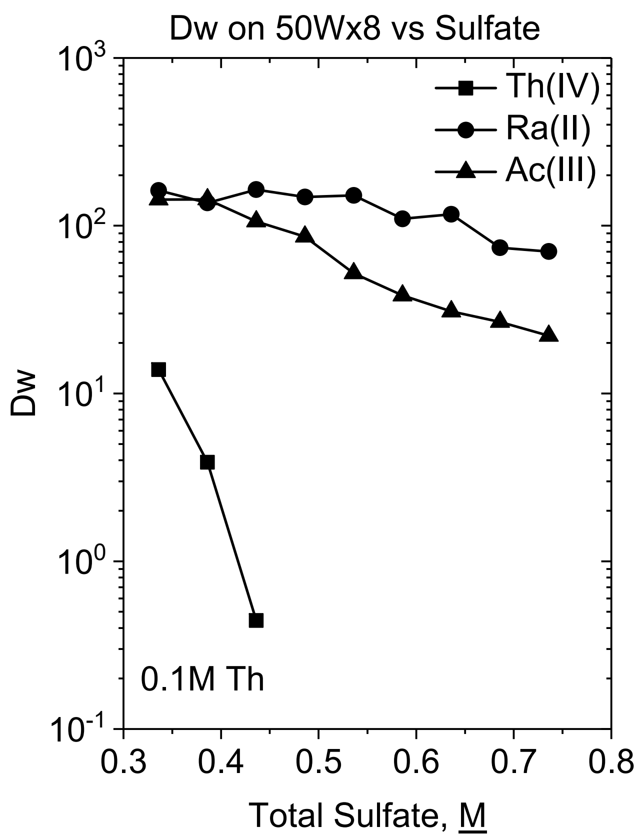
Ac Separations ($^{225/227}$Ac from Th)

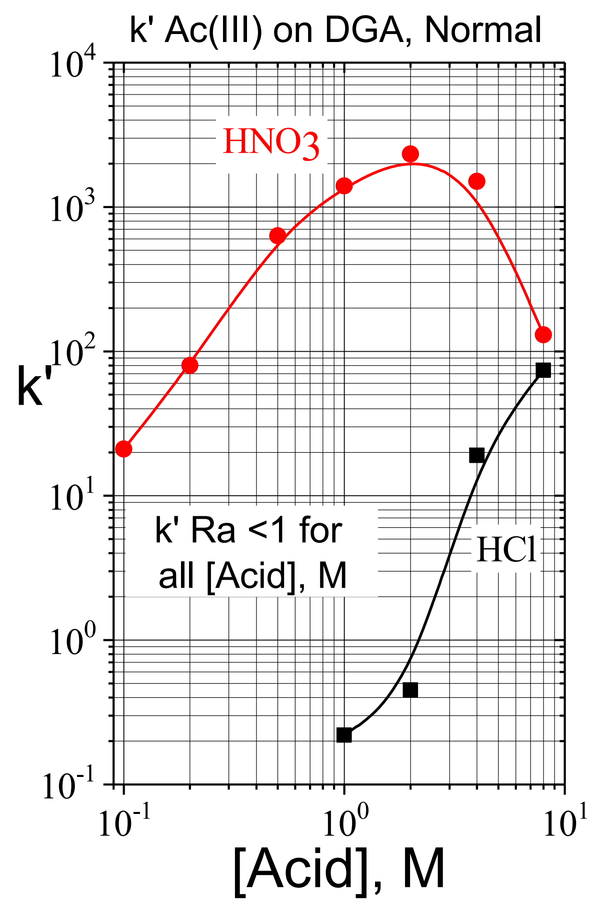


Extracting Th (10-50g) from HNO_3 requires very large columns (1-2 L) or Solvent Extraction (500 mL).

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 Separations



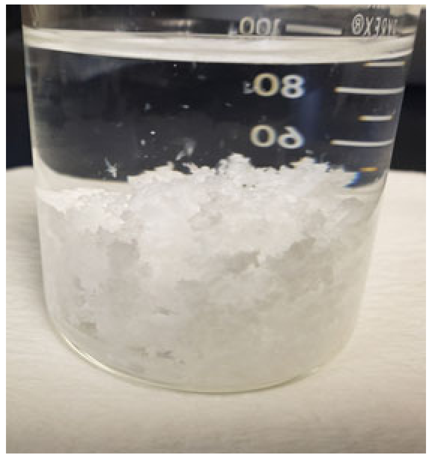


D.R. McAlister, E.P. Horwitz, "Selective Separation of Radium and Actinium from Bulk Thorium Target Material on Strong Acid Cation Exchange Resin from Sulfate Media," *Applied Radiation and Isotopes*, 140, 18-23 (2018).

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

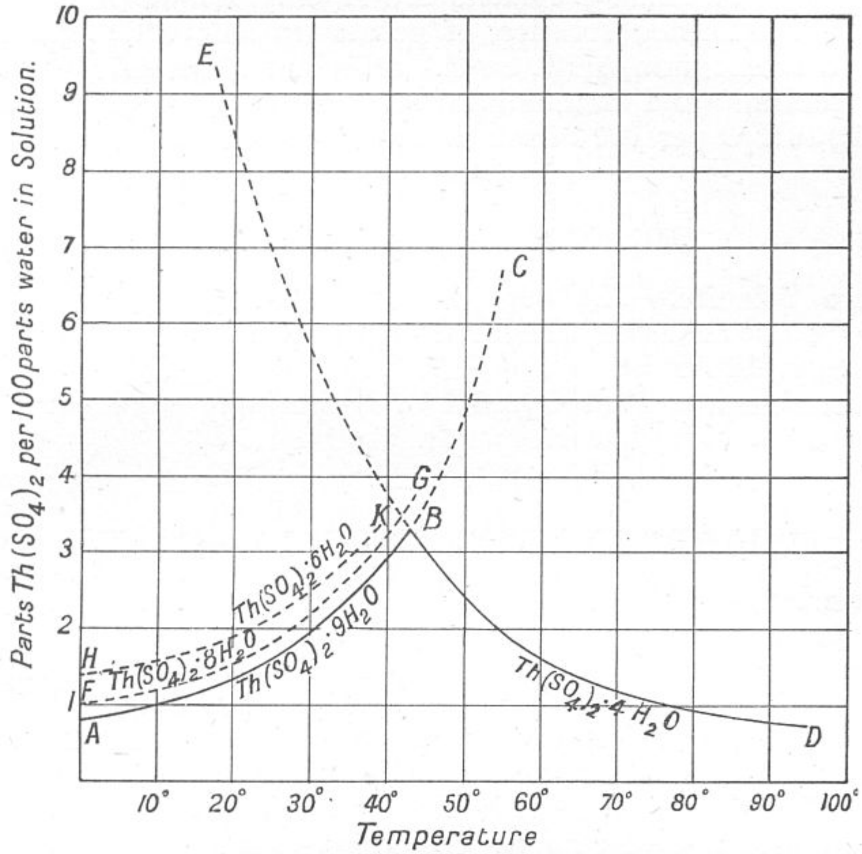
Dissolution of Th in H_2SO_4/HF

H_2SO_4
HF
H_20



Heat
H_20
Low Solubility??!!

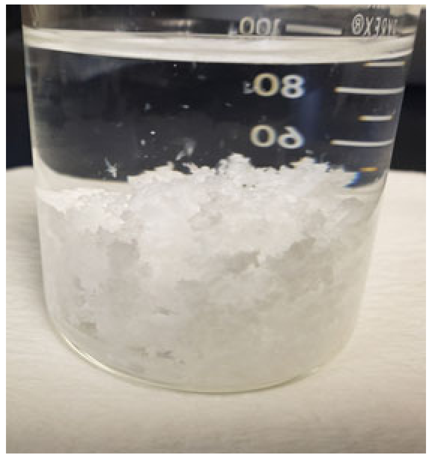
Solubility curves of the hydrates of thorium sulphate.



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

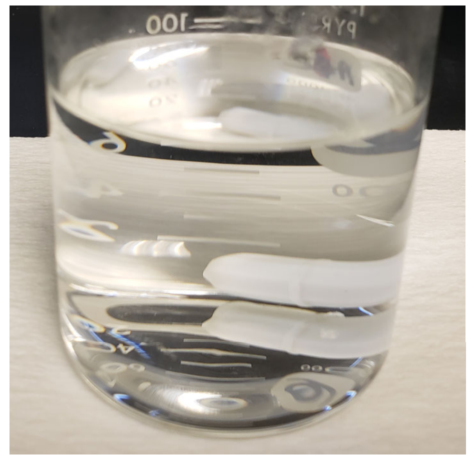
Dissolution of Th in H_2SO_4/HF

H_2SO_4
HF
H_20

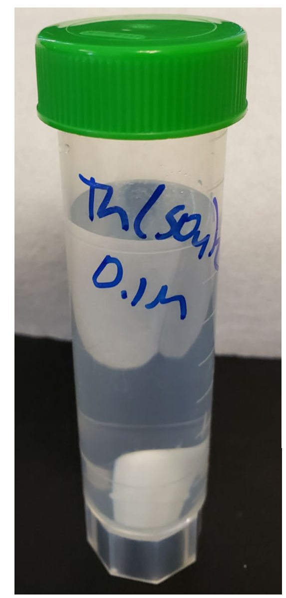


Heat
H_20
Low Solubility??!!

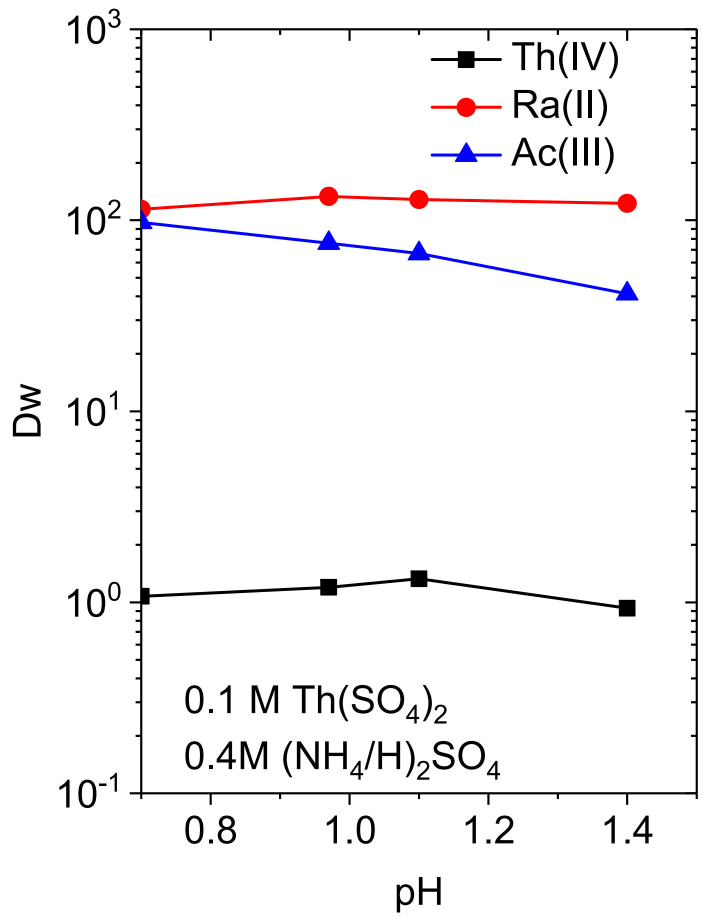
Cool. Mix.



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



Selectivity on Cation Exchange from H_2SO_4



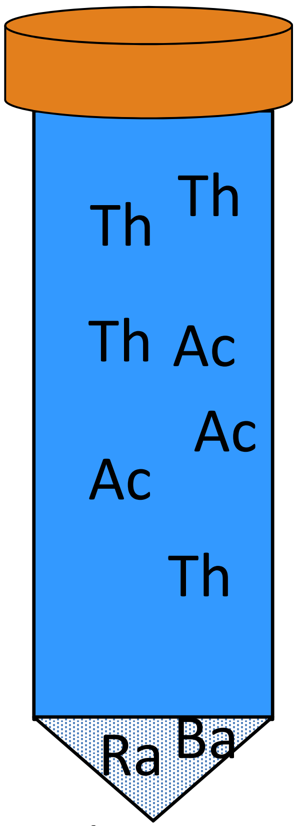
- 30-50 grams of Th as $Th(SO_4)_2$, $Th(SO_4)_3^{2-}$, $Th(SO_4)_4^{4-}$ rejected

- Ra^{2+} and Ac^{3+} uptake decreases above 0.4-0.5M sulfate at pH = 2.0

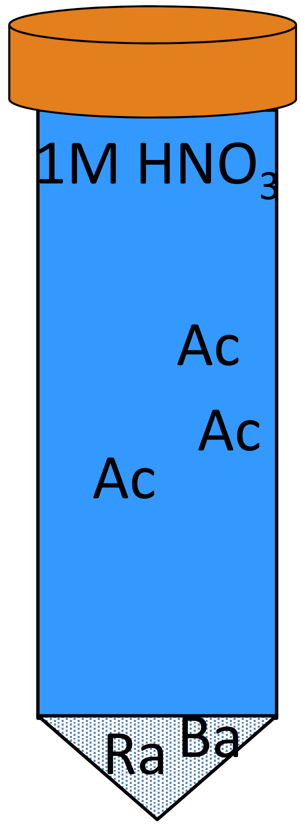
- >99% recovery Ra
- 93-98% recovery Ac

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).

Precipitation $Ba(^{225}Ra)SO_4$



>95% Ra on 1-2 mg/L $Ba(SO_4)$

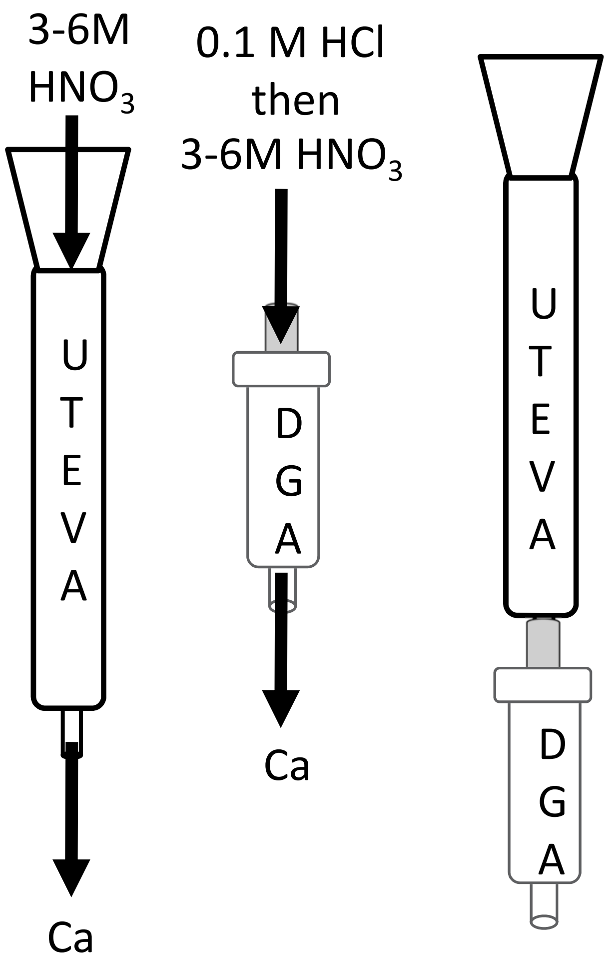


Only 10-15% ^{225}Ac released.

Dissolve $BaSO_4$ in NaOH/EDTA

Adjust to 1-2M HNO_3

Separate Ac on DGA (>95% Ac recovery)



Ac Polishing Steps

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

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

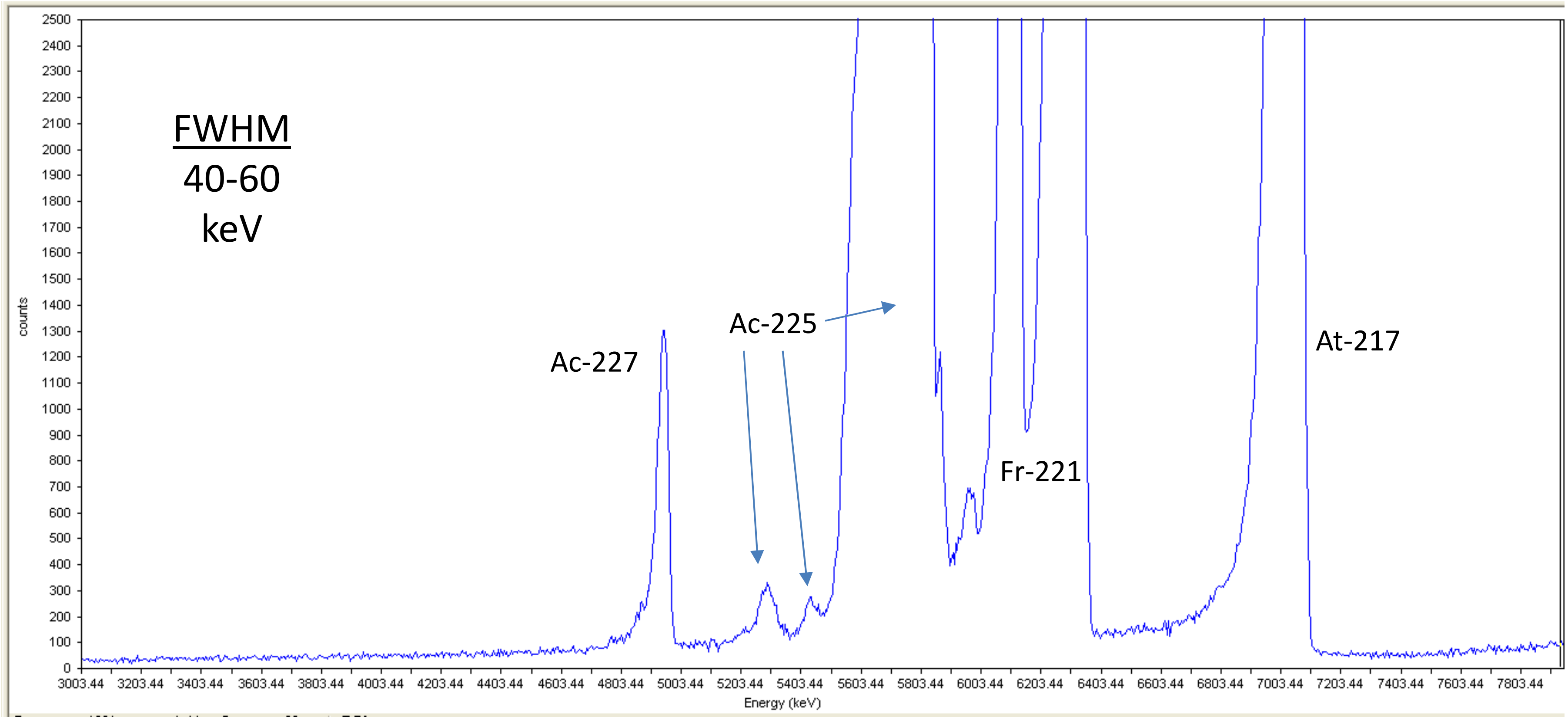
- Ra^{2+} passes both columns (Fe, Ba, Al, many fission products)

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

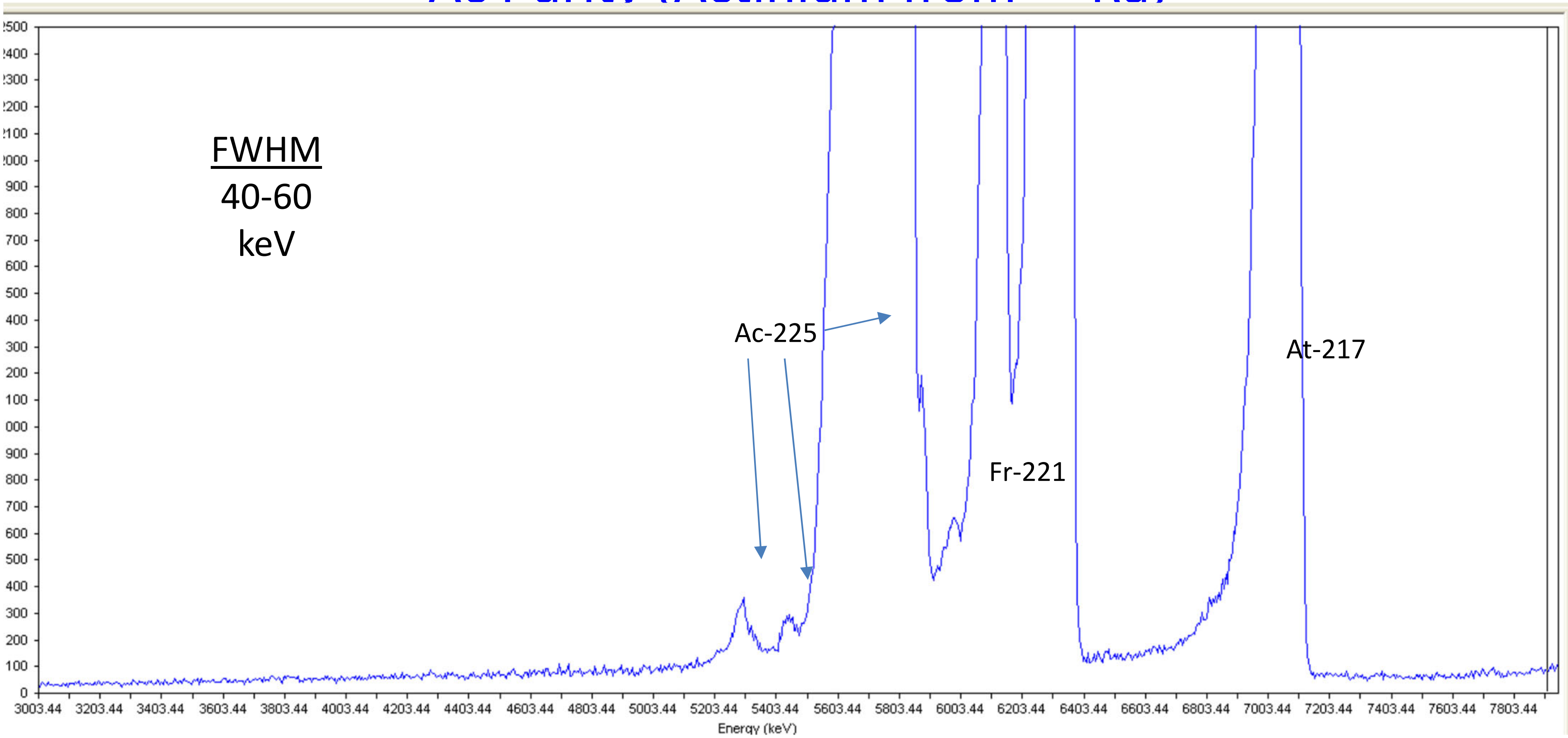
- DGA can be used to separate Ca and rare earths from Ac fraction.

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

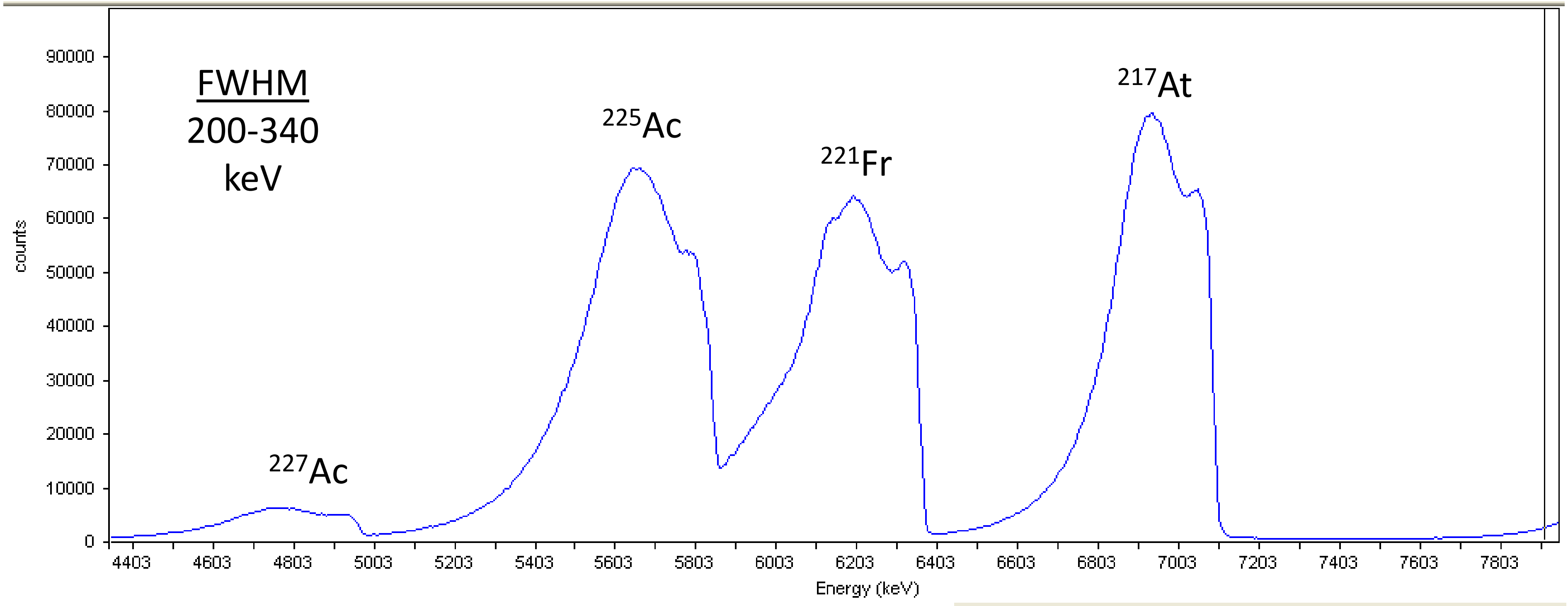
^{225}Ac Purity (Direct Actinium Product)

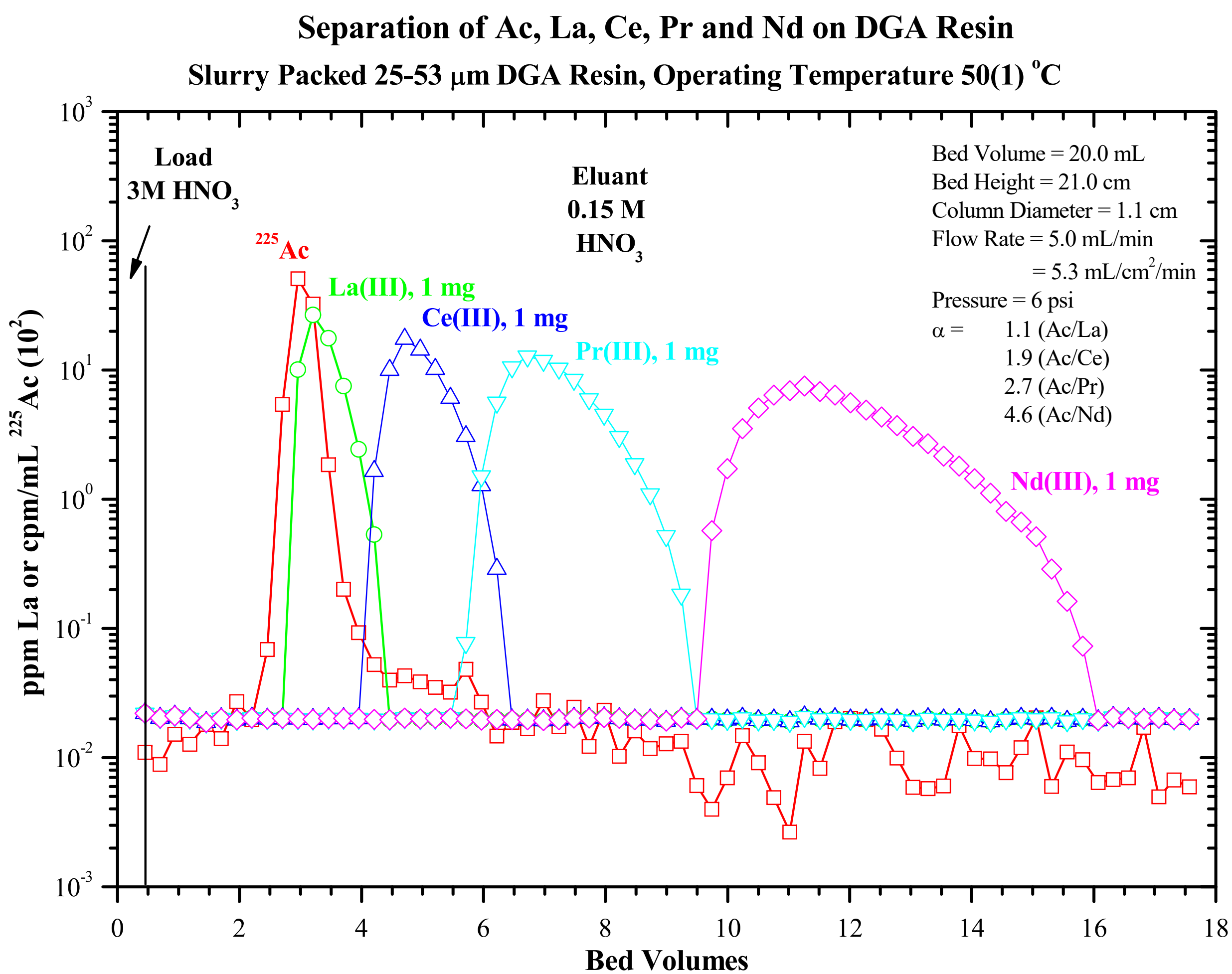


^{225}Ac Purity (Actinium from ^{225}Ra)

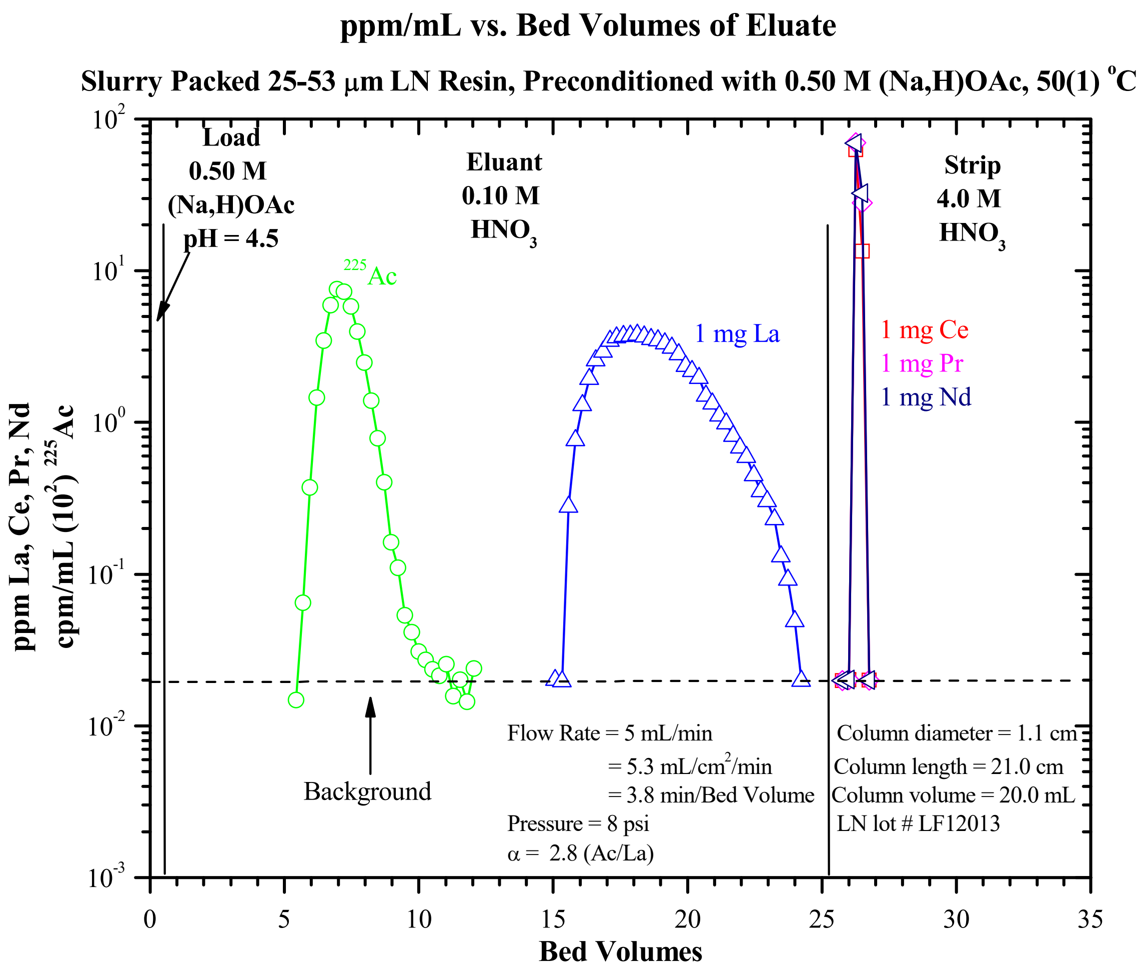


^{225}Ac Purity

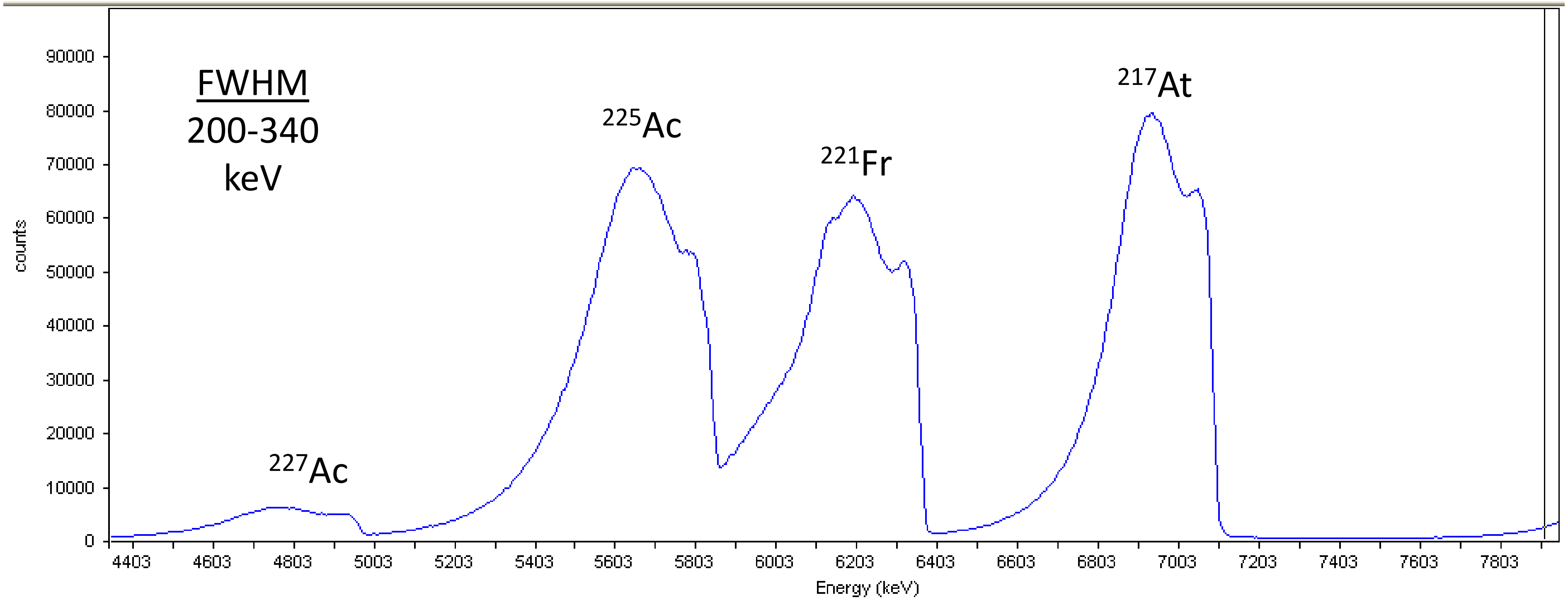




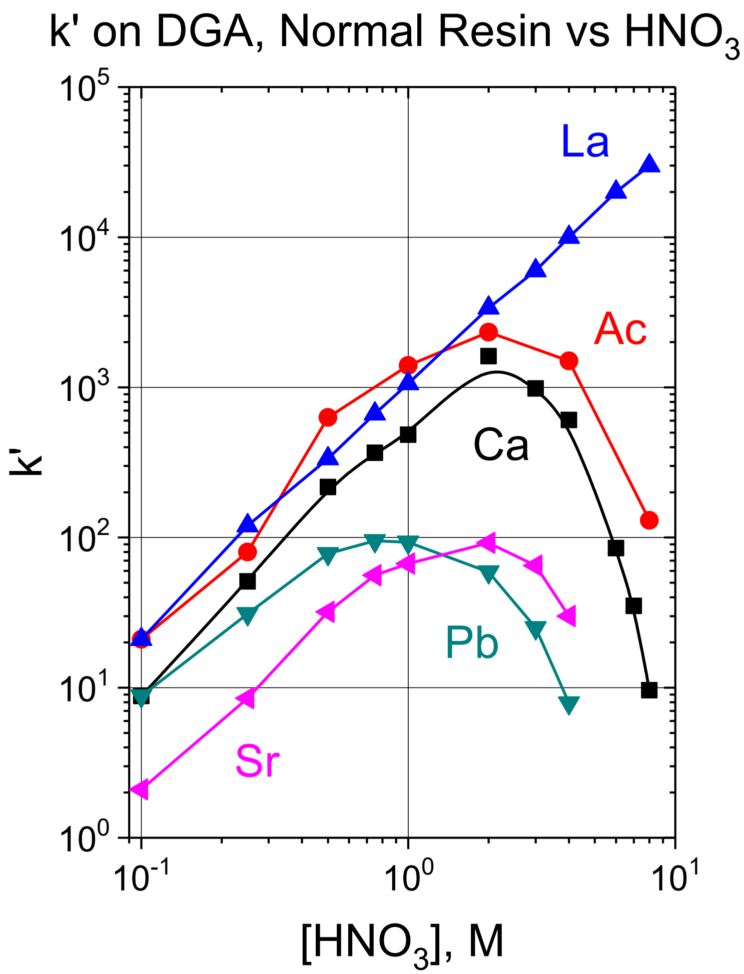
Separation of Ac, La, Ce, Pr and Nd on DGA Resin
Slurry Packed 25-53 μm DGA Resin, Operating Temperature 50(1) °C
Load
3M HNO3
Eluant
0.15 M
HNO3
225Ac
La(III), 1 mg
Ce(III), 1 mg
Pr(III), 1 mg
Nd(III), 1 mg
Bed Volume = 20.0 mL
Bed Height = 21.0 cm
Column Diameter = 1.1 cm
Flow Rate = 5.0 mL/min
= 5.3 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 (10^2)
Bed Volumes

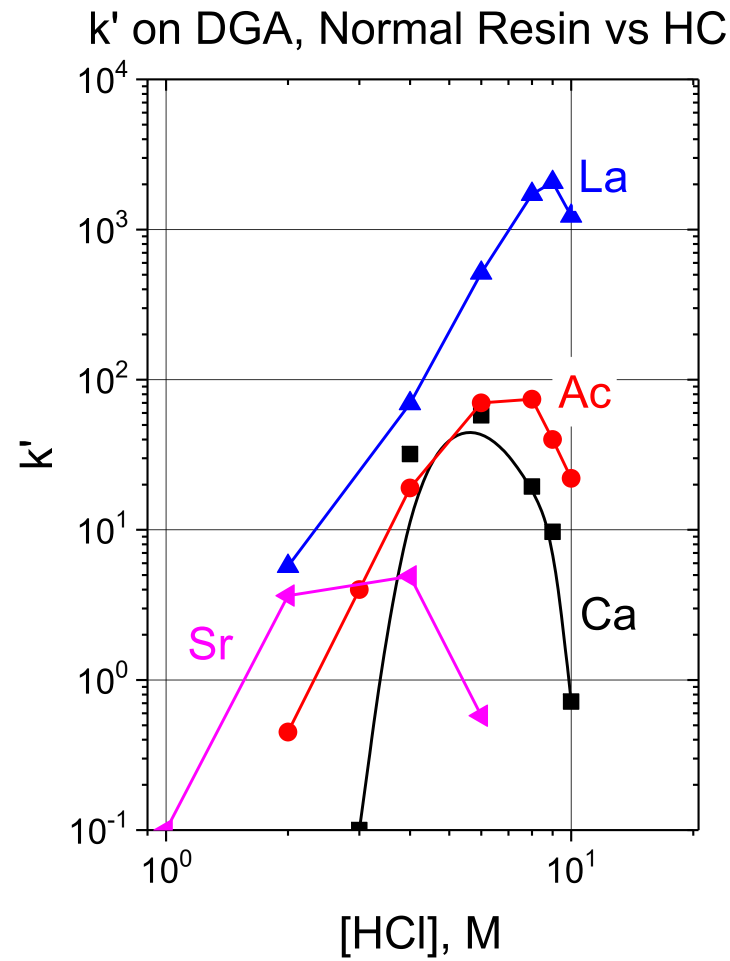

ppm/mL vs. Bed Volumes of Eluate
Slurry Packed 25-53 μm LN Resin, Preconditioned with 0.50 M (Na,H)OAc, 50(1) °C
Load
0.50 M
(Na,H)OAc
pH = 4.5
Eluant
0.10 M
HNO3
Strip
4.0 M
HNO3
225Ac
1 mg La
1 mg Ce
1 mg Pr
1 mg Nd
Background
Flow Rate = 5 mL/min
= 5.3 mL/cm2/min
= 3.8 min/Bed Volume
Pressure = 8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

^{225}Ac Purity (Rare Earth Removal)

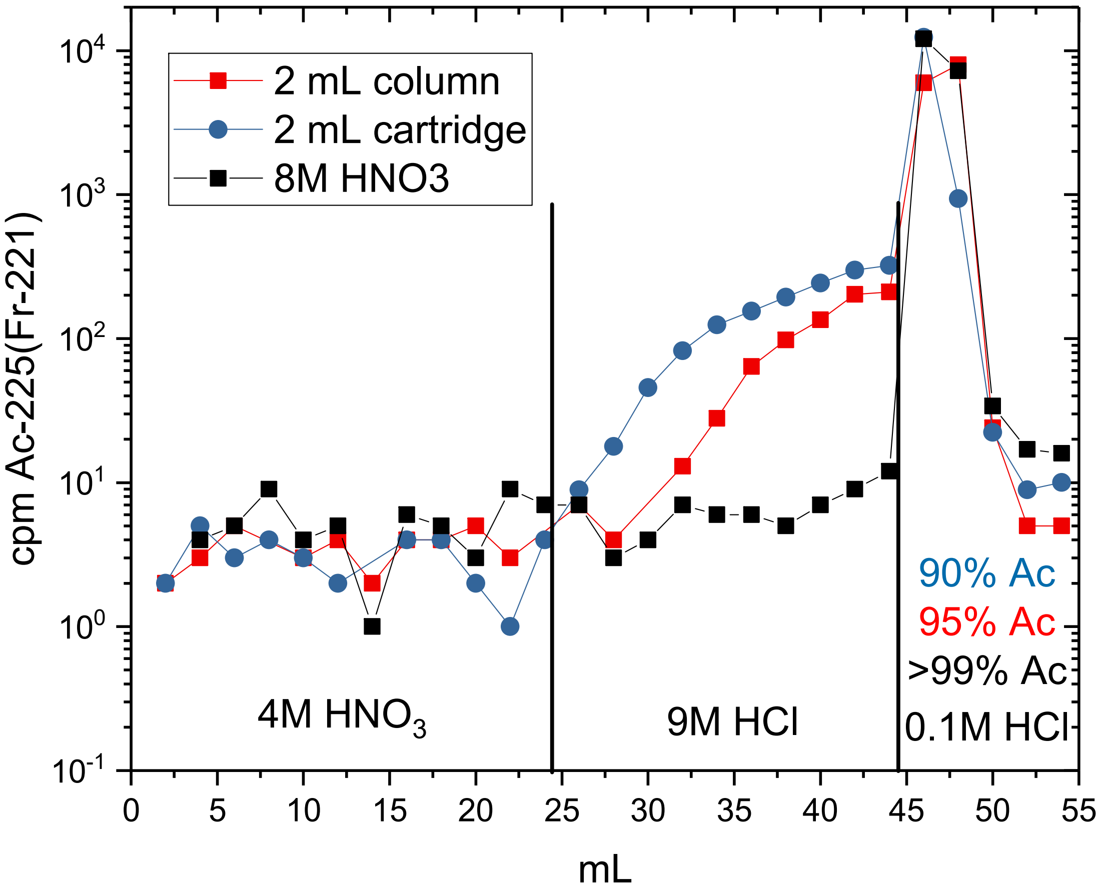


Ac Separation from Calcium and La





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

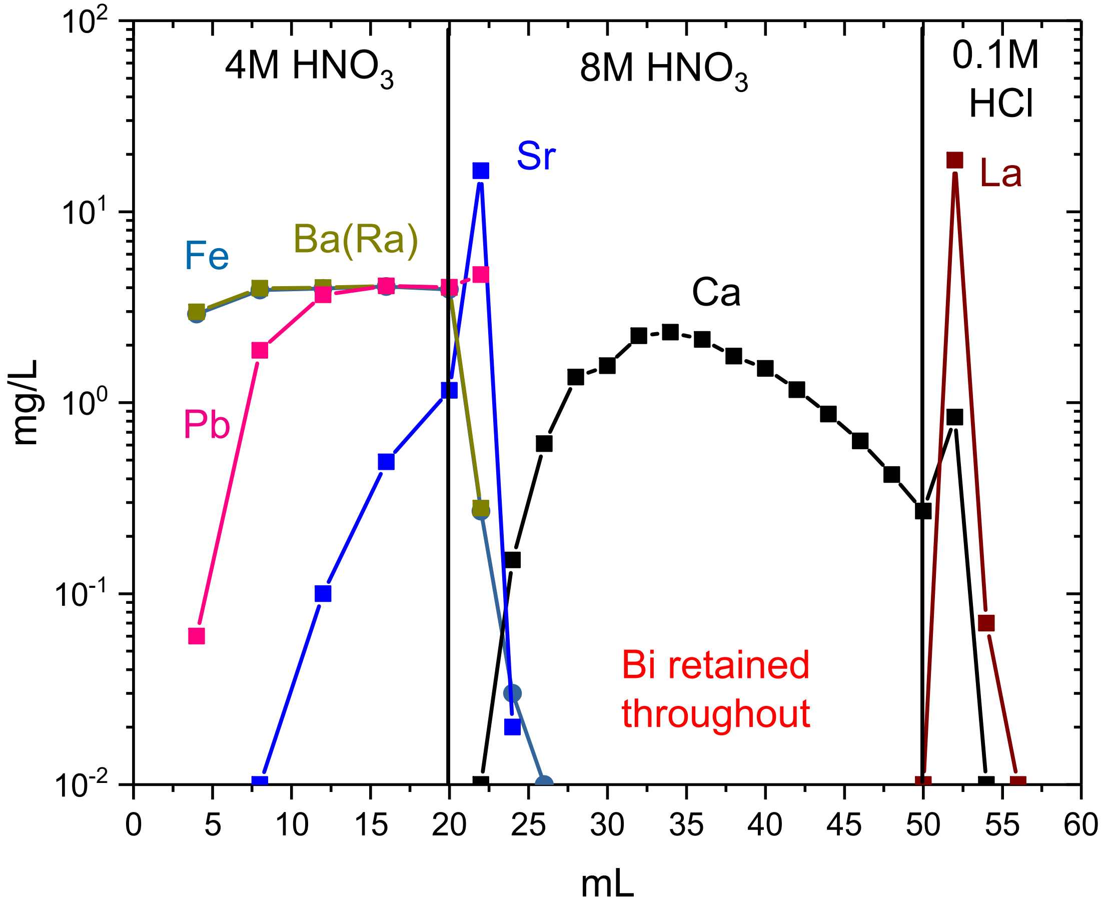


50-100 μm DGA, Normal Resin

Column
4.2 cm length
0.7 cm diameter

Cartridge
2.7 cm length
0.9 cm diameter

^{225}Ac Separation (8M HNO_3)

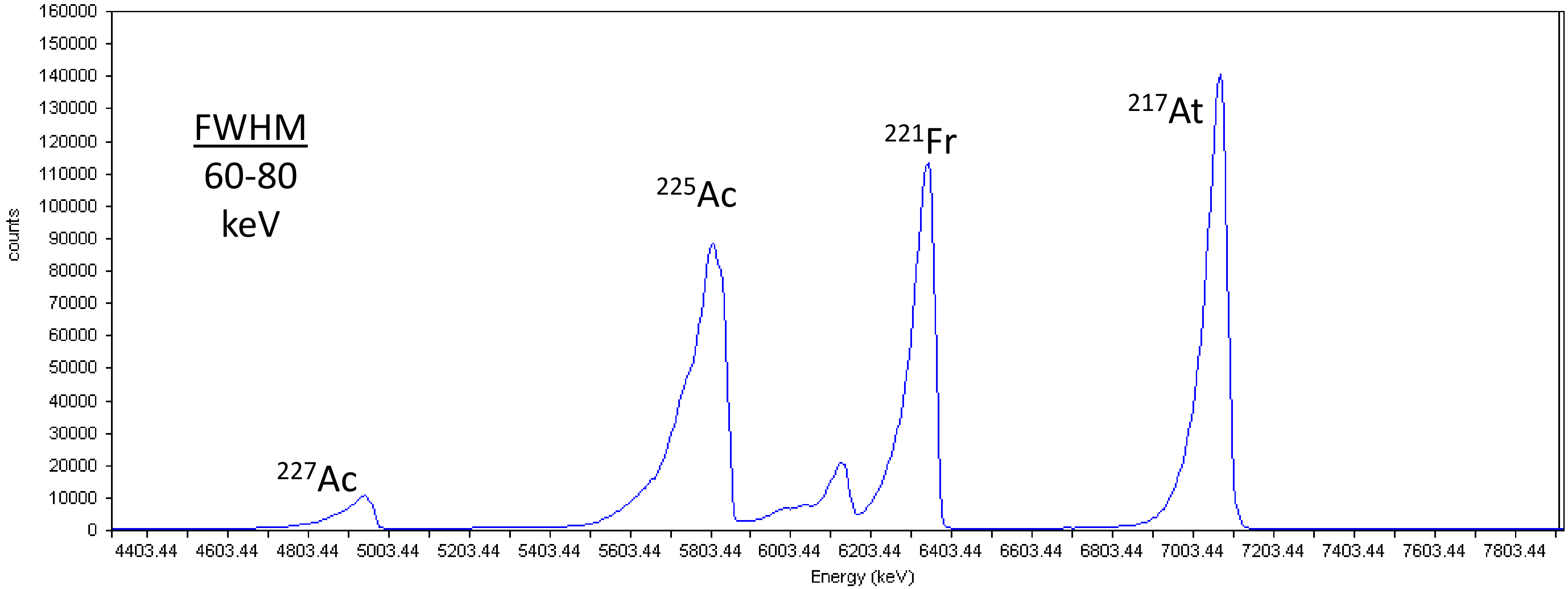


50-100 μm DGA, Normal Resin

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 Purity (Ca Removal)



Conclusion

Thank you

Questions???