Overview and new Developments RadPharm

TKI Workshop

Steffen Happel

01/09/2026

TRISKEM
Expertise in Separation Chemistry

TrisKem International



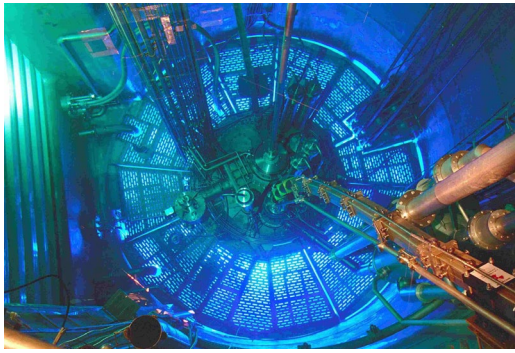
- Based in Rennes (France)
- Independent company since 2007 (before part of Eichrom Europe)
- Main product line: extraction chromatographic resins and other separation materials
- Staff : 25
- R&D, QC and production/packing labs (incl. organic synthesis)
- R&D and TechSupport group:
  - 3 RadChem PhD, 2 Technicians (+ 1 PhD student)
  - ICP-MS/OES, IC, TOC, IR, TGA / UB: alpha spec, LSC, SEM
- R&D: Development of new resins, techniques and applications

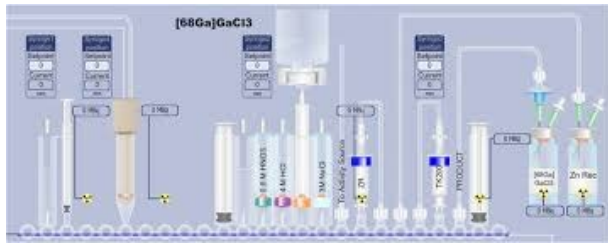


Radionuclide production

- ‘Legacy materials’
  - “Th”/Pb-212, Th-229/Ac-225
- Cyclotron
- Reactors (or other neutron sources)
  - Fission (e.g. Mo-99)
  - ‘Carrier added’ Lu-177 => Lu-176 (n, γ) Lu-177
  - ‘Non-carrier added’ Lu-177 => Yb-176 (n, γ) Yb-177 → Lu-177 + β^-
- Common challenges:
  - Large excess of matrix (target material) => Very high decontamination factors required
  - Cyclotron, often short-lived => rapid separations
  - Very high radioactivity levels => increased radiation stability
- Requirements for resins:
  - Choice of right resin particularly important
    - No selectivity for target material, high selectivity for product
    - Elution under ‘soft‘ conditions in small volume => labelling/injection
    - Fast kinetics
  - Combining several resins can facilitate the separation
    - Conversion (high acid to dilute acid)
    - Removal of impurities upfront







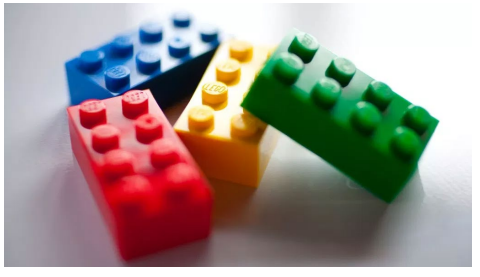




Research interests - Radiopharmacy



- Radionuclide production/purification
  - Resin and method development ‘cold’
    - Cooperation with cyclotrons & reactors (NL, RN producers,…)
    - Equipment provider (targetry, synthesizer,…)
  - Separation of radionuclides from irradiated targets
    - Diagnostics: Zr-89, Cu-64, Ga-68, Ge-68, Ti-44/5, Tc-99m, Sc-43/4…
    - Therapy: alpha emitters, Lu-177, Tb-161, Cu-67, Sn-117m, Sc-47…
  - Requirements for resins:
    - Choice of right resin particularly important
      - No selectivity for target material, high selectivity for product
      - Elution under ‘soft‘ conditions in small volume => labelling/injection
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    - Combining several resins can facilitate the separation
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      - Removal of impurities upfront



Research interests - Radiopharmacy



- Quality control
  - Cartridge based methods (e.g. Sr-90 in Y-90,…)
    - Use of “TK-ELScint cartridges”?
  - **“Sheets”**
    - p.ex. DGA sheets (functionalized TLC for Ra-223, Ga-68, Pb-212,…. => CVUT Prague), CU Sheets,…
- Decontamination of effluents/waste (Ge-68, lanthanides, radioiodine,…)
- ‘Recycling’/valorization of long-lived RNs (Ge-68,…) and target materials
- Radiolysis stability (polymer, radical scavengers,…)
- **Determination of radionuclides (mainly used in therapy, generally Lu-177 and Ac-225) in environmental and bioassay samples**

Overview

- ZR Resin
  - Zr-89 from Y targets
  - Zr-89 via TBP/TK400
  - Ga-68 from Zn targets
  - Ti separation
  - Ge separation
- Cu-61/4/7
  - TK201 Resin
  - CU Resin
  - TK250 Resin
- Radiolanthanides
  - Lu-177 from Yb targets
  - Tb-161 from Gd targets
- Ac-225
- Ra-226
- Tc-99m from Mo
- Quality Control – Sheets
- Extractive Discs
- Other on-going R&D

ZR Resin

Original scope: Hydroxamate based resin

- Different form Holland et al.
- Standard for Zr separation from Y targets
- Ready to use / no activation
- Facile Zr elution (avoid 1M oxalic acid)

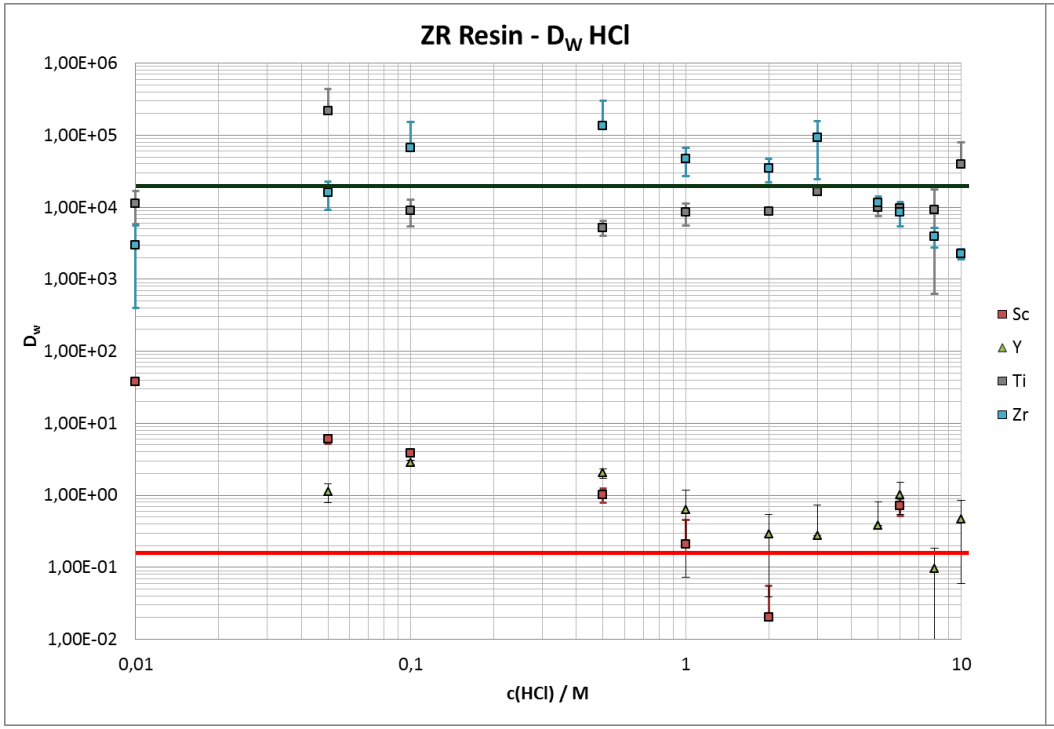
Zr-89 production via (p,n) reaction from ^{nat}Y targets

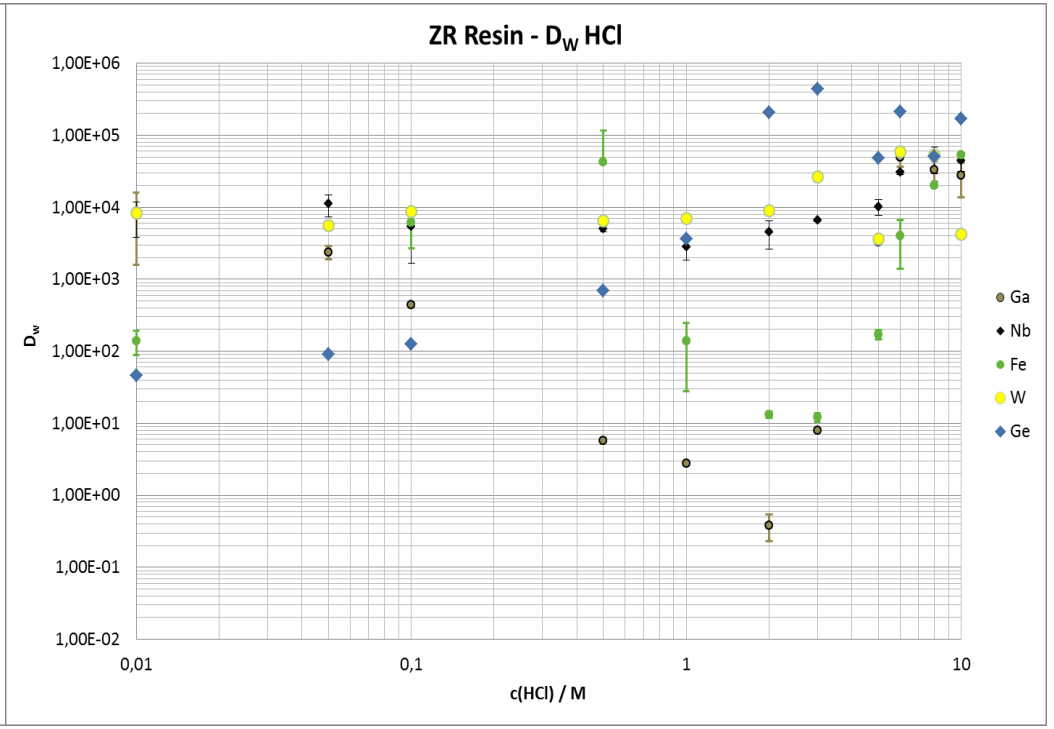
- High Zr/Y selectivity necessary
- Alternative e.g. TBP Resin (=> Graves et al.)

Application for other separations: **Ti/Sc**, **Ga/Zn, Ge/Ga**

On-going work => improvement of radiolysis stability

ZR Resin – HCl

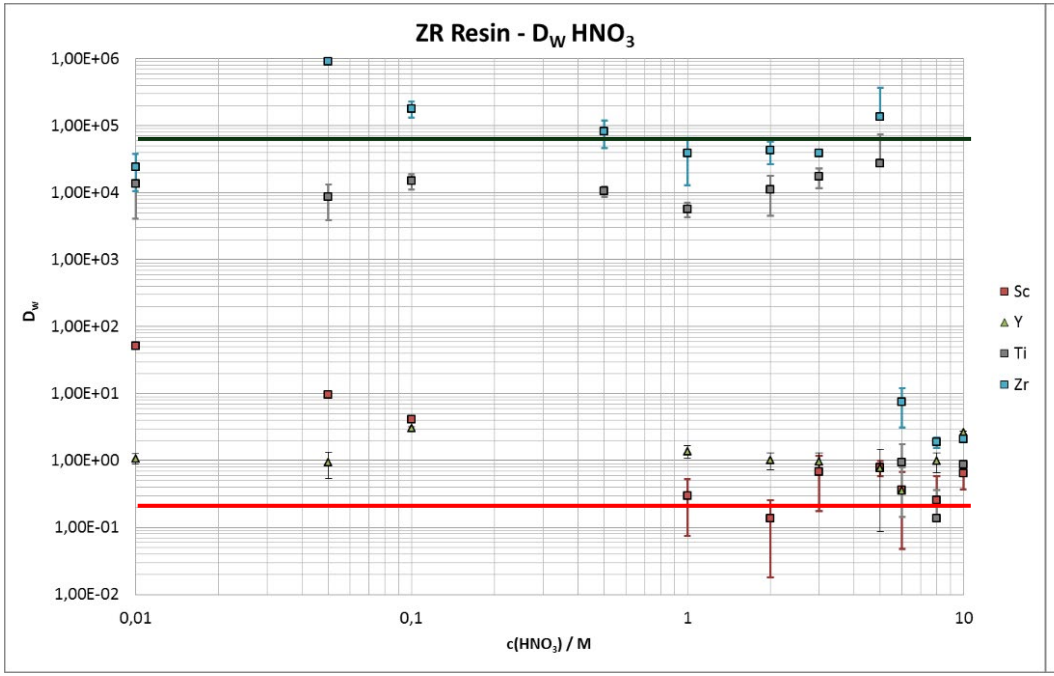


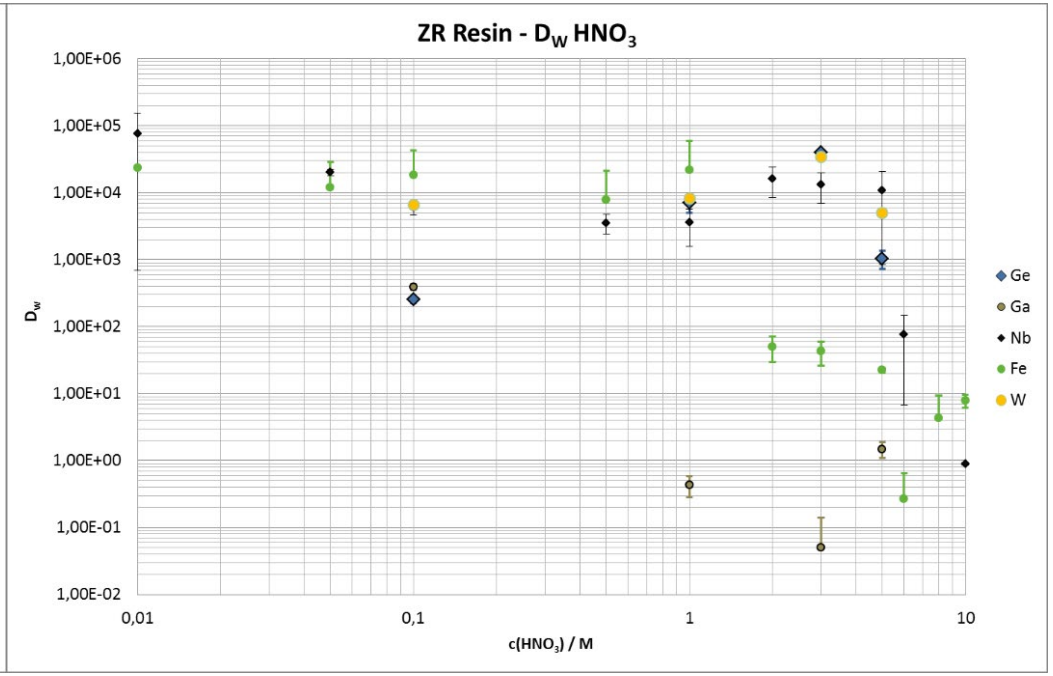


- No selectivity for Y, Sc
- High selectivity for Zr, Ti, Nb, W over wide HCl conc. range
- High Ge/Ga selectivity at elevated HCl

- No selectivity for alcalines and earth alcalines
- Lanthanides not retained
- Fe retention (dip at 2 – 3M HCl)

Zr Resin – HNO_3



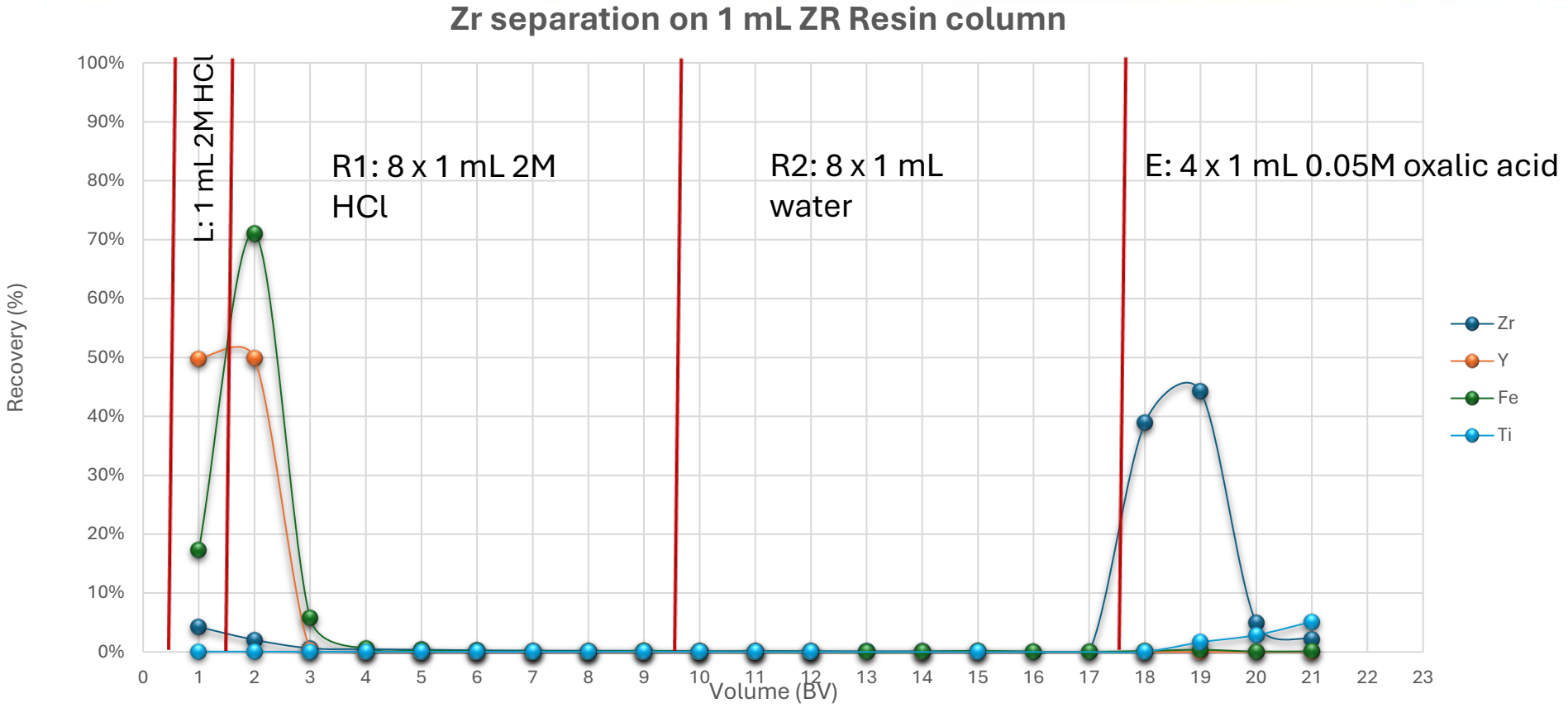


- High selectivity for Zr, Ti, Nb, W over wide HNO_3 concentration range
  - Loss of selectivity at 6M HNO_3

  => Resin shows colour change

- No selectivity for Y, Sc, lanthanides, earth alcalines, most transition metals,…
- High Ge/Ga selectivity at 3M HNO_3

Zr-89 separation from Y targets



- Load from 2 – 6M HCl
- Rinsing described by Holland may be used
- No activation with acetonitrile

- Quantitative Zr elution in 1.5 - 2 mL ≥ 0.05M oxalic acid
- Clean Fe removal
- Requires oxalate to e.g. chloride conversion

Zr-89 chloride via TBP and TK400

Nuclear Medicine and Biology 136–137 (2024) 108943

Contents lists available at ScienceDirect

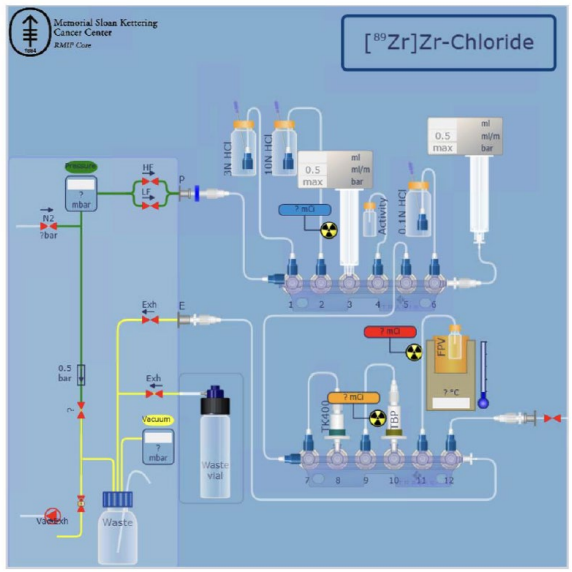
Nuclear Medicine and Biology

journal homepage: www.elsevier.com/locate/nucmedbio

[^{89}Zr]$ZrCl_4$ for direct radiolabeling of DOTA-based precursors☆

Serge K. Lyashchenko [a,b,*], Tuan Tran [a], Steffen Happel [c], Hijin Park [a], David Bauer [b], Kali Jones [b], Tullio V. Esposito [b], NagaVaraKishore Pillarsetty [b], Jason S. Lewis [a,b,d]

[a] Radiochemistry and Molecular Imaging Probe Core Facility, Memorial Sloan Kettering Cancer Center, New York, NY, USA
[b] Department of Radiology, Memorial Sloan Kettering Cancer Center, New York, NY, USA
[c] Triskem International, Inc., USA
[d] Program in Molecular Pharmacology, Memorial Sloan Kettering Cancer Center, New York, NY, USA



- Improvement of method published by Graves et al. (TBP only) => insufficient Fe removal
- Load and rinse on TBP Resin at ~10M HCl, elution in dilute HCl
- Use of 2xTK400 before TBP Resin for Fe removal
- Production of 11.1 – 14.4 GBq of [^{89}Zr]Zr-PSMA-617 and [^{89}Zr]Zr-PSMA-I&T
- Apparent specific activities of 11.1 - 14.4 MBq/µg
  - 2–3x more than before at industrial quantities.
- On-going:
  - Use of TK201 instead of TK400 for impurities removal (catch additional impurities? E.g. Cu)
  - Alternative methods for Zr oxalate conversion to Zr chloride (avoiding QMA)

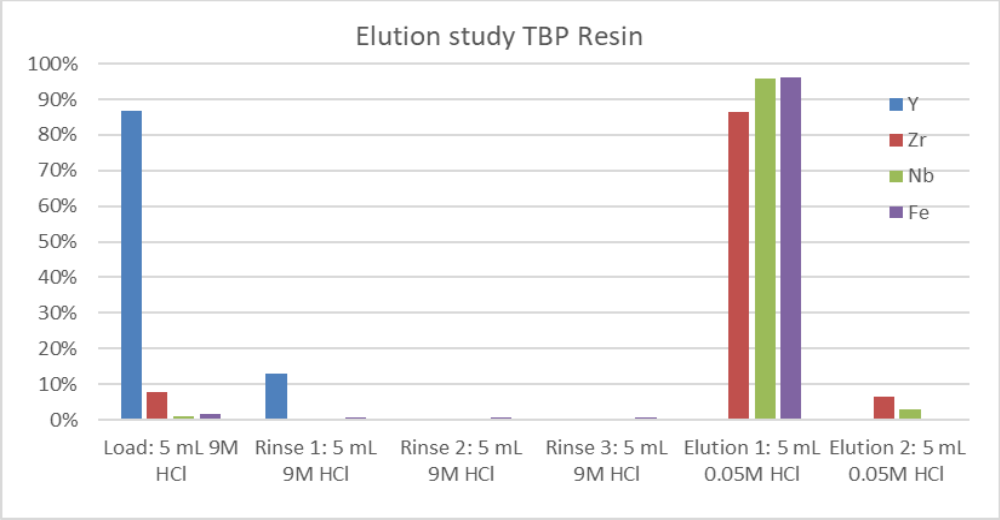
Table 1. Summary of Measured Iron Content in TBP-purified solutions.

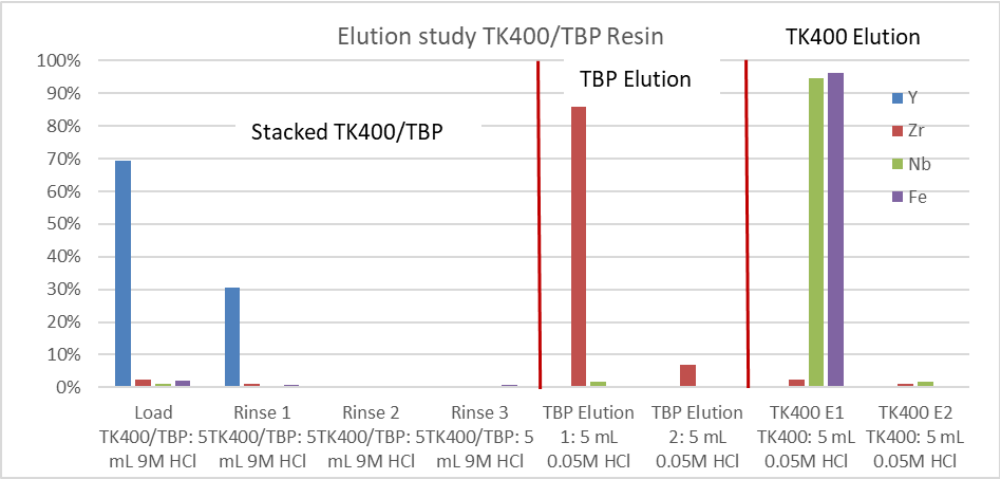
Purification Intervention	Measured Iron Content (ppm)	Source
No TK400, TBP only	32.7–38.8 (n = 6)	Graves et al.
Single TK400, followed by TBP	8 (n = 3)	This Study
Double TK400, followed TBP	< 1 (n = 3)	This study

Table 2. Summary of Radionuclide Purity Measurements in [^{89}Zr]$ZrCl_4$ Solution.

Batch	[^{89}Zr]$ZrCl_4$ - Batch 1	[^{89}Zr]$ZrCl_4$ - Batch 2	[^{89}Zr]$ZrCl_4$ - Batch 3	[^{89}Zr]$ZrCl_4$ - Batch 4
Radionuclidic Purity	≥99.9%	≥99.9%	≥99.9%	≥99.9%
% of ^{88}Zr	6.9×10^{-10}%	2.9×10^{-10}%	4.7×10^{-9}%	1.2×10^{-8}%
% of ^{88}Y	3.6×10^{-10}%	2.0×10^{-10}%	2.2×10^{-9}%	5.1×10^{-9}%

Use of TK400 for Fe/Nb removal

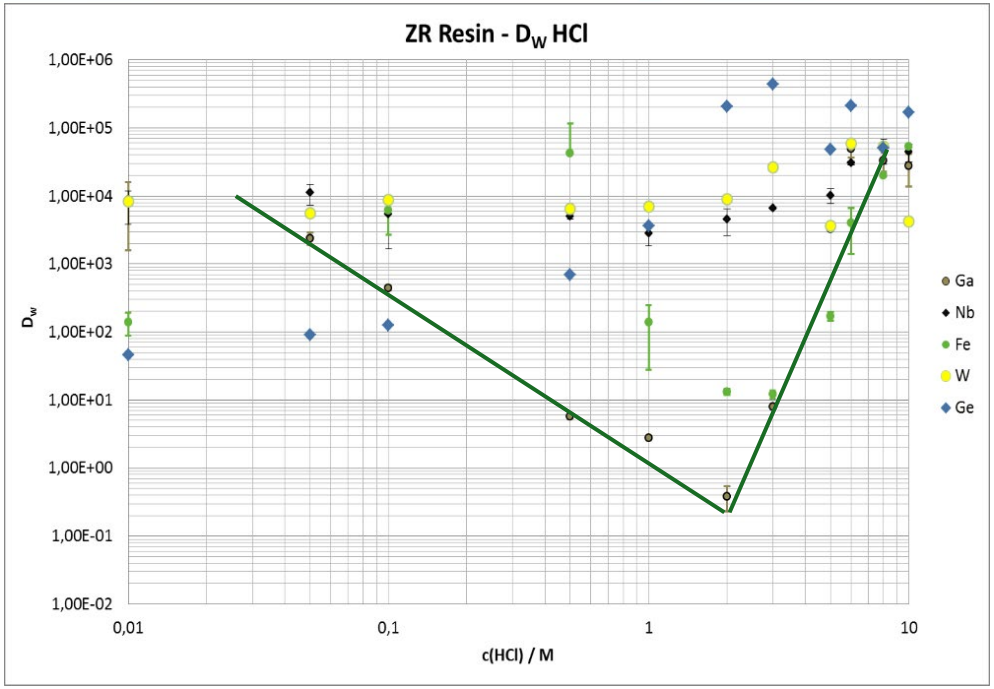


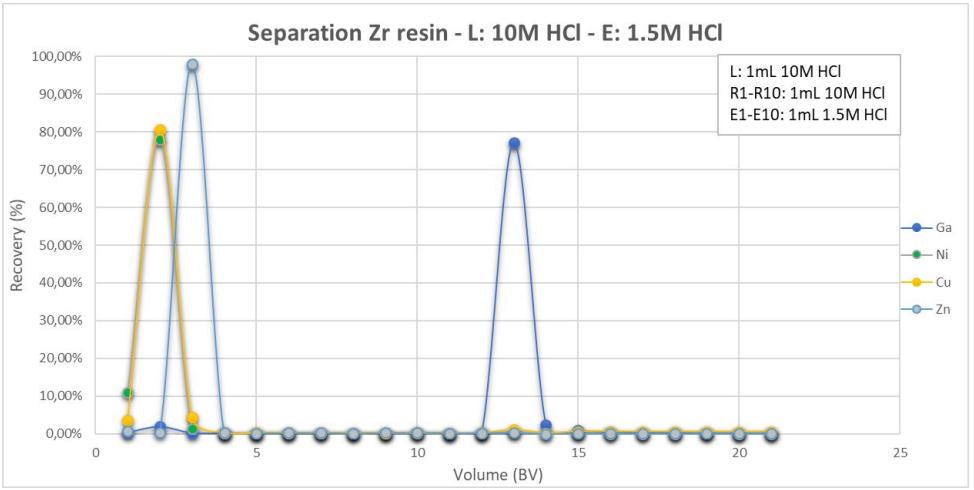


- On TBP only: Fe and Nb follow Zr
- Removal of Fe & Nb upfront possible using TK400 Resin
- Test with stacked 2 mL TK400/TBP cartridges
  - Load and Rinse at 10M HCl with TK400 stacked above TBP
  - Splitting of cartridges and separate elution with dilute Hcl
    - TBP => ZR only
    - TK400 = > Fe & Nb
    - For Nb/Fe separation => Fe(II)
    - Y passes through both
- Potential for Nb separation from Zr targets

Ga-68 separation from Zn targets

- Irradiation of Zn-68 targets in cyclotron
- Ga-68 separation on ZR Resin
  - No selectivity for Zn (target material)
  - Loading possible from:
    - dilute acid (**liquid targets => typically HNO_3**)
    - >6M HCl (**solid targets**)
  - Rinse under loading condition
  - Elution with ~1 - 2M HCl
- Too acidic for injection or labelling





- Ga-68 'conversion' necessary
  - Evaporation & dissolution difficult to automize
- Easier => use of another resin
- TK200 Resin (TOPO) load from 1 - 2M HCl
- Rinse with e.g. 1 - 2M HCl
- Elution in 2 – 3 BV water, dilute acid,..

⇒ **New IAEA TechDoc:**

https://www-pub.iaea.org/books/IAEABooks/13484/Gallium-68-Cyclotron-Production

Cyclotron production of Ga-68

Rodnick et al. EJNMMI Radiopharmacy and Chemistry (2020) 5:25
https://doi.org/10.1186/s41181-020-00106-9

EJNMMI Radiopharmacy and Chemistry

RESEARCH ARTICLE Open Access

Cyclotron-based production of ^{68}Ga, [^{68}Ga]$GaCl_3$, and [^{68}Ga]Ga-PSMA-11 from a liquid target

Melissa E. Rodnick[1], Carina Sollert[2], Daniela Stark[3], Mara Clark[1], Andrew Katsifis[3], Brian G. Hockley[1], D. Christian Parr[2], Jens Frigell[2], Bradford D. Henderson[1], Monica Abghari-Gerst[1], Morand R. Piert[1], Michael J. Fulham[4], Stefan Eberl[5*], Katherine Gagnon[2*] and Peter J. H. Scott[1*]

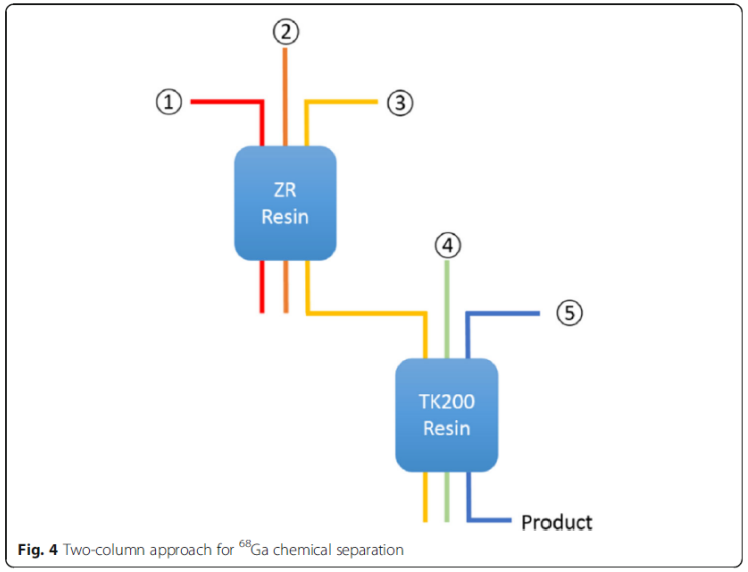


Fig. 4 Two-column approach for ^{68}Ga chemical separation

Table 1 High level schemes of [^{68}Ga]$GaCl_3$ purifications

	Scheme A*	Scheme B
1 ZR Load	< 0.1 M HNO_3	
2 ZR Wash	15 mL 0.1 M HNO_3	
3 ZR Elution / Trapping on TK200	5–6 mL ~ 1.75 M HCl	
4 TK Wash	–	3.5 mL 2.0 M NaCl in 0.13 M HCl
5 TK Elution	H_2O	1–2 mL H_2O followed by dilute HCl to formulate

*Process as reported previously (Nair et al. 2017)

J. Kumlin et al.

ZR, LN & TK200 for solid targets

- High Ga-68 activities
- ARTMS/Odense: 10 Ci production

One column separation possible using TK400 Resin => solid targets

- Ga retention on TK400 from high HCl
- No Zn retention
- Faster kinetics than ZR Resin

W. Tieu et al. use of single TK400 cartridge for solid Zn targets

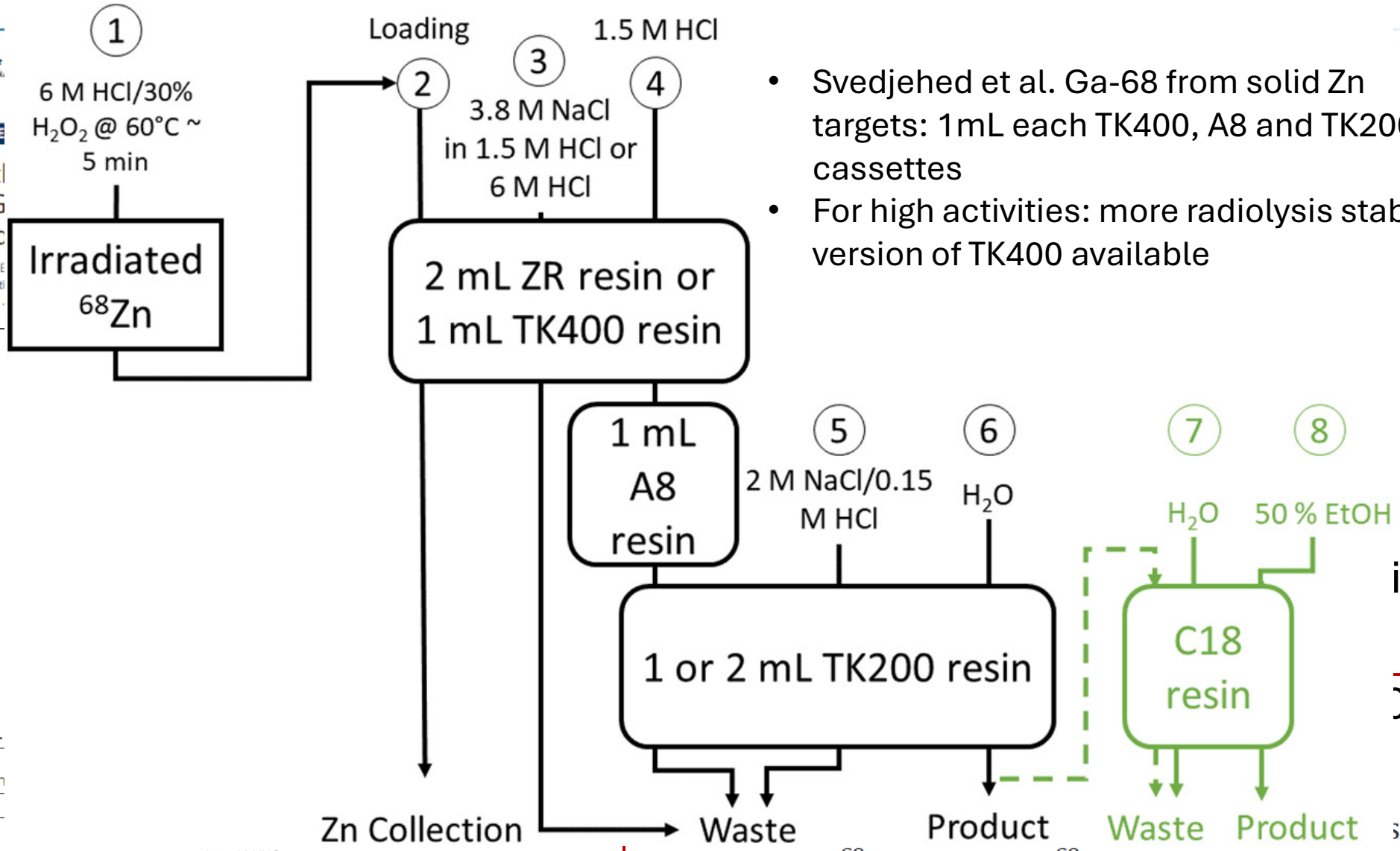
Svedjehed et al. use of TK400/A8/TK200 for solid Zn targets

Demystifying solid targets: Simple and rapid distribution-scale production of [^{68}Ga]$GaCl_3$ and [^{68}Ga]Ga-PSMA-11

Johan Svedjehed, Martin Pärnaste, Katherine Gagnon *

Cyclotrons and TRACERcenter, GEMS PET Systems AB, GE Healthcare, Uppsala, Sweden

Cyclotron production of Ga-68



- Svedjehed et al. Ga-68 from solid Zn targets: 1mL each TK400, A8 and TK200 cassettes
- For high activities: more radiolysis stable version of TK400 available

Table 1 High

(1) ZR Load		
(2) ZR Wash	15 mL 0.1 M HNO_3	
(3) ZR Elution / Trapping on TK200	5–6 mL ~ 1.75 M HCl	
(4) TK Wash	–	3.5 mL 2.0 M NaCl in 0.13 M HCl
(5) TK Elution	H_2O	1–2 mL H_2O followed by dilute HCl to formulate

*Process as reported previously (Nair et al. 2017)

production of [^{68}Ga]$GaCl_3$ and [^{68}Ga]Ga-PSMA-11

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Ag/Pd separation

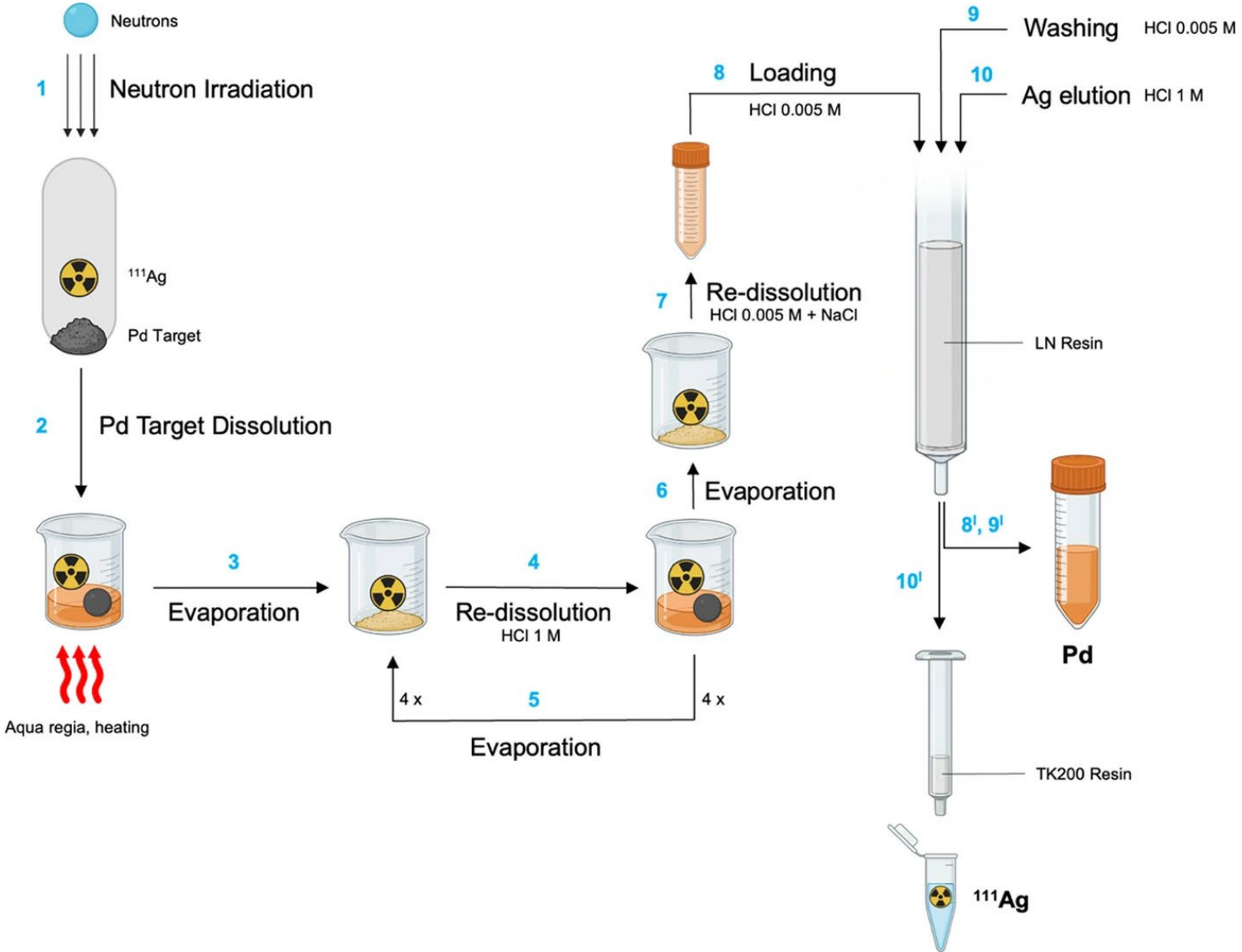
Tosato *et al.*
EJNMMI Radiopharmacy and Chemistry (2023) 8:43
https://doi.org/10.1186/s41181-023-00232-0

EJNMMI Radiopharmacy and Chemistry

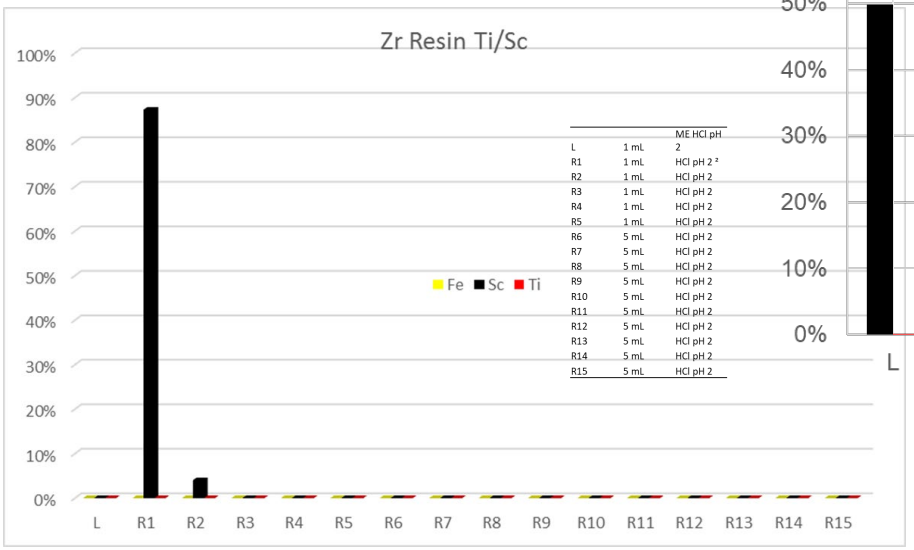
RESEARCH ARTICLE Open Access

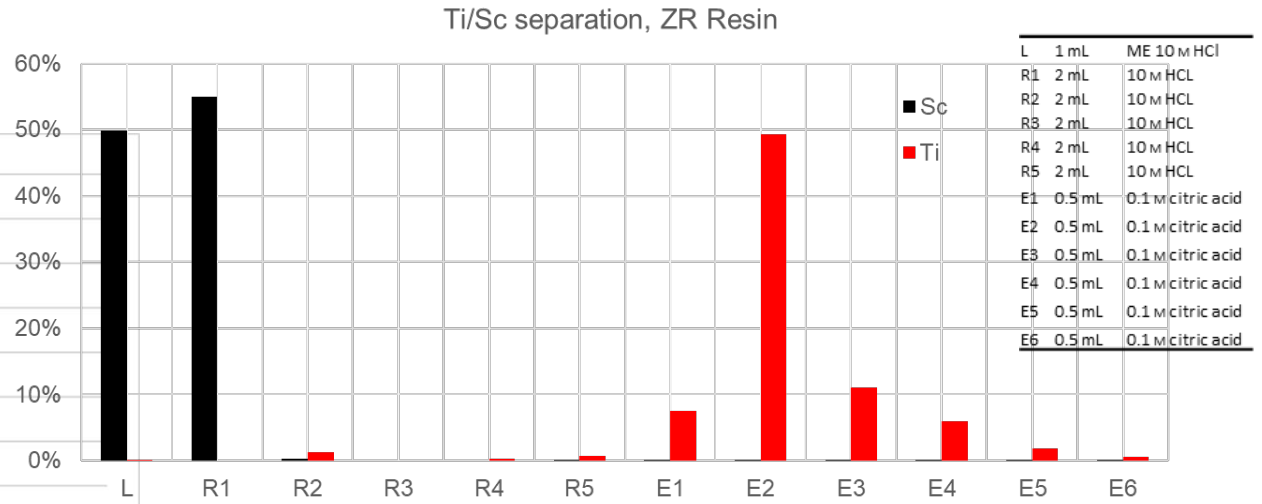
Chromatographic separation of silver-111 from neutron-irradiated palladium target: toward direct labeling of radiotracers

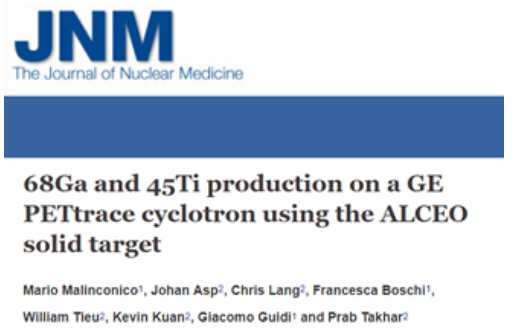
Marianna Tosato[1,2], Andrea Gandini[3], Steffen Happel[4], Marine Bas[4], Antonietta Donzella[5,6], Aldo Zenoni[5,6], Andrea Salvini[3], Alberto Andrighetto[7], Valerio Di Marco[2] and Mattia Asti[1*]



Ti-Sc Separation (Ti-44/5)







- Ti retained from (high) HCl, Sc not retained
- Ti also retained in dilute acid, Sc not => Ti generator?
- Ti elution with 0.1M citric, >0.2M oxalic acid, 0.1M H_2O_2
- K. Olguin: https://www.triskem-international.com/scripts/files/5fc95b3398a614.03970900/olguin_sfu_vugm20_production-and-purification-of-titanium-45-for-positron-emission-tomography.pdf
- Publication:
  - Malinconico et al.: J Nucl Med May 1, 2018 vol. 59 (supplement 1 664)

Ti-44/Sc-44

Separation of ^{44}Ti from proton irradiated scandium by using solid-phase extraction chromatography and design of ^{44}Ti/^{44}Sc generator system

V. Radchenko, C.A.L. Meyer, J.W. Engle, C.M. Naranjo, G.A. Unc, T. Mastren, M. Brugh, E.R. Birnbaum, K.D. John, F.M. Nortier, M.E. Fassbender*

Chemistry Division, Los Alamos National Laboratory, P.O. Box 1663, Los Alamos, NM 87545, USA

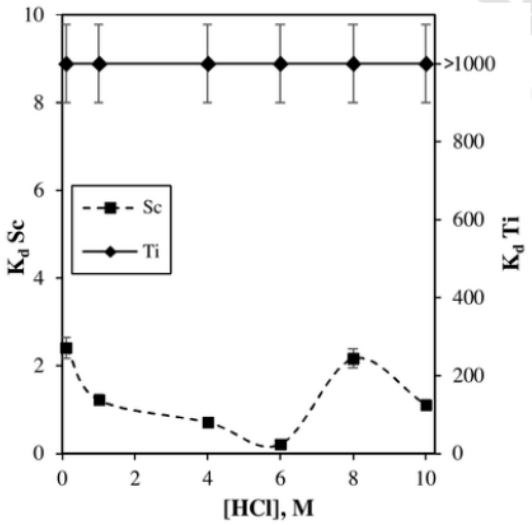


Fig. 3. HCl concentration dependency of K_d for ^{44}Ti/^{46}Sc on ZR hydroxamate resin.

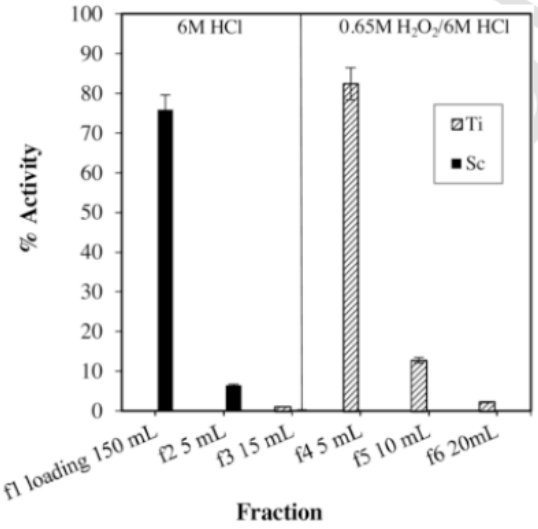


Fig. 5. ^{44}Ti/^{46}Sc elution profile using ZR hydroxamate resin with a load of 4 g of scandium.

- **Ti-44 production**
  - 4g irradiated Sc
  - 5 mL Zr Resin
  - Ti-44 yield >95%
  - 65.2 MBq Ti-44
  - D_f(Sc): 10^5

Use of ZR Resin as support in Ti-44/Sc-44 generators

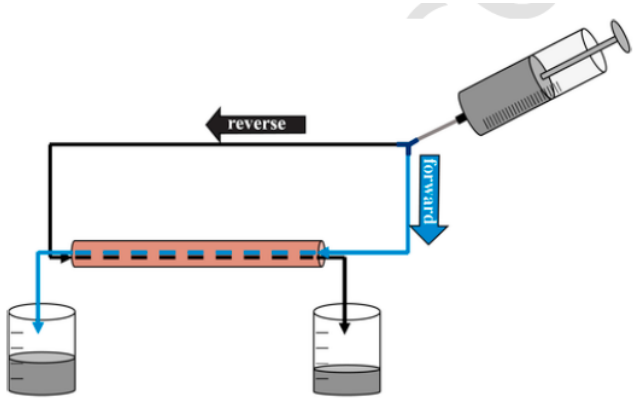


Fig. 1. Schematic concept of a forward/reverse flow radionuclide generator.

Direct (1 mL ZR) and reverse elution (2 mL ZR)

65 column volumes tested up until publication

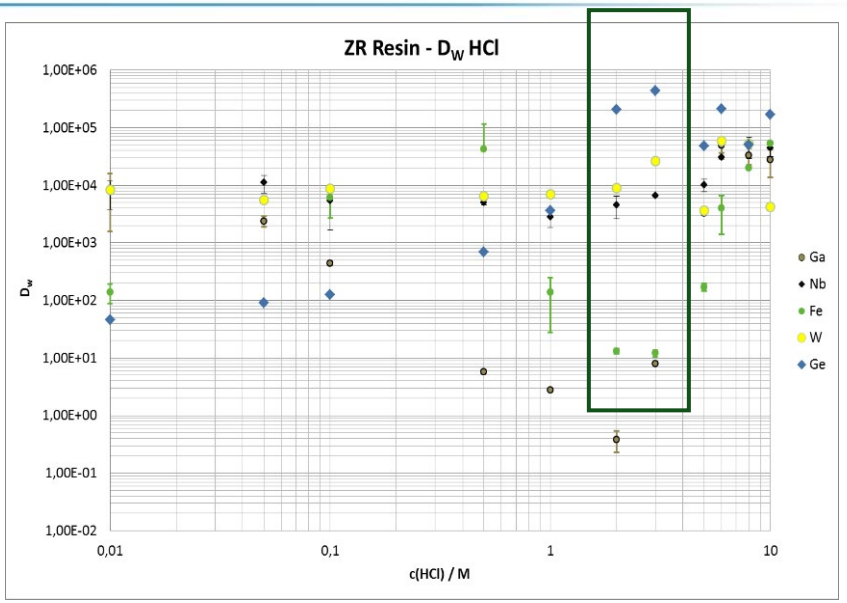
High Sc yields, max. Ti-44 breakthrough: 4.1^{E}-4%

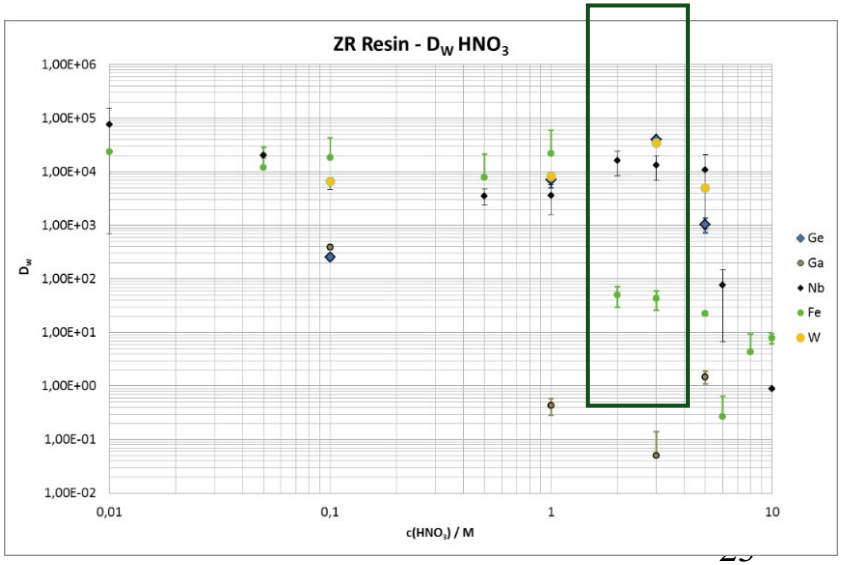
Obtained Sc gave labelling yields > 94%

- Generator been set-up at BNL/SBU => Poster S. Houclier ISRS 2019

Ge-68 separation from GaNi or GaCo

- Loading from HNO_3, HCl or **H_2SO_4** possible
  - Target dissolution in H_2SO_4
- Cold tests on >5g GaNi
- First cycle on ZR (**2 mL ZR Resin cartridge**):
  - Load/rinse from ≥5M H_2SO_4 or 2M HNO_3
  - High Ge retention/purification from Ga, Ni & Co
  - Elution: 0.1M citric acid (pH 3)
- Second cycle on ZR (**1 mL ZR cartridge**):
  - Adjustment of eluate to ≥5M H_2SO_4 or 2M HNO_3
  - Load/rinse from ≥5M H_2SO_4 or 2M HNO_3
  - Elution with 0.1M citric acid (pH 3)
- Conversion step
  - pH adjustment and Sephadex
  - Alternative: PF or GR Resin (9M HCl)
  - Under testing: TK230 instead of ZR Resin





Germanium

Ge removal using CeO_2-PAN (TK-GeRem)

- Extracts Ge from dilute acid, seawater…
  - Decontamination of waste
  - Tests on-going: Ge-68 breakthrough elimination from generator effluents

Combination of several Ge-68 generator eluents

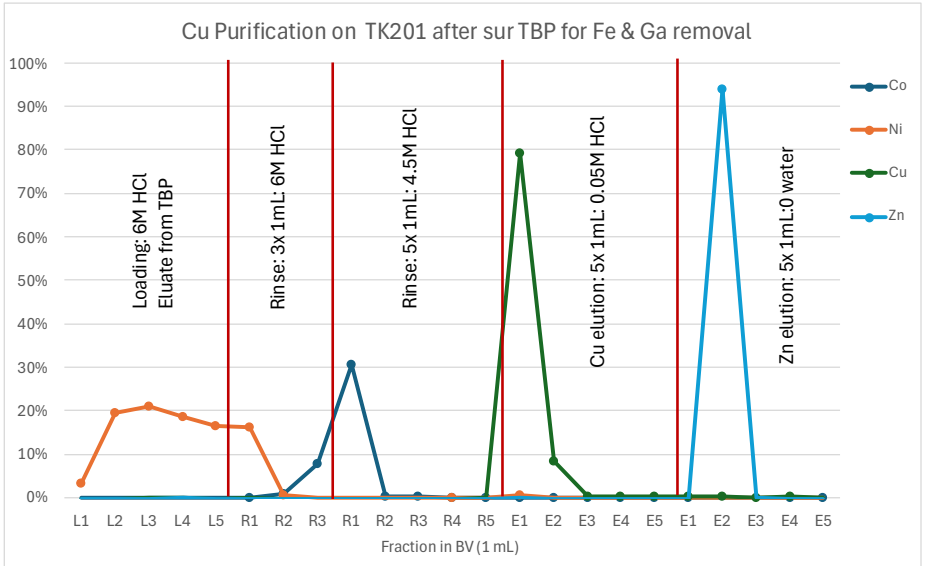
- Direct ZR/TK200 or
- Acidification and load onto one TK200
- Elution in dilute HCl

Ge recycling

- Evaluation of possibility to elute Ge from ‘spent’ generators e.g. using 9M HCl
- Use of two subsequent Guard Resins cartridges to collect and purify Ge

Cu-61/4 separation on TK201

- Cu-61/4 separation from solid Ni targets
  - Target dissolution in high HCl => 6M HCl
  - TK201 retains Cu, Zn, Co, Fe, Ga at 6M HCl
  - Run through TBP (or TK400) for Fe/Ga removal
  - Load eluate on TK201 and rinse at 6M HCl
    - Ni removal and recovery/recycling
  - Co elution with 4 – 5M HCl => Co separation
  - Cu elution in 0.05M HCl
    - HCl concentration of Cu eluate >0.05M HCl
  - Preferably avoid water (risk of Zn co-elution)



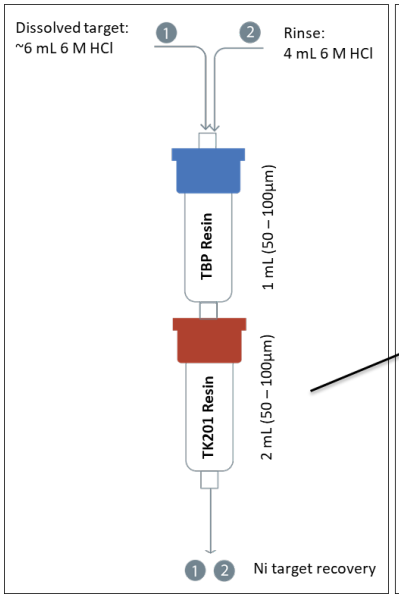
Svedjehed et al. EJNMMI Radiopharmacy and Chemistry (2020) 5:21
https://doi.org/10.1186/s41181-020-00108-7

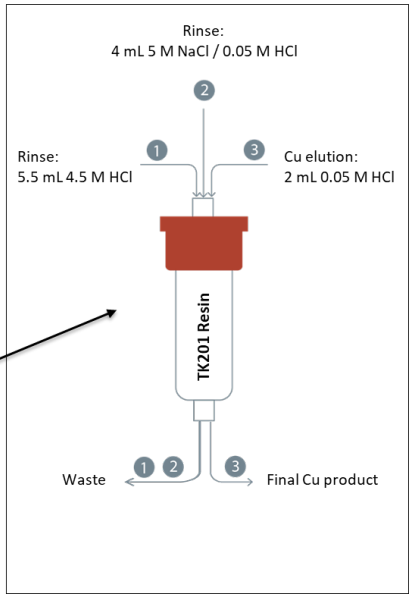
EJNMMI Radiopharmacy and Chemistry

RESEARCH ARTICLE Open Access

Automated, cassette-based isolation and formulation of high-purity [^{61}Cu]$CuCl_2$ from solid Ni targets

Johan Svedjehed[1], Christopher J. Kutyreff[2], Jonathan W. Engle[2,3] and Katherine Gagnon[1*]





- Svedjehed et al. use of NaCl/HCl for better pH control of eluate
- Also being used for Zn separation
- Not applicable to solid Zn targets
- Higher activity version

Co separation

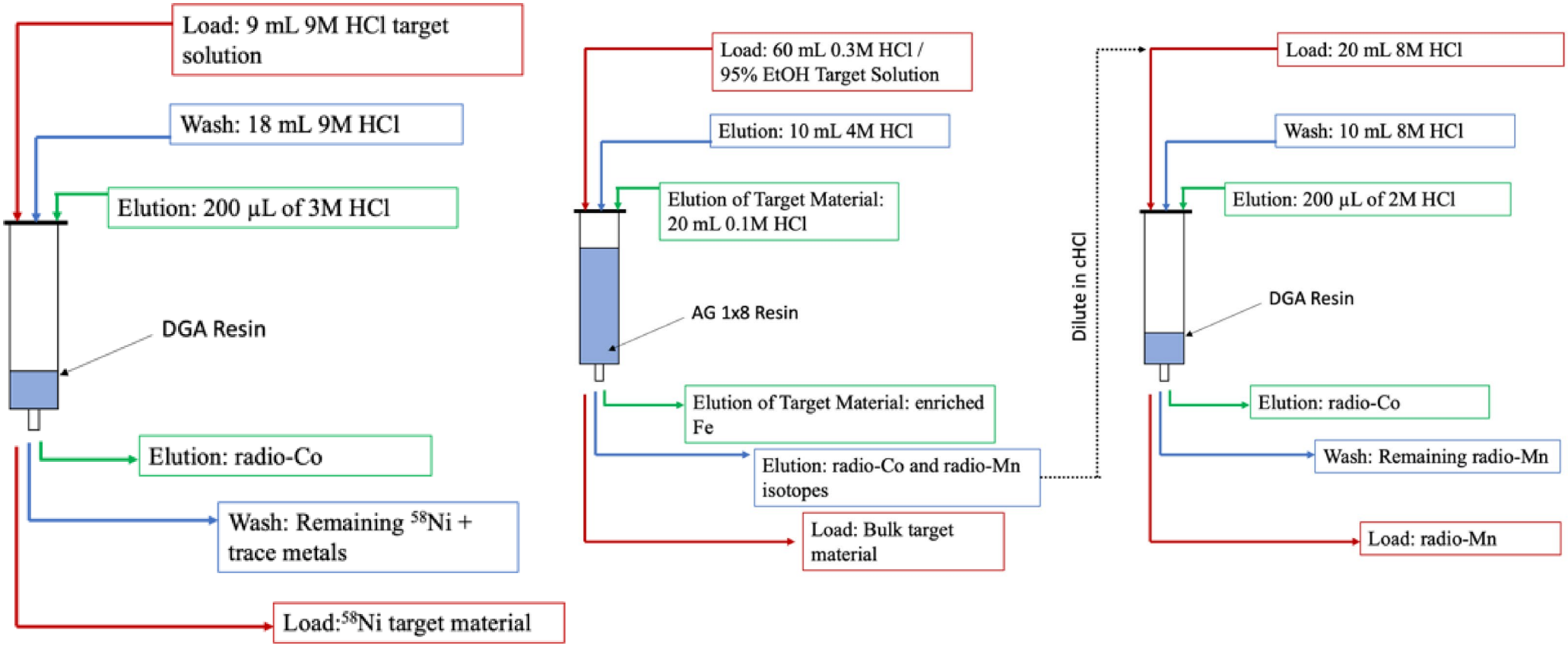
diagnostics

MDPI

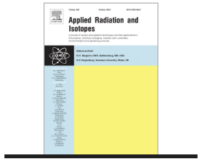
Review

Production, Purification, and Applications of a Potential Theranostic Pair: Cobalt-55 and Cobalt-58m

Kendall E. Barrett [1,†], Hailey A. Houson [2,†], Wilson Lin [1], Suzanne E. Lapi [2] and Jonathan W. Engle [1,3,*]



Co separation



Applied Radiation and Isotopes

Date: October 2023
Article: 110980
Volume: Volume 200

Research article Get rights and content ↗

Separation of cyclotron-produced cobalt-55/58m from iron targets using cation exchange chromatography with non-aqueous solvents and extraction chromatography

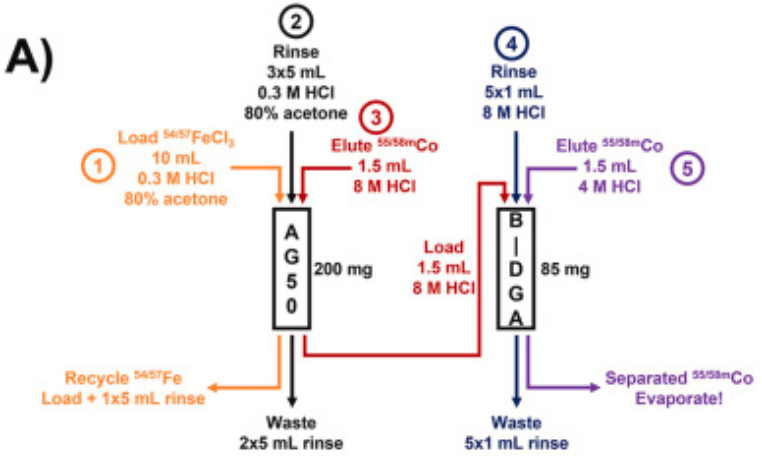
Wilson Lin [a], Eduardo Aluicio-Sarduy [a], Kendall E. Barrett [a], Todd E. Barnhart [a], Jason C. Mixdorf [a], Molly C. DeLuca [a], Jonathan W. Engle [a b] Show more

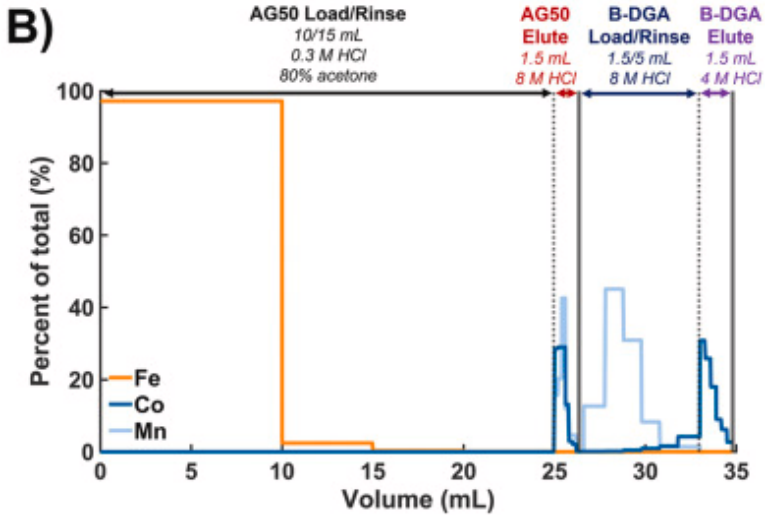
Cite Add to Mendeley Share 10.1016/j.apradiso.2023.110980 ↗

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Co separation from Fe targets method update





TK200 Resin

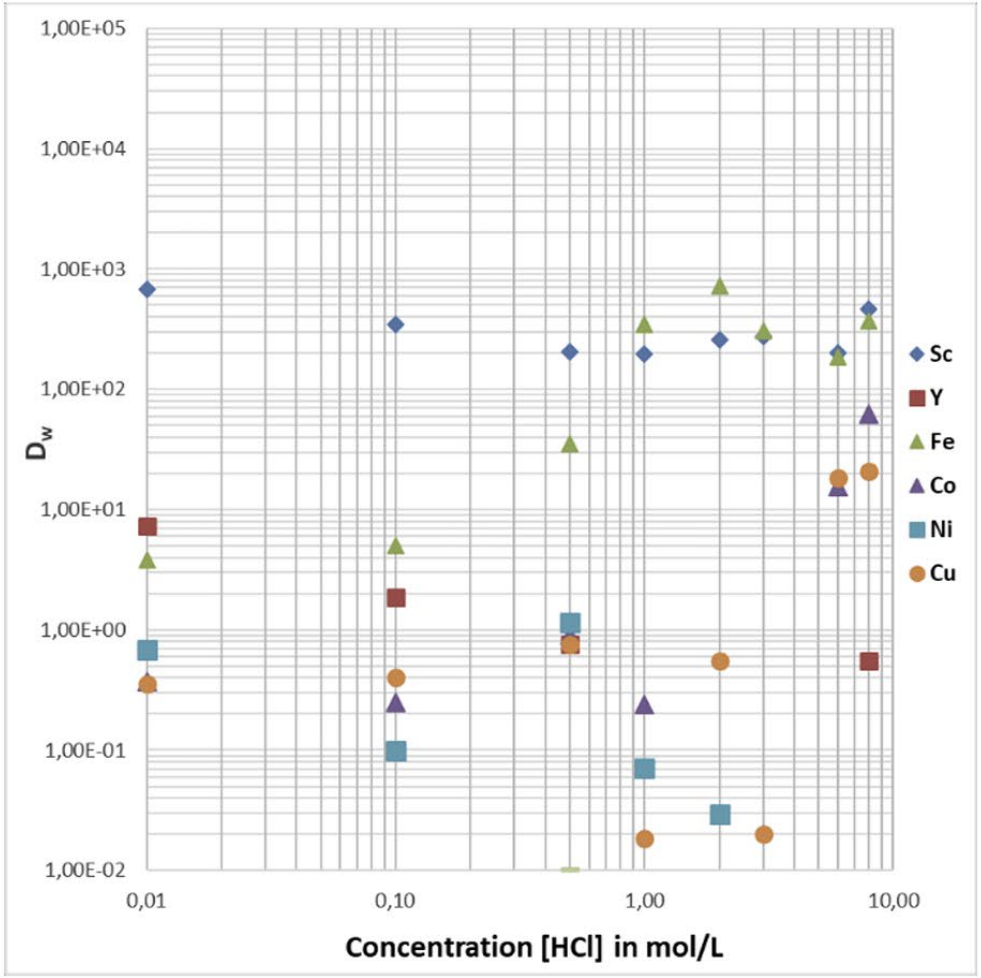


Figure 10: Dw values of selected elements on TK200 Resin in HCl

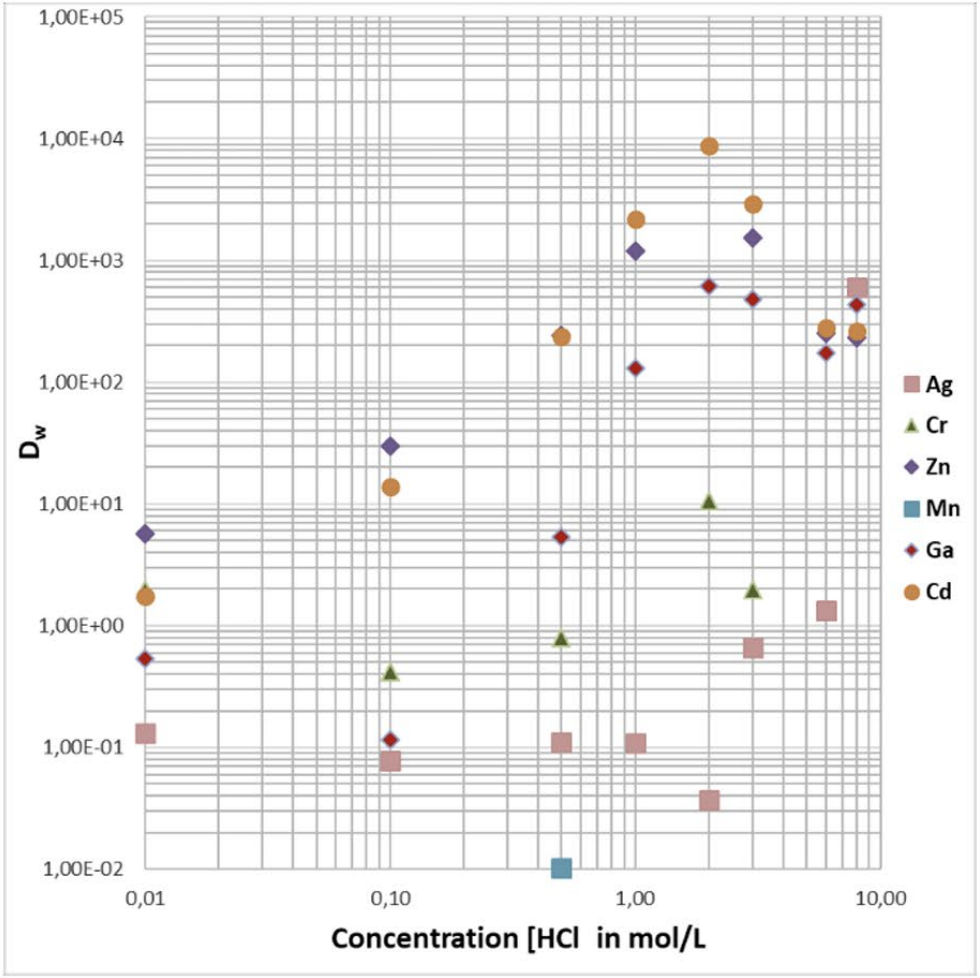


Figure 12: Dw values of selected elements on TK200 Resin in HCl

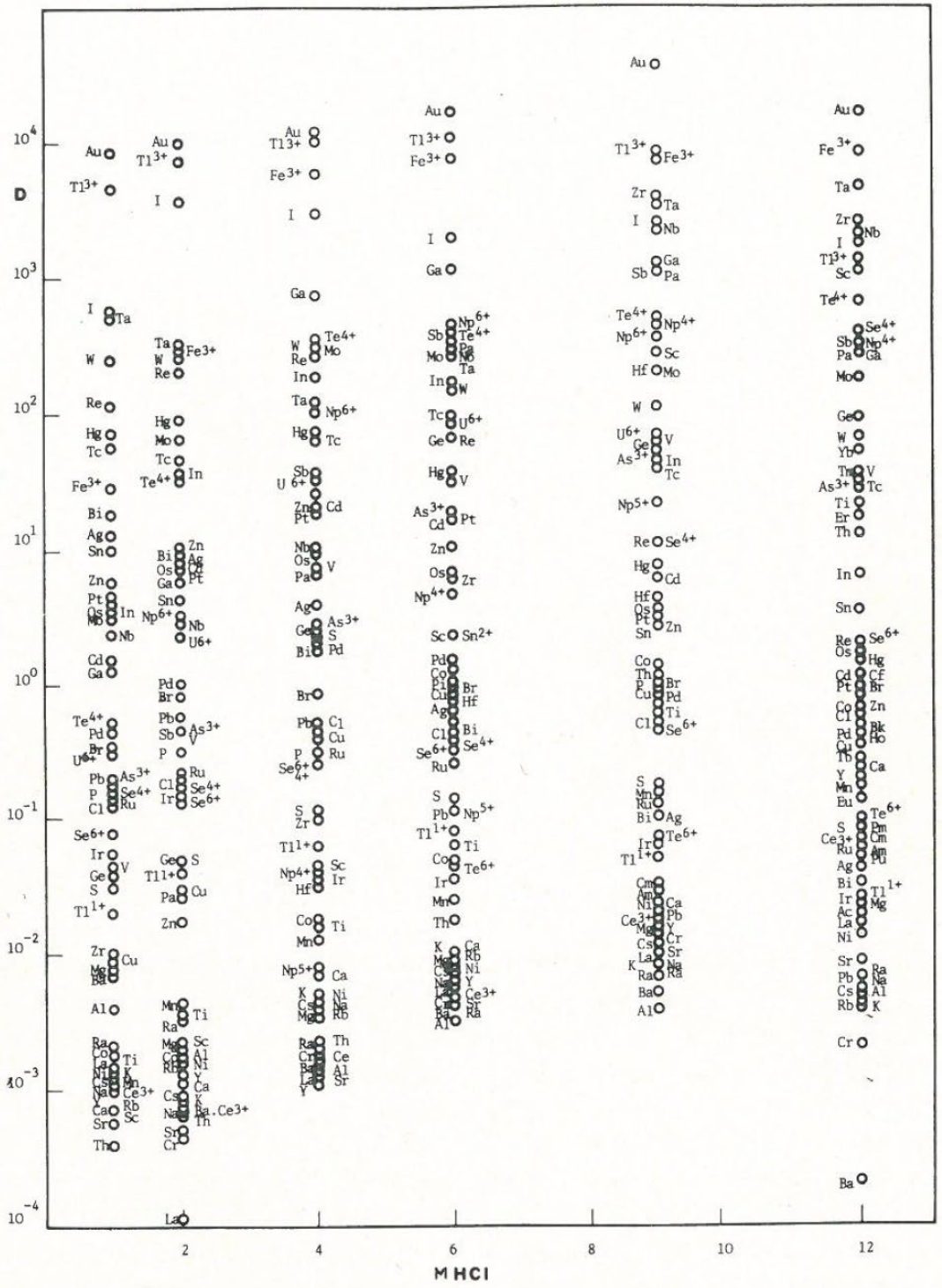


Fig. 7. Distribution coefficients of trace elements between 100% TBP and aqueous hydrochloric acid (from Ref.[51], by courtesy of the authors)

TBP Resin

Lack of data on TBP in product sheet

Use of Ghersini/Braun as guide – LLX data

Fe(III) very well retained

Co reasonably well retained up to 6M HCl, then sharp drop

Zn well retained up to 4M HCl, then sharp drop

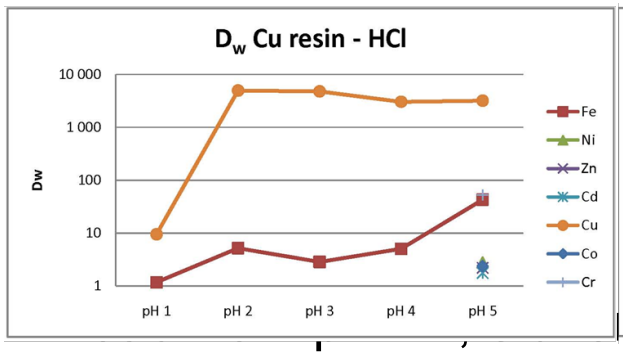
No Ni Retention

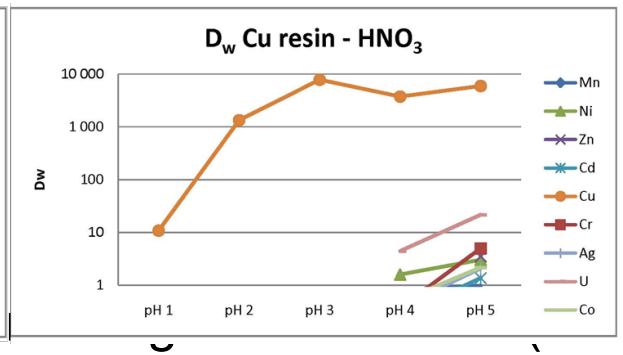
CU Resin

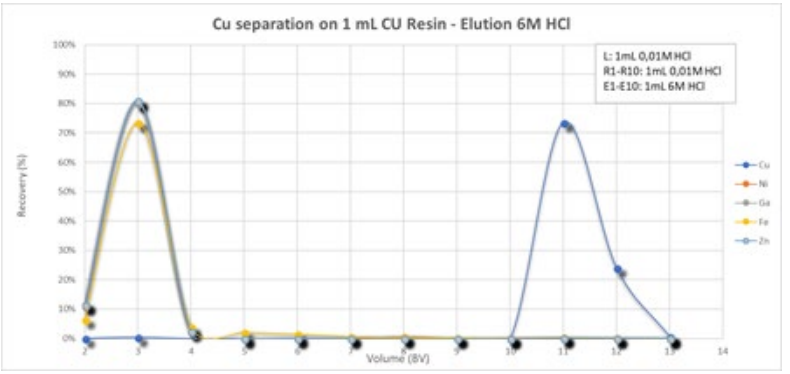
TK201 can not be used for Cu separation from Zn targets (e.g. Cu-67)

Use of oxime based CU Resin instead

High selectivity for Cu particularly with respect to Zn, Ni, Fe, Co,…







- Used for (large) solid **Zn** targets (=> Cu-67)
- Not ideal for solid Ni targets (usually high HCl) => TK201
  - Works for liquid targets (pH 2 – 3) => Fonseca et al.
  - Requires pH adjustment…
- Elution in high HCl not compatible with labelling/injection
  - Evaporation/redissolution or
  - Conversion to dilute HCl e.g. via TK201 (additional Zn removal) e.g. Kawabata et al.

Cu-67 at BNL (DeGraffenreid et al.)

Purification of ^{67}Cu and Recovery of its Irradiated Zn Target

A.J. DeGraffenreid[a] , R. Nidzyn[a], B. Jenkins[a], D.E. Wycoff[b], T.E. Phelps[b], A. Goldberg[a], D.G. Medvedev[a], S.S. Jurisson[b], C.S. Cutler[a]
[a]Brookhaven National Laboratory, C-AD/MIRP—Upton, NY (USA)
[b]University of Missouri, Department of Chemistry—Columbia, MO (USA)

Poster presented at ISRS 2017

- 13.7g Zn metal dissolved to give 312 mg $ZnCl_2$/mL solution at pH 2
- Loading of 60,6 mL => 18.9g $ZnCl_2$ onto 2.4g CU Resin column => 8 mL
- Rinse with 80 mL pH2 HCl
- Elution in 2 x 20 mL 6M HCl
- Evaporation to dryness
- Chemical yield ~100%
- Single column D_f for Zn ~10 000
  - Additional removal indicated
- Ideally further Zn and Co removal

Cu Resin

Nuclide	EOB Activity (mCi ± 1σ)	Recovery (%) Load w/ Quant. Transfer	pH 2 HCl Rinse	Acid #1	Acid #2
^{64}Cu	4700 ± 200	ND	ND	102	ND
^{65}Zn	41.0 ± 0.8	103	ND	0.04	ND
^{58}Co	63 ± 1	104	0.04	0.1	0.01

- Produced 143 mCi ^{67}Cu
- Quantitative recovery of radiocopper
- 99.5% radionuclidic purity—single column
- ICP-OES: 132.9 µg Cu and 1.3 mg Zn
  - Anion exchange column still needed to remove trace Zn
- Specific activity ^{67}Cu at EOB: 1.07 mCi/µg

Cu Resin

Robust separation that could shorten the overall processing time to separate co-produced radionuclides and large quantities of Zn from radiocopper
Cation and anion exchange columns still needed to suitably purify radiocopper

- Alternative to evaporation: Cu elution with 6M HCl directly onto TK201
- Cu elution from TK201 in dilute acid
- Optional: rinse with NaCl/HCl for better pH control

Cu-67 from Zn targets – following Zn sublimation – Kawabata et al.

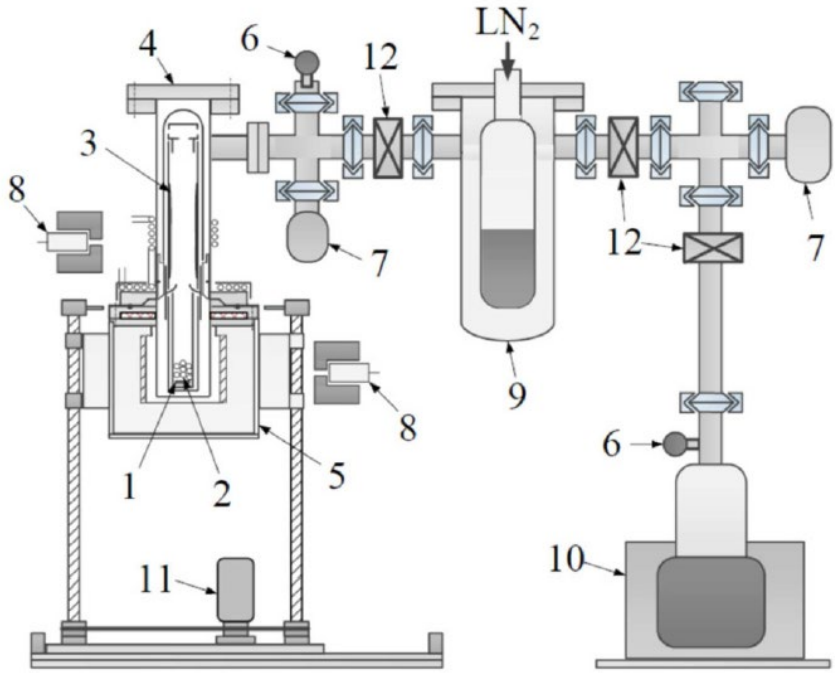


FIGURE 4
Layout of the sublimation separation apparatus for an irradiated Zn sample. (1) Irradiated Zn sample containing ^{67}Cu activity, (2) quartz beads, (3) sublimated Zn element, (4) vacuum chamber, (5) electric tubular furnace, (6) electric leak valve, (7) vacuum gauge, (8) CZT γ-ray detector, (9) cold trap, (10) turbomolecular pump, (11) motor, (12) butterfly valve.

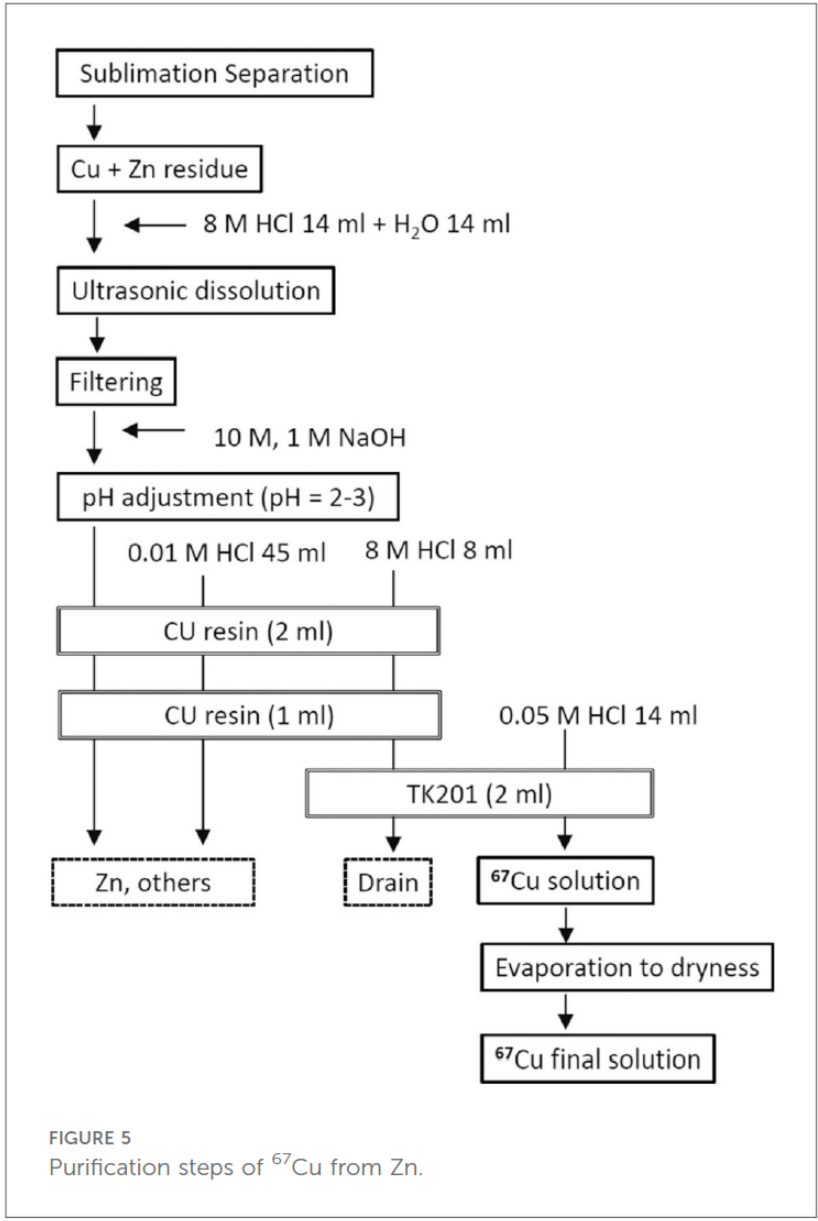


FIGURE 5
Purification steps of ^{67}Cu from Zn.

Cu-67 from Zn targets – following Zn sublimation – Kawabata et al.

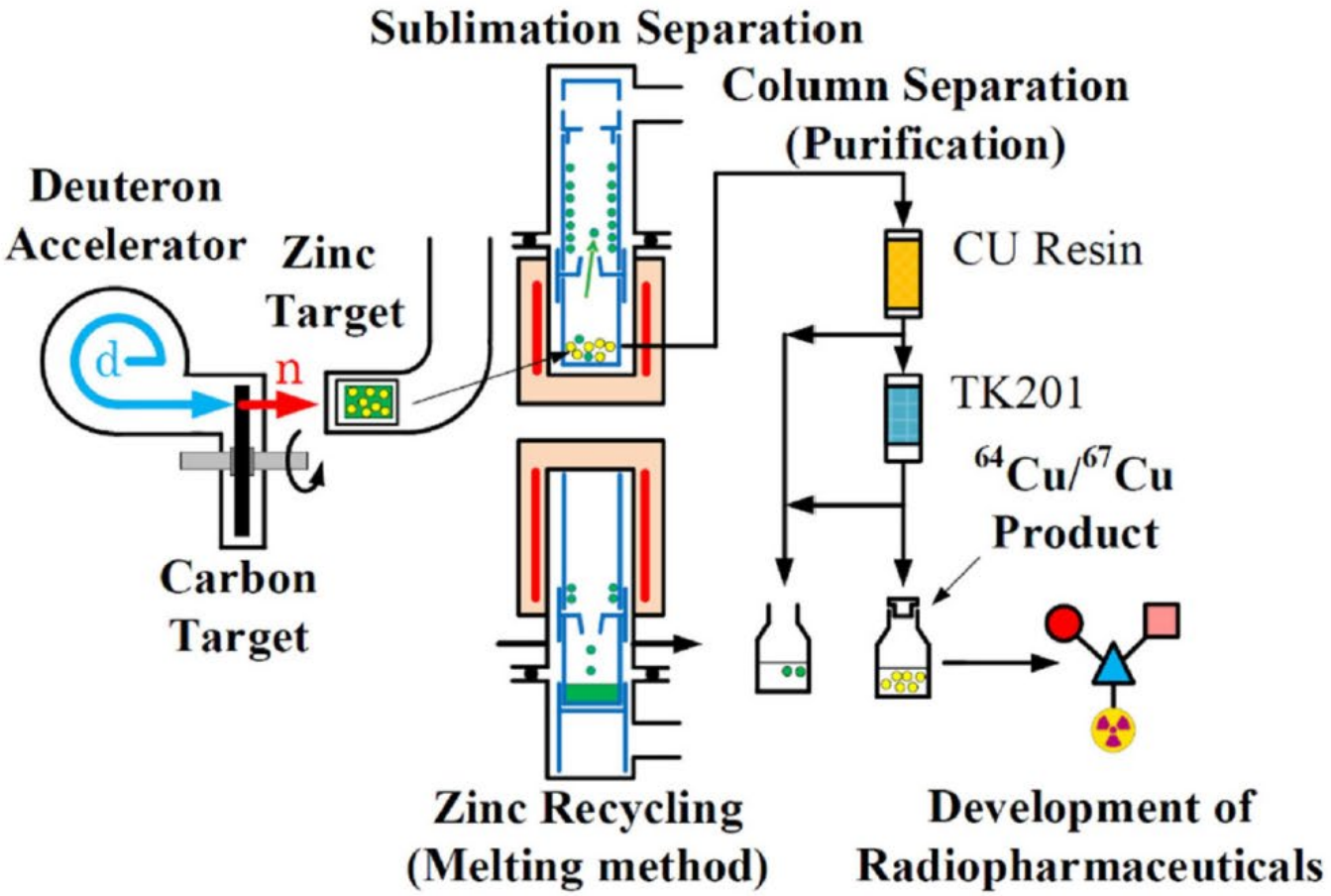
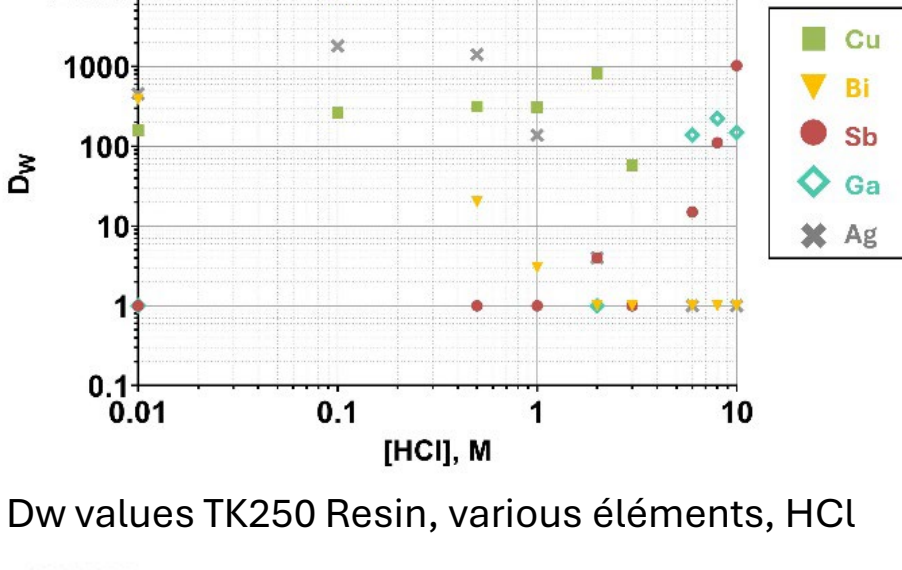


FIGURE 2
Schematic diagram of ^{67}Cu and ^{64}Cu production using accelerator neutrons generated by deuterons, and their subsequent separation from ^{68}Zn and ^{64}Zn. The accelerator neutrons were produced via the $^{nat}C(d,n)$ reaction in a vacuum. The ^{nat}C target was placed in a vacuum chamber and equipped with a rotating cooling system to manage the thermal load associated with high-intensity deuteron beams.

Upcoming: TK250 Resin

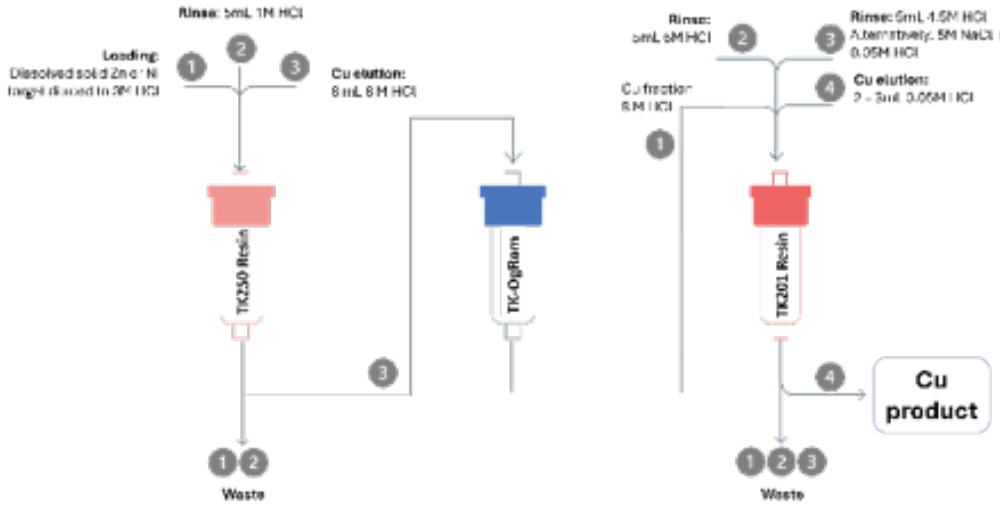
- CU Resin high selectivity for Cu over Zn but loading from pH >2 required
- Difficult to automize in case of solid Zn targets
- Upcoming TK250 Resin:
  - Cu retention from elevated acid up to 3M HCl and 1M HNO_3
  - Rather low Cu capacaity (~0.2mg/g)
  - No selectivity for Ni **and Zn**
    - Tested up to 300mg each
  - Cu elution in 8M HCl
  - 8M HCl to low HCl on TK201 Resin
  - D_f typically >10^3 - 10^4
  - Important: TK-OgRem for organics removal
- Next steps:
  - Upscale and stability testing
  - Integration in sequential separation of Cu and Ga from Zn targets e.g. with TBP Resin (Ga)

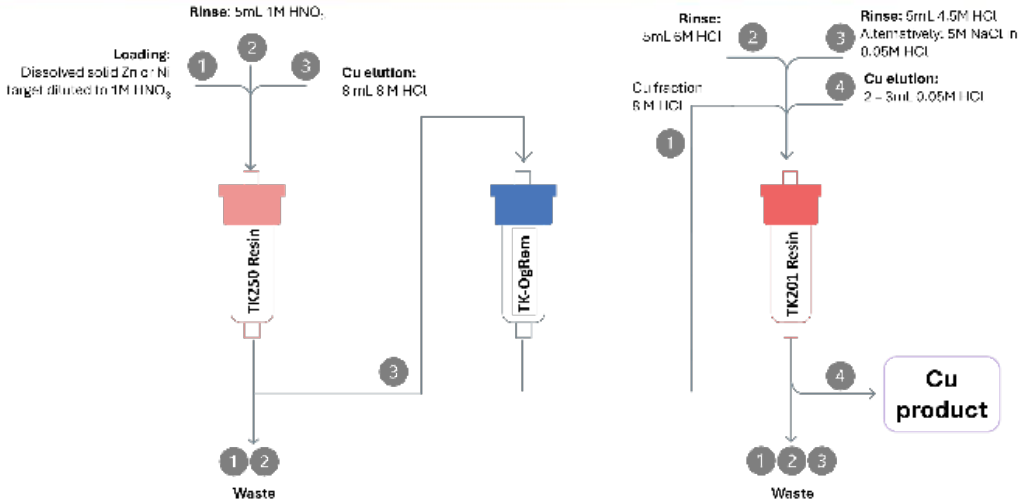


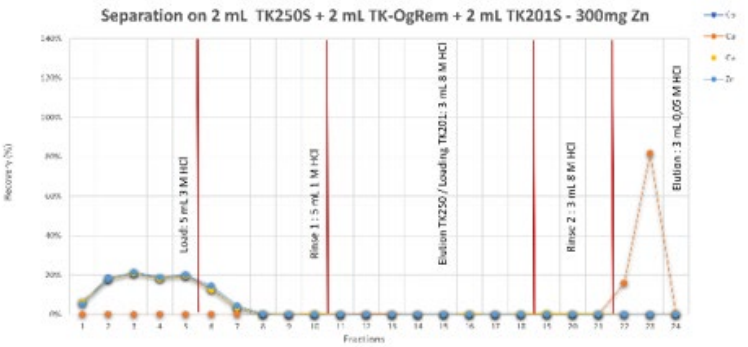
Dw values TK250 Resin, various éléments, HCl

Dw values TK250 Resin, various éléments, HNO3

Upcoming: TK250 Resin

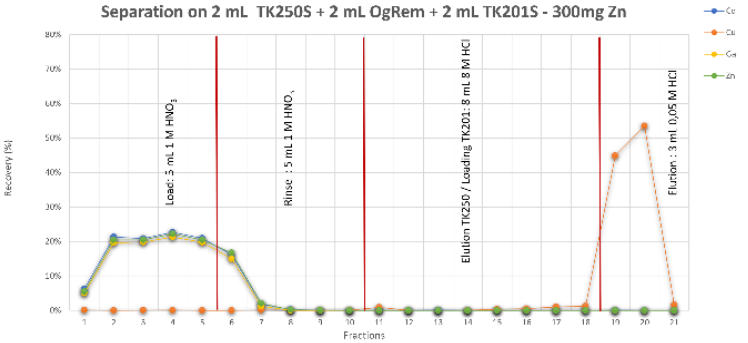






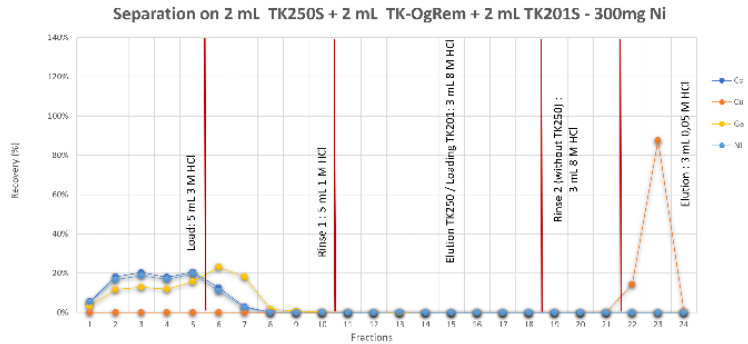
1 – 3M HCl

300mg Zn

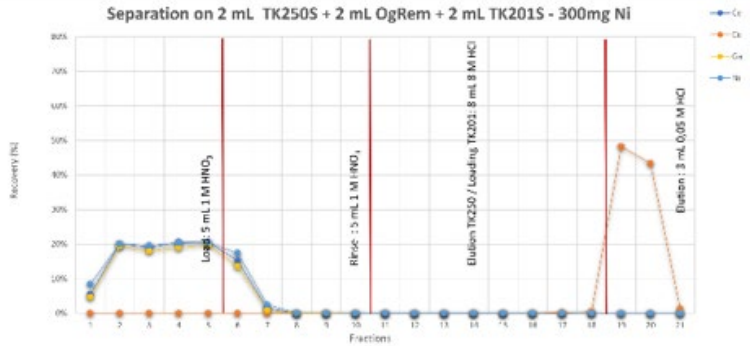


1 M HNO_3

300mg Zn



300mg Ni



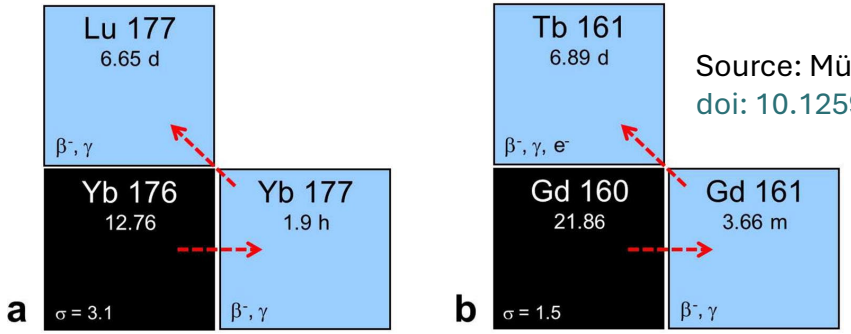
300mg Ni

Lu-177 / Tb-161/55

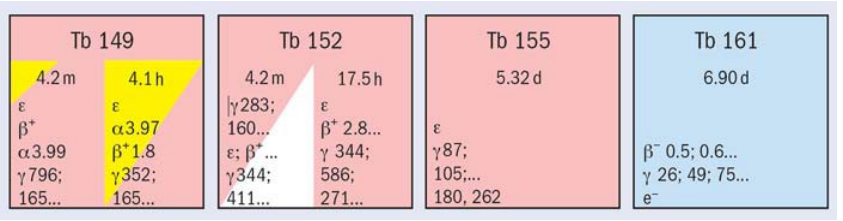
nca Lu-177 still more frequently used but Tb-161 getting strong interest

- Part of the ‘Swiss knife of nuclear medicine’ => Tb isotopes

Similar production for both



Source: Müller et al. 2018
doi: 10.1259/bjr.20180074



Terbium: a new ‘Swiss army knife’ for nuclear medicine
Source: https://cerncourier.com/a/terbium-a-new-swiss-army-knife-for-nuclear-medicine/

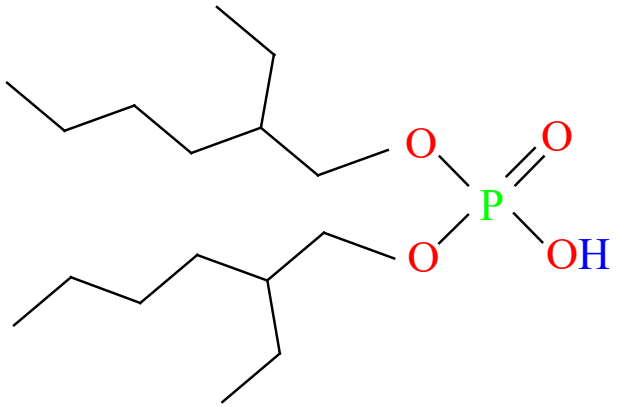
- Irradiation of several hundreds of mg or more
- Upscale on-going (incl. recycling) => typically 1g

Prepacked PP columns

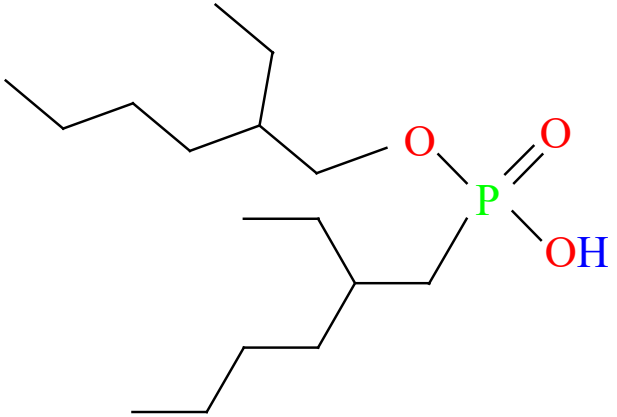
- **4cm x 30cm (375 mL)**, 2.5cm x 30cm,
  1.5cm x 30cm & 1.1cm x 30cm
- Connection: ¼’’ 28G, up to ~10bar
- QC/CoA per column (peak asymmetry) for TK211/2/3
- TK221 => dry packing



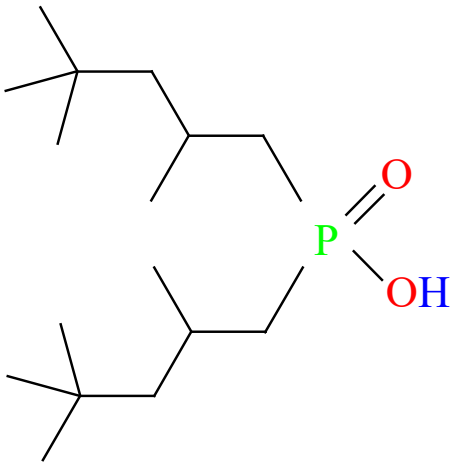
Lanthanide separation on TK211/2/3



HDEHP (LN)



HEH[EHP] (LN2)



H[TMPeP] (LN3)

Cyanex 572

$$M^{3+} + 3\overline{(HY)_2} \leftrightarrow \overline{M(HY_2)_3} + 3H^+$$

- Mixtures of different extractants
- Modified for higher radiation stability

TK212, TK211 and TK221 Resins

Increasing demand for separation from larger Yb, Gd,… targets

Resins exposed to high radiation throughout separation process

Desire to re-use columns several times

- Improvement of radiolysis stability

Feedback from earlier project => stability against radiolysis can be improved via:

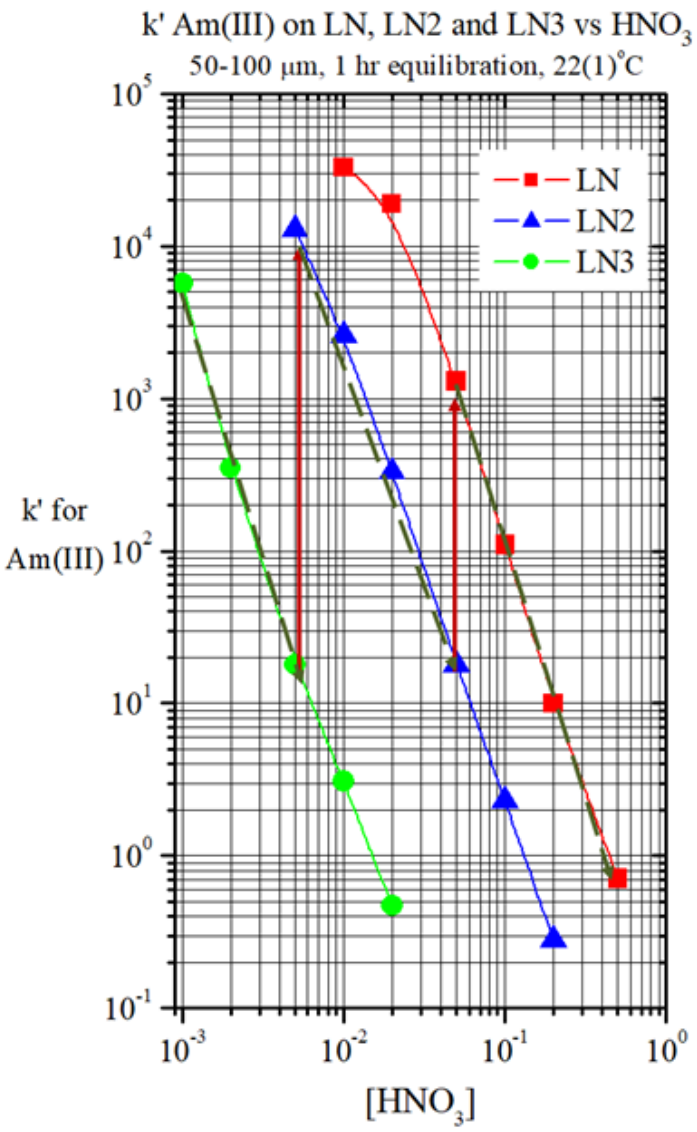
- Use of polymer containing aromatic groups as inert support
- Addition of radical scavenger (e.g. long chained alcohols) into stationary phase
- Increased amount of extractant and nature of extractant
- EtOH in aqueous phase

Applied to TK211/2/3, TK221/2, TK102,…

- Note: resins are more hydrophobic, require soaking in ≥20% EtOH for column packing

TK211/2/3 => standard ~30µm mean particle size, upcoming: 20µm

Sequential separations



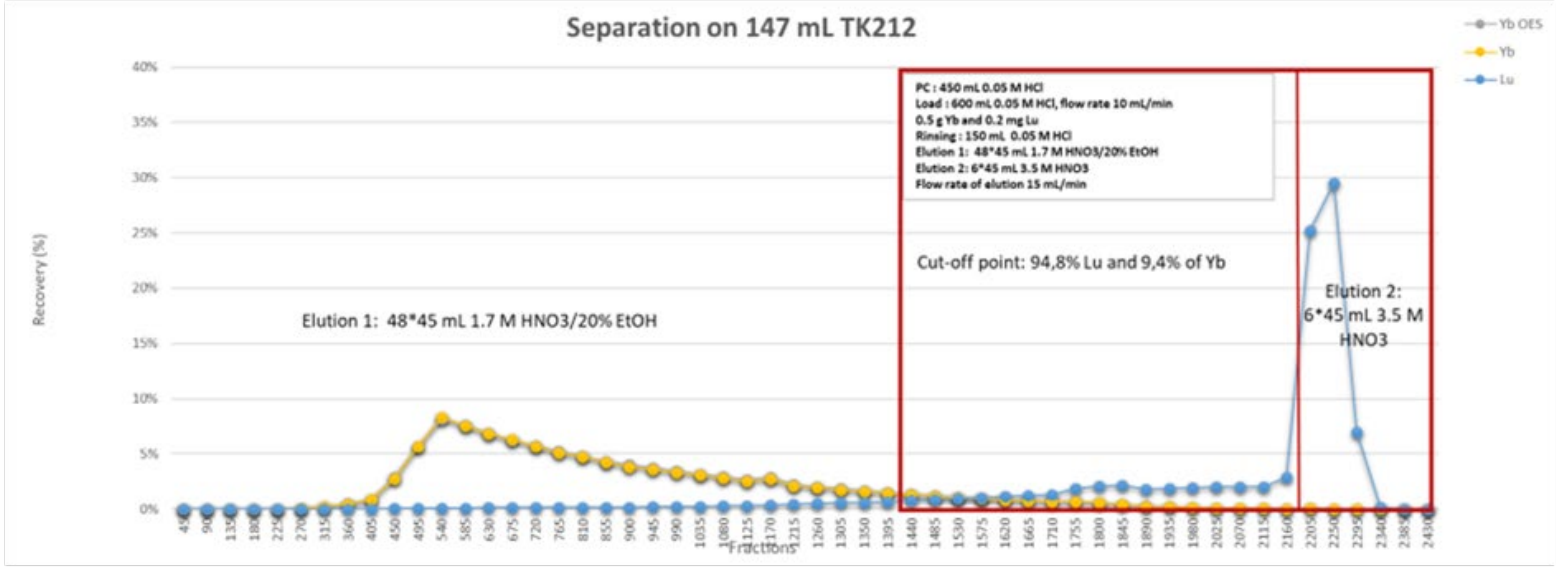
Lanthanide separations now main focus on TK212 and TK211.

- Better separation performance on-column than LN/LN2
- Especially for Yb/Lu and other complex systems with 10 – 20% EtOH

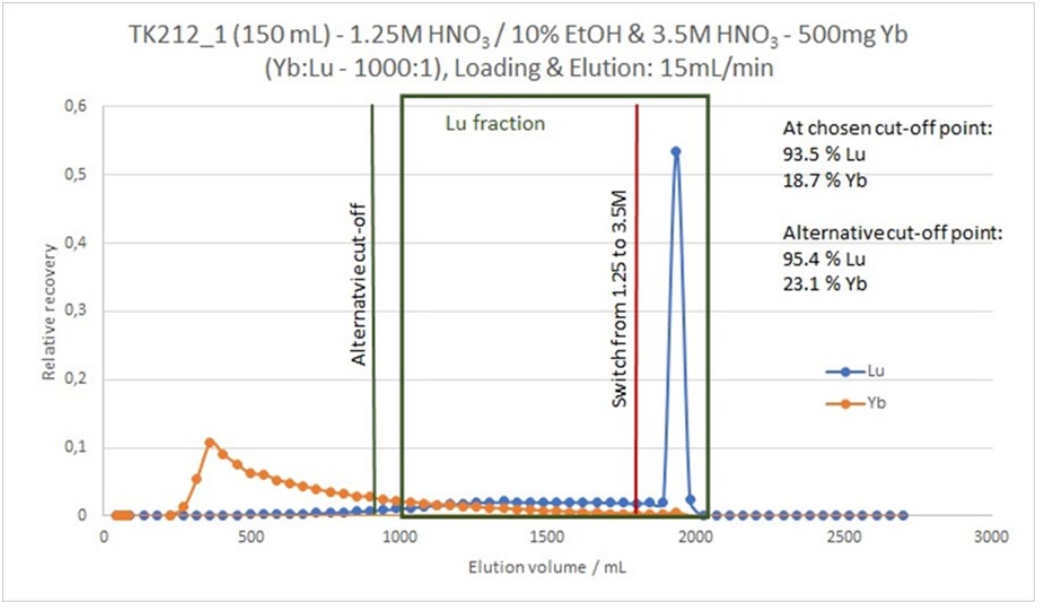
TK221 or DGA very useful for conversion of lanthanides from high HNO_3 (e.g. 3.5M HNO_3) to low acid (e.g. 0.05M) but small losses of Lu/Tb

Alternative: Direct load from TK212 to TK211

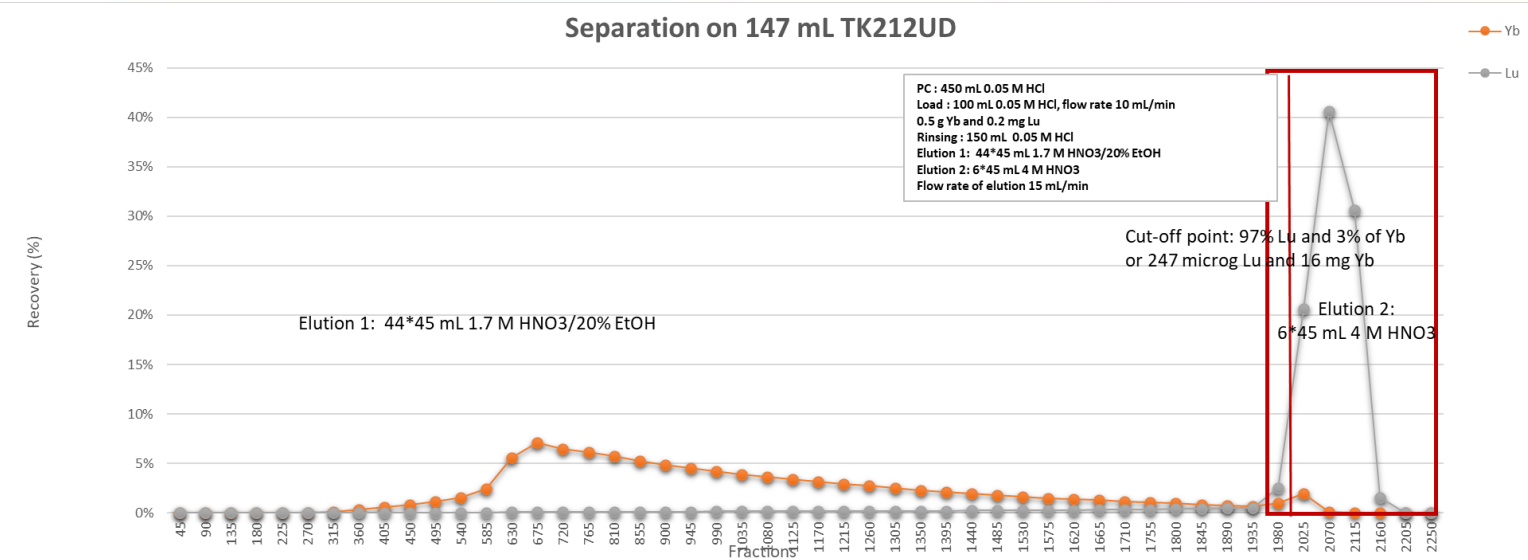
On-going improvement – amount of EtOH



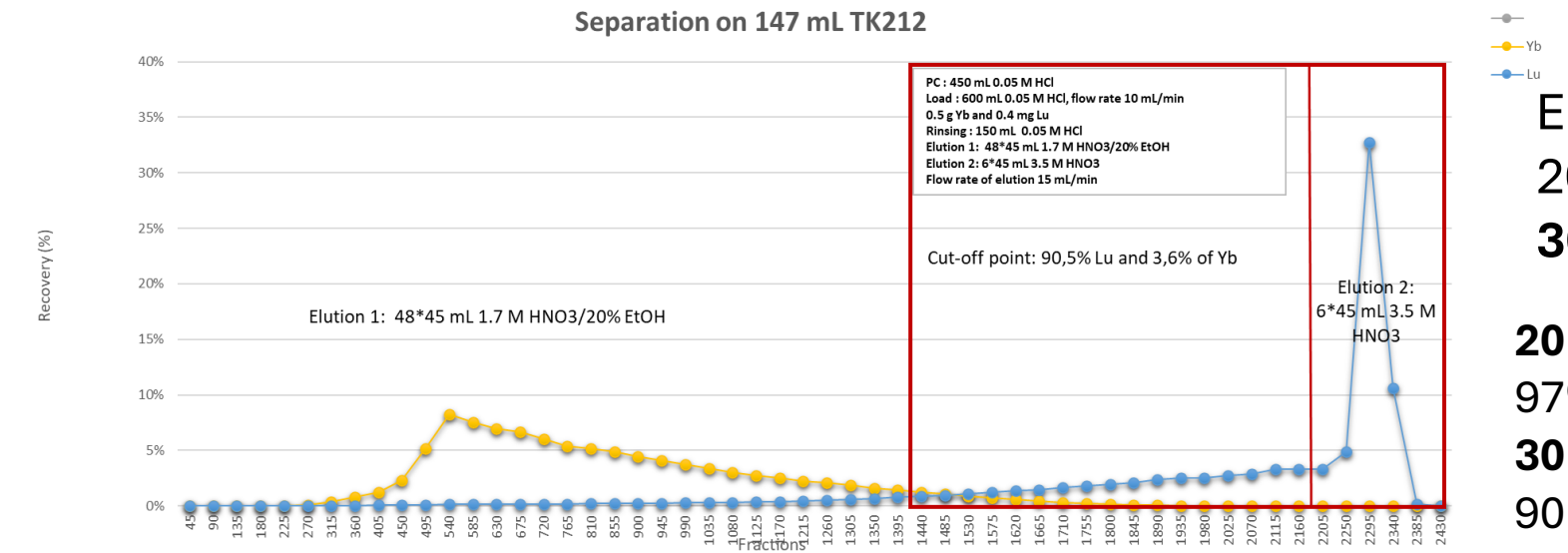
- Use of 1.7M HNO_3 / 20% EtOH
- Better Yb removal compared to 1.25HNO_3/10%EtOH
- Better Yb removal also improves separation on later columns
- Higher %-age of EtOH shifts peaks to higher elution volumes
- Higher acid to lower elution volumes / gain time



On-going improvement – Particle size – 20µm vs 30µm



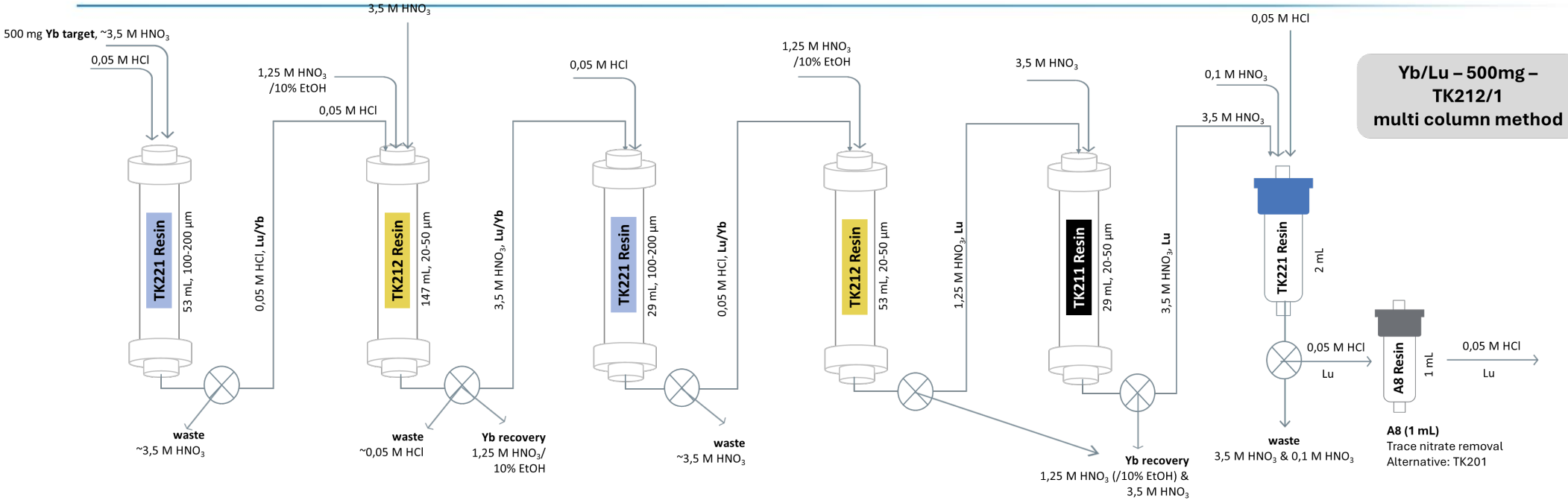
Elution with 1.7M HNO_3 / 20% EtOH – **20µm** particles



Elution with 1.7M HNO_3 / 20% EtOH – **30µm** particles

20µm at chosen cut-off:
97% Lu and 3% Yb
30µm at chosen cut-off:
90.5% Lu and 3.6% Yb
BUT higher pressure needed

Current ‘simplified’ method for Lu separation from 500 mg Yb – TK211/2 & TK221



Sequential separation step (direct load from TK212 onto TK211 for polish)

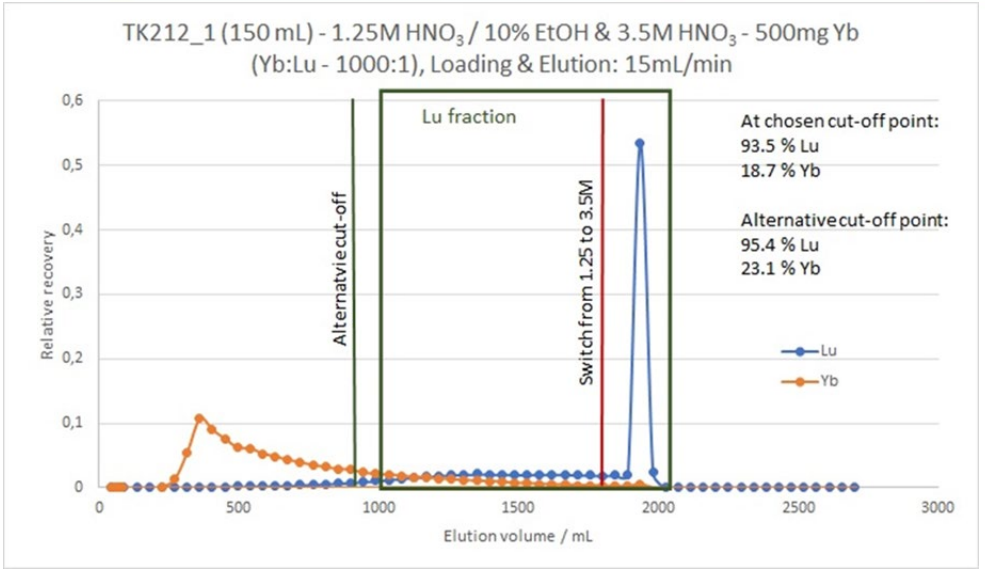
Unfortunately complete sequential TK213=>TK212=>TK211 didn’t work out

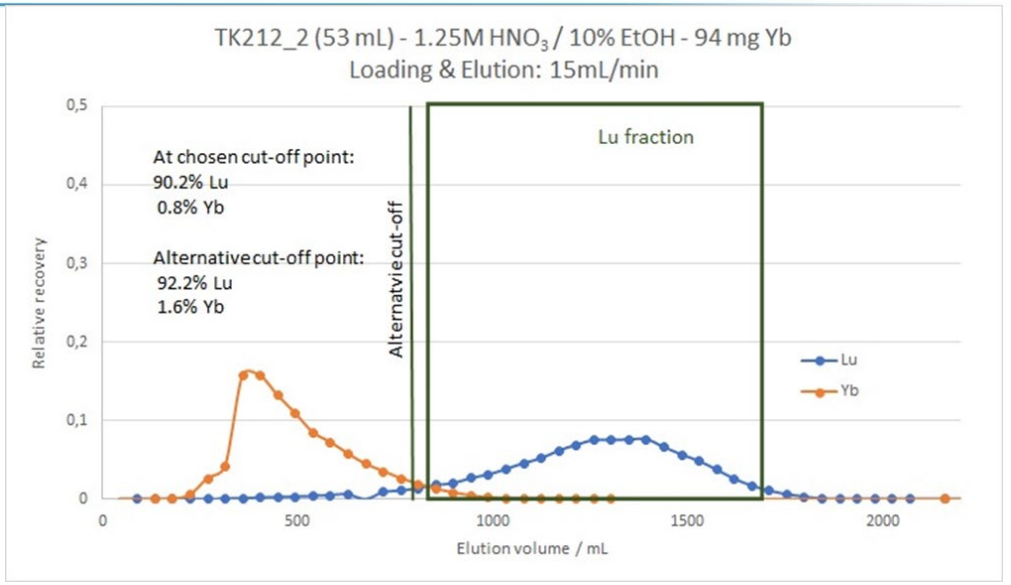
Can be upscaled (larger columns,…)

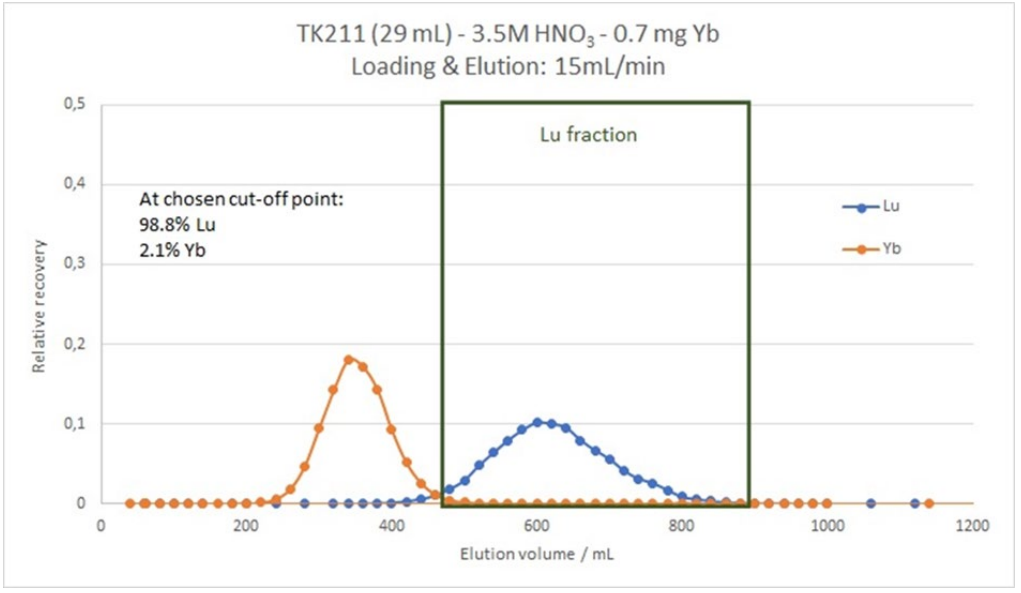
Further optimisation on-going

Upscale ongoing (now 4 – 5 g Yb)

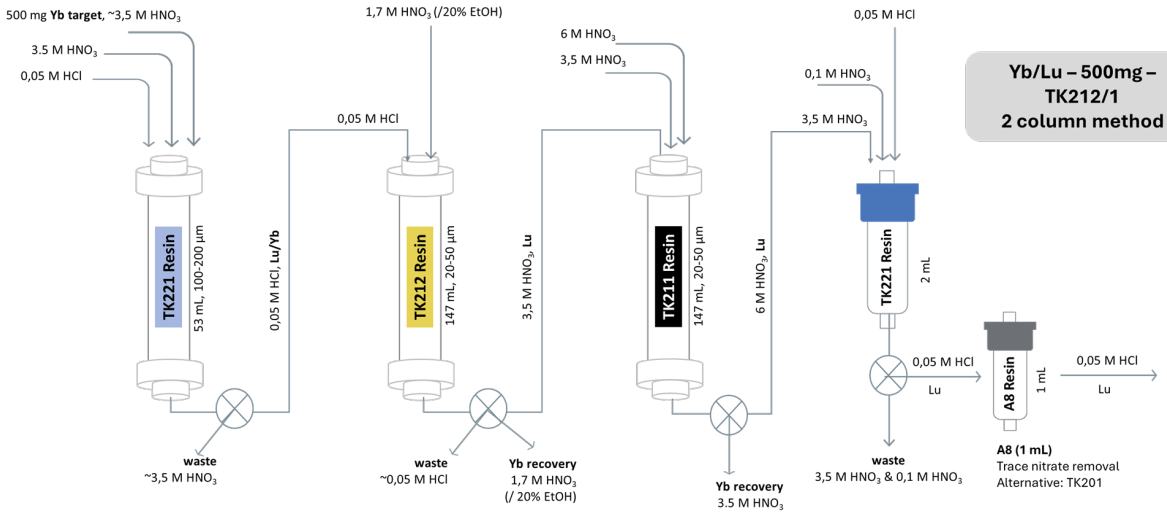
Current 500mg Yb target method







500 mg Yb: TK212/1 column approach



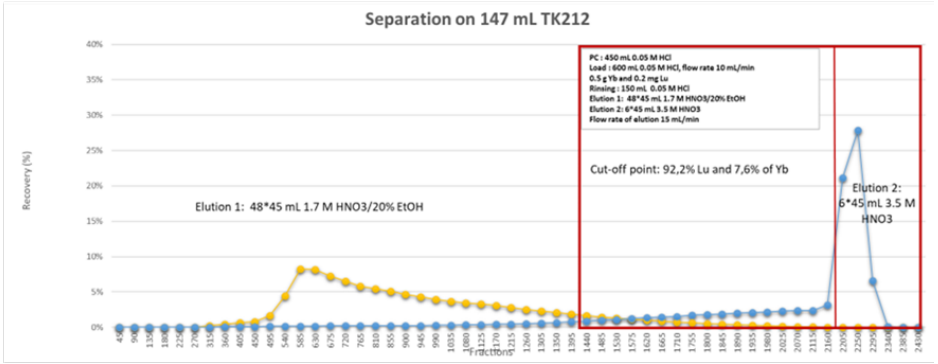
On-going work

Use of two 147mL TK212/1 columns instead of 3 TK212/1 columns+ TK221

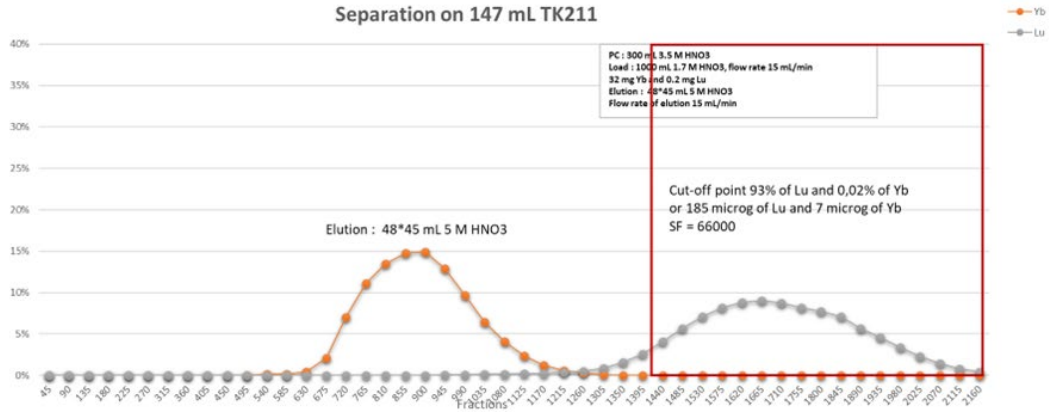
Faster and easier to automize

Better yields

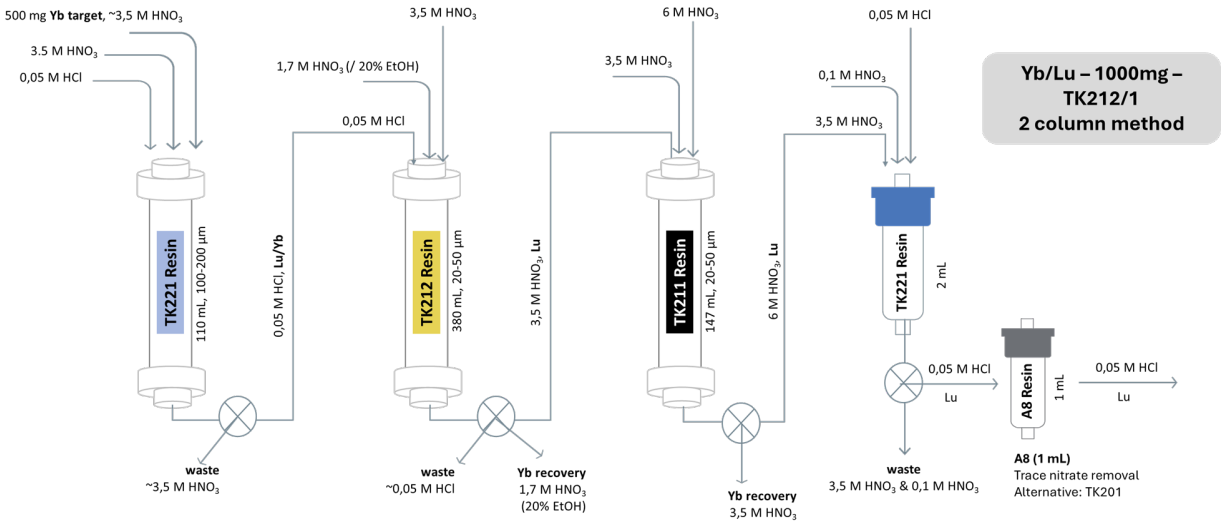
Also applicable to 1g targets (larger TK221 and TK212)



The 1st step separation on 147 mL TK212



1000 mg Yb: TK212/1 column approach



On-going work

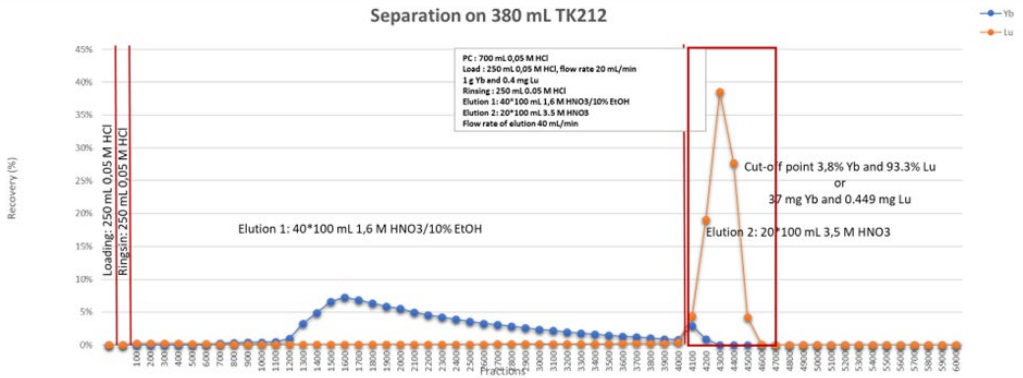
Larger TK221 column (min. 110 mL)

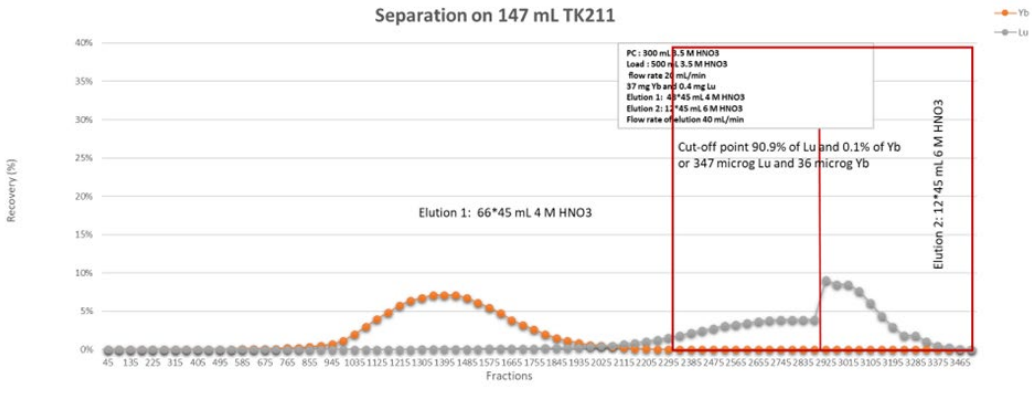
Use of one 380 mL TK212 and one 147mL TK211 columns Faster and easier to automize

Change of first two columns

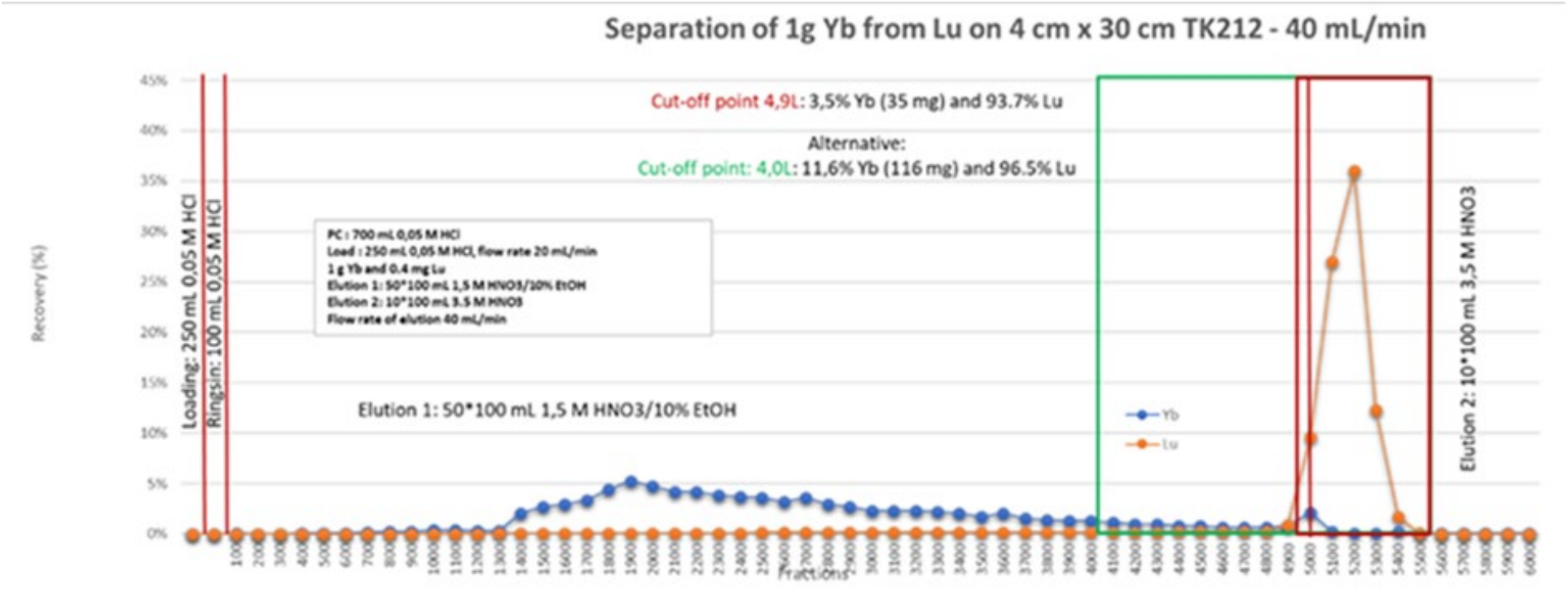
Good separation on first column at 40mL/min

< 3mg Yb/mLresin





1000mg Yb targets



30 x 4cm TK212 column
40mL/min flow rate
May be integrated into 500mg Yb flow scheme (modification of two columns)

Tb separation from 1000 mg Gd targets

Irradiated target typically oxide => dissolved in >3M HNO_3

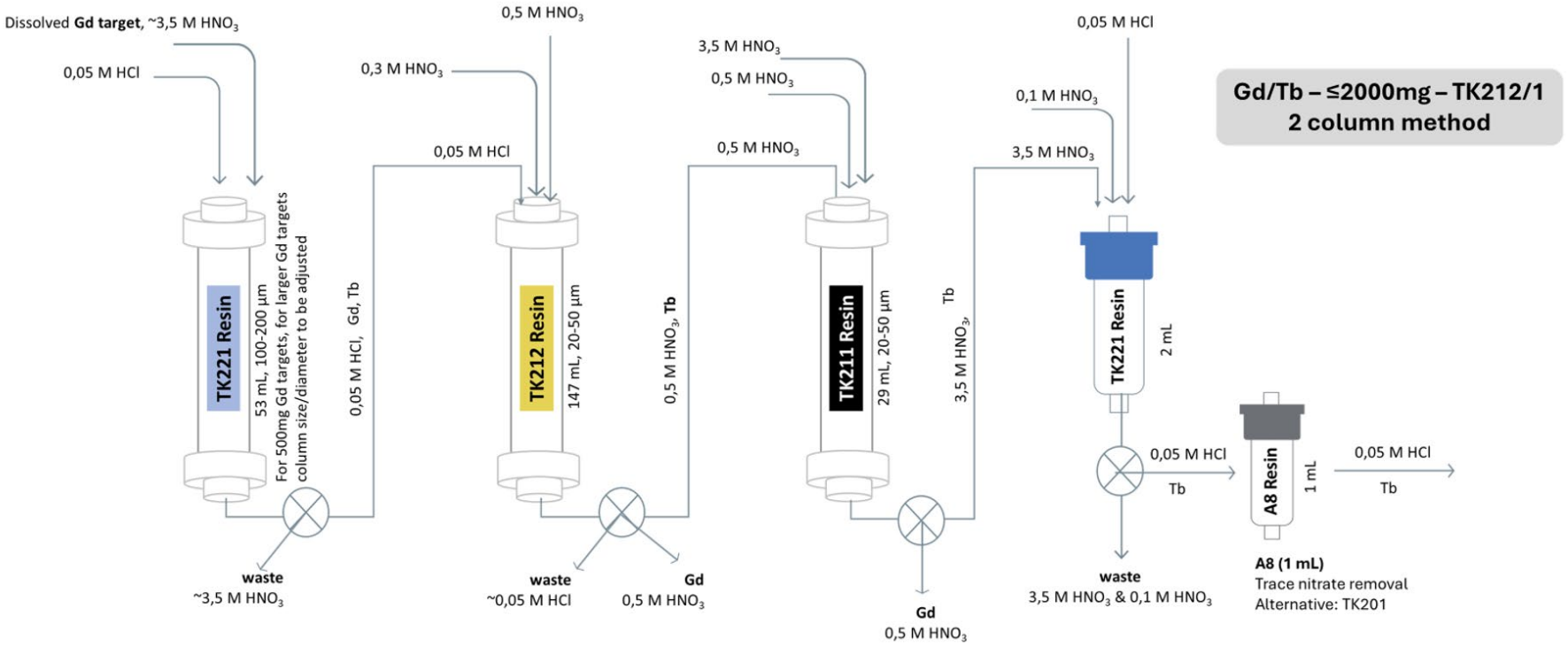
- For separation solution needs to be dilute acid

Conversion via TK221 Resin

Sequential separation on TK212/TK211

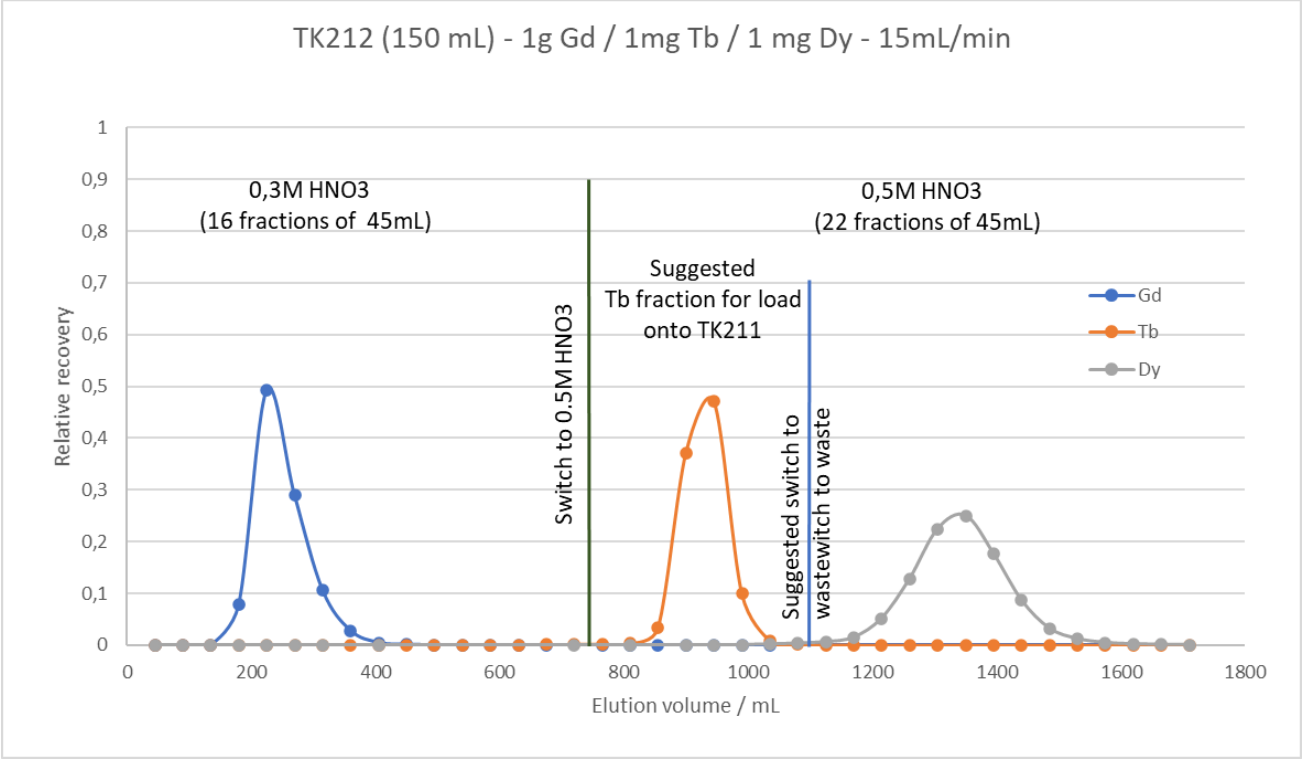
Final conversion to dilute HCl on TK221 + trace nitrate removal on AIX

Mainly Tb-161, also Tb-155



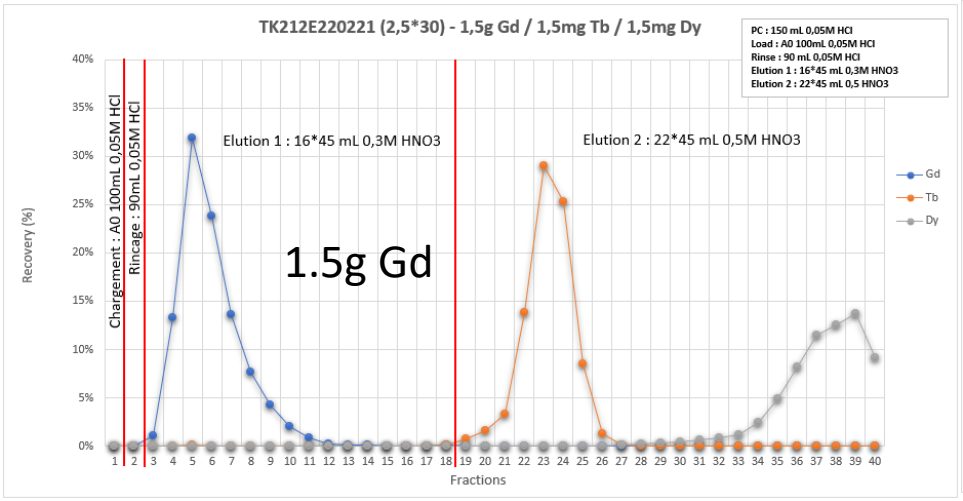
Tb separation from 1000 mg Gd targets

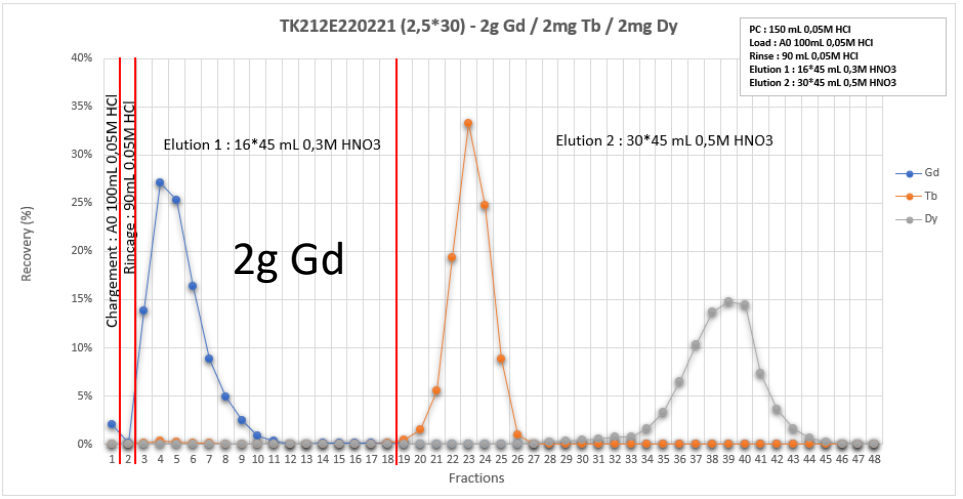
- Initial separation on TK212 – 150 mL column (30cm x 2.5cm)
- Allows for working with up to 2g of Gd
- Gd recovery => very expensive & difficult to find
- Tb separation from Gd and Dy – ideally using online detection
- Fine purification on TK211 (29 mL)

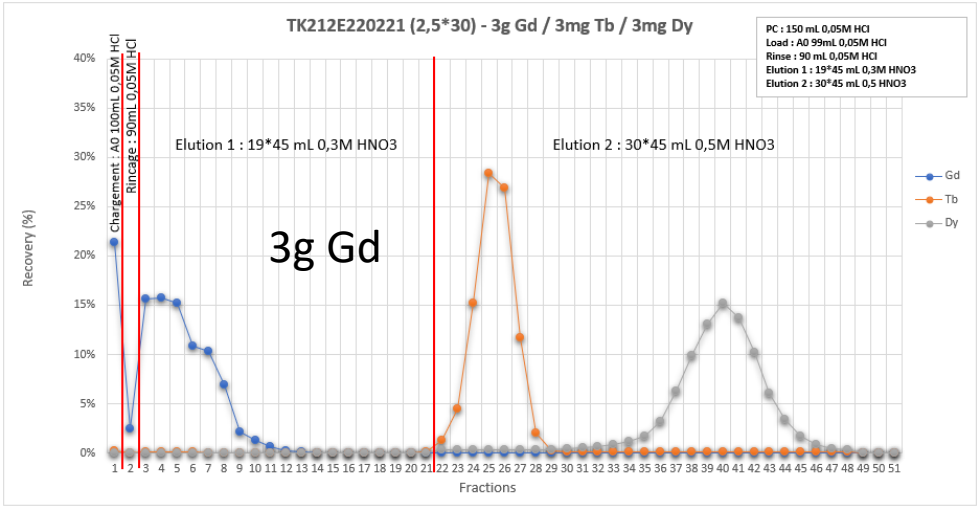


Tb separation from 1000 mg Gd on TK212 (147 mL column)

Increasing amouts of Gd

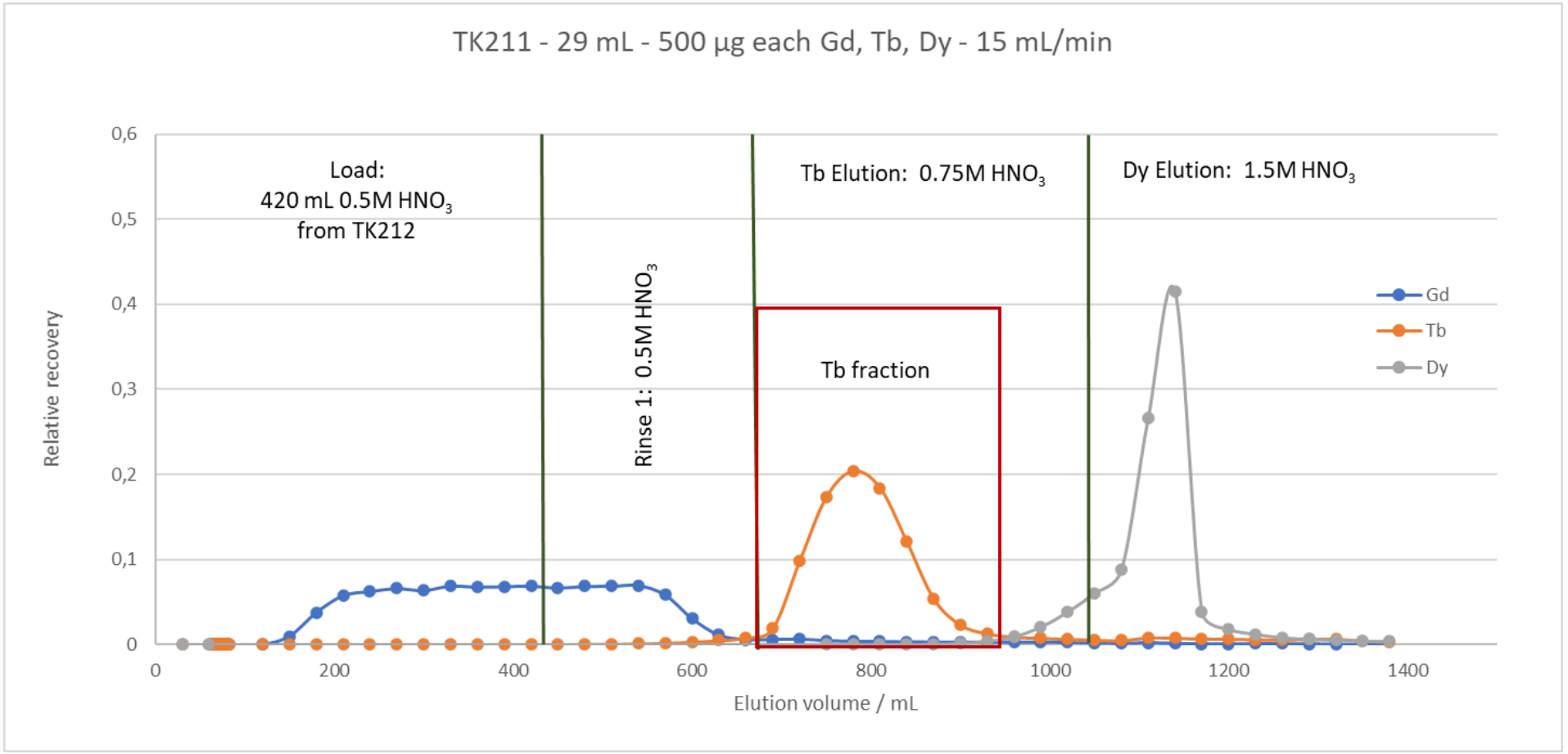






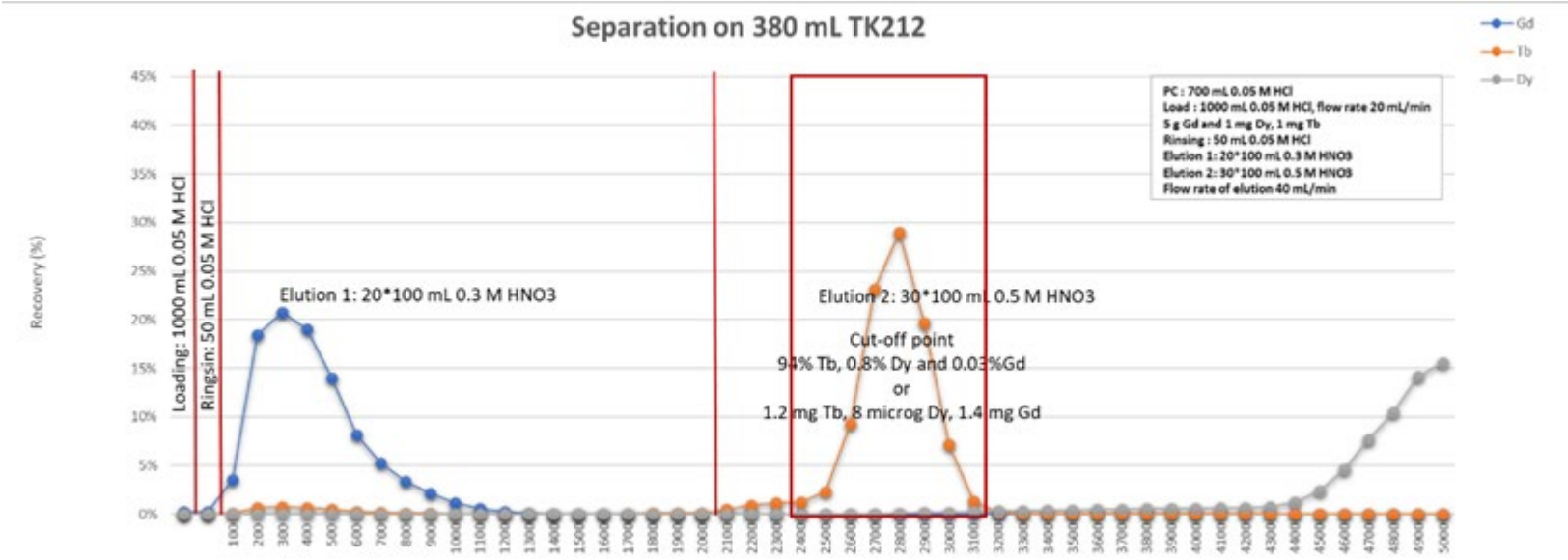
- On the same TK212 column
- More Gd => earlier elution
  - At 3g Gd start of breakthrough
  - More than 3g possible? Tb needs to remain retained…
- Little effect on Tb
- Small impact on Dy
- Tb / Dy sepration remains good.

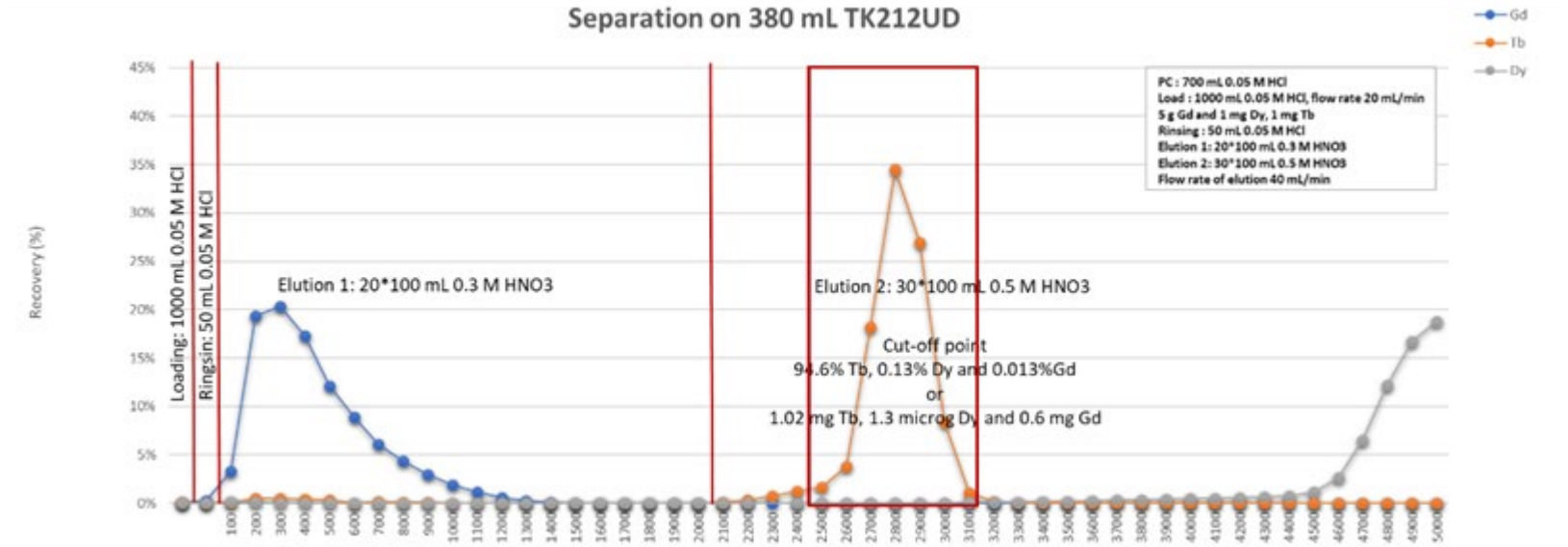
Tb polishing on TK211



- Direct load of Tb fraction from TK212 onto TK211 (29 mL – 30cm x 1.1cm)
- Gd breakthrough during load & rinse with 0.5M HNO_3 (alternatively HCl)
- Tb elution (Dy sufficiently well removed before) preferably in **>3M HNO_3**
- Conversion to dilute HCl via TK221, A8 for nitrate removal

5g Gd, 4cmx30cm TK212, 20µm vs 30µm, separation at 40 mL/min

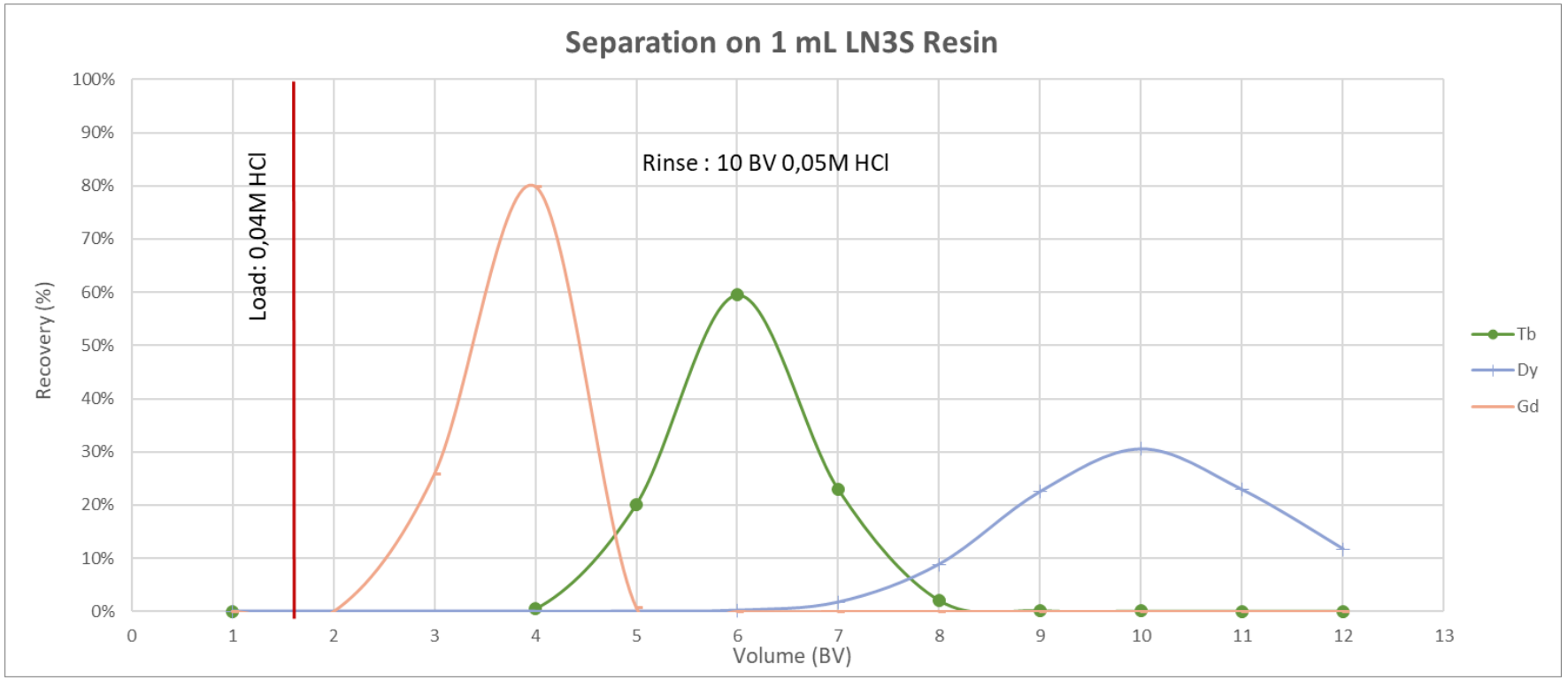




On-going: Tb/Dy separation

Request:

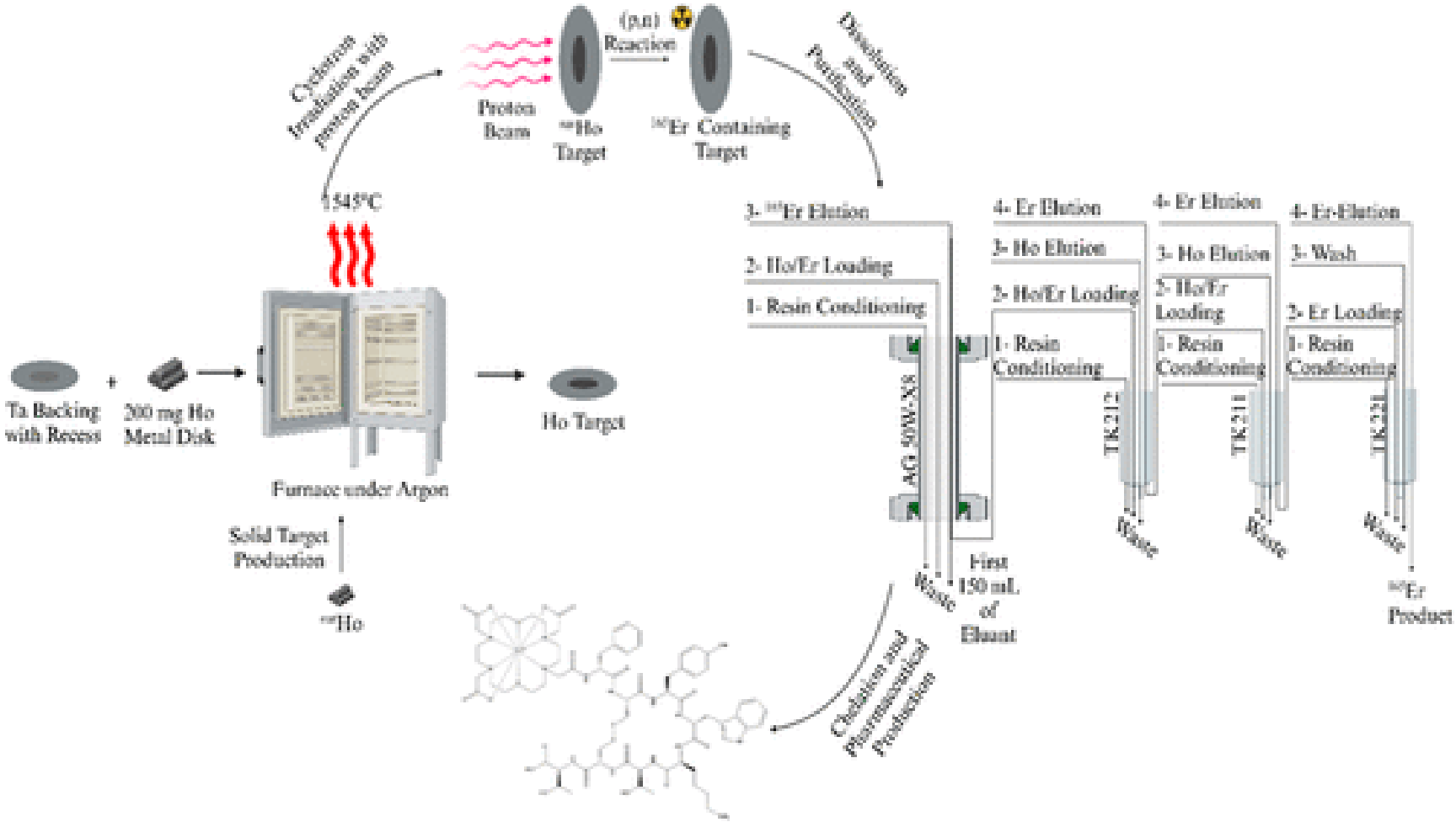
- Removal of Dy ingrown e.g. during transport
- Aim: rapid removal, no significant change of volume and acidity of Tb
- On-going work



ARTICLE | February 7, 2024

High Separation Factor, High Molar Activity, and Inexpensive Purification Method for the Production of Pure ^{165}Er

Behrad Saeedi Saghez, Hua Yang, and Valery Radchenko*



Ac separation

Reference method: TEH-DGA (e.g. Zielinska et al.)

Before often TRU or RE (CMPO based)

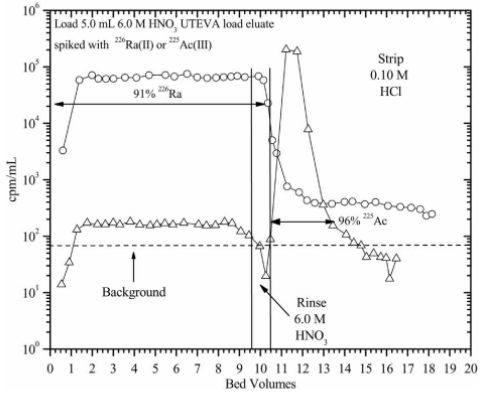


Figure 13. Separation of Ac(III) and Ra(II) on TODGA resin (50–100 µm) with 6.0 M HNO_3 and 0.1 M HCl, 0.5 mL bed volume, flow rate equals 2 mL/min load/rinse, 1 mL/min strip, 22(1)°C.

An Improved Method for the Production of Ac-225/Bi-213 from Th-229 for Targeted Alpha Therapy

B. Zielinska, C. Apostolidis, F. Bruchertseifer, and A. Morgenstern

European Commission, Joint Research Centre, Institute for Transuranium Elements, Karlsruhe, Germany

Marsten, Radchenko (LANL)

SCIENTIFIC REPORTS

OPEN

Simultaneous Separation of Actinium and Radium Isotopes from a Proton Irradiated Thorium Matrix

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Tara Mastren[1], Valery Radchenko[1,3], Allison Owens[2], Roy Copping[2], Rose Boll[2], Justin R. Griswold[2], Saed Mirzadeh[2], Lance E. Wyant[2], Mark Brugh[1], Jonathan W. Engle[1,4], Francois M. Nortier[1], Eva R. Birnbaum[1], Kevin D. John[1] & Michael E. Fassbender[1]

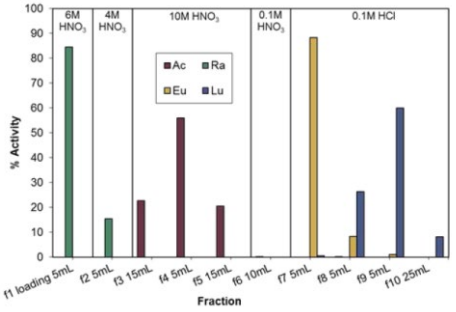


Fig. 4. Elution profile for $^{223/225}Ra$, ^{225}Ac, ^{173}Lu, and ^{155}Eu with TEHDGA resin in HNO_3 media and HCl for lanthanide elution.

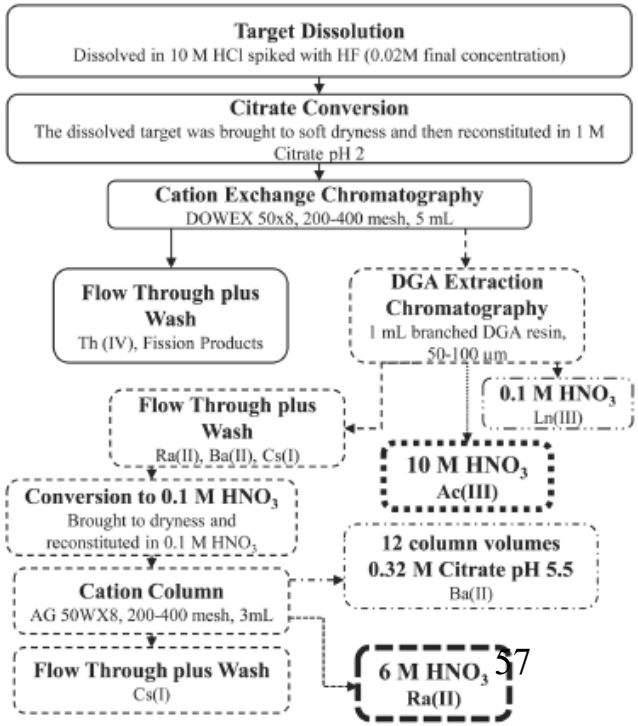


Figure 4. Final ^{225}Ac separation schematic with recovery of radium isotopes.

Ac-225 separation

Ac-225 separation chemistry well established

- DGA (mainly B is used) allows for facile Ac/Ra and LN/Ac separation
  - Imperfect La/Ac separation and U/Th removal
  - Radiolysis stability sufficient?

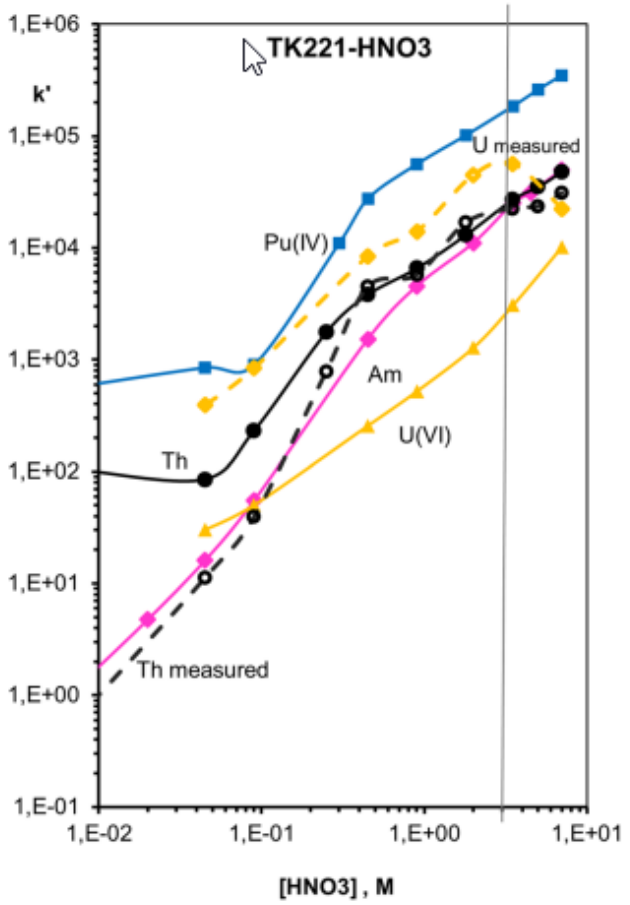
Alternatives:

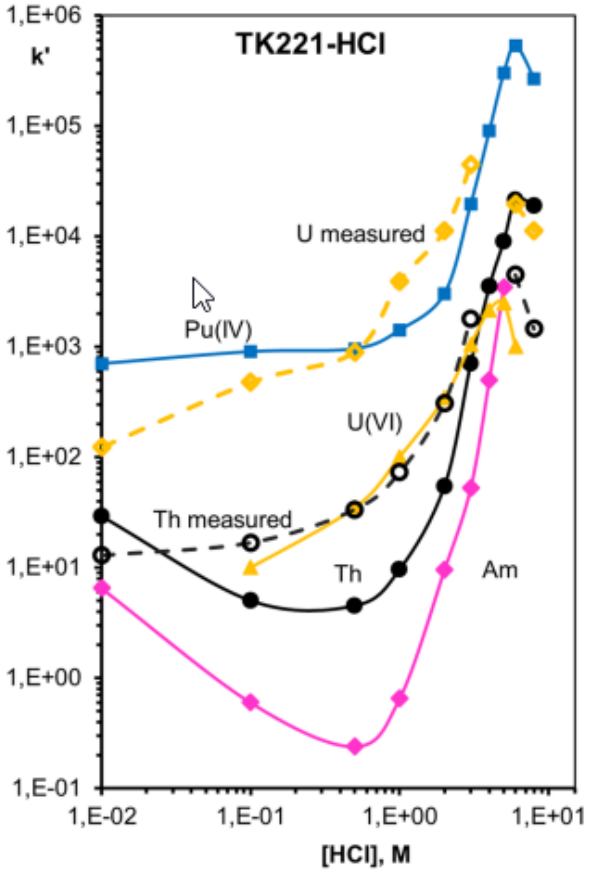
- Use of TK221 (TO-DGA / phosphine oxide) or TK222 (TEH-DGA / phosphine oxide)
  - Focus on La/Ac separation
  - Ac elution in HCl necessary
  - Resalting possible? Ac nitrate => Ac chloride
  - ‘Normalisation’ of Ac-225 from different sources
  - Further purification (especially from Fe) and concentration
  - Improved radiolysis stability?

TK221 Resin

Resin based on a mixture of diglycolamide and phosphine oxide + traces long chained alcohol on inert support with aromatic groups.

- Main applications in RadPharm:
  - Lu, Tb concentration from high acid and elution in small volume of dilute HCl
  - Ac-225 purification
  - Improved radiolysis stability
- Potential use in actinide separations?





(Papp, I., Vajda, N. & Happel, S. An improved rapid method for the determination of actinides in water. *J Radioanal Nucl Chem* **331**, 3835–3846 (2022). https://doi.org/10.1007/s10967-022-08389-9)

TK221 Resin

DGA well suited for ‘conversion’ and purification (Ca, Al, Fe,… removal)

- Convert Lu from high nitric acid to dilute HCl

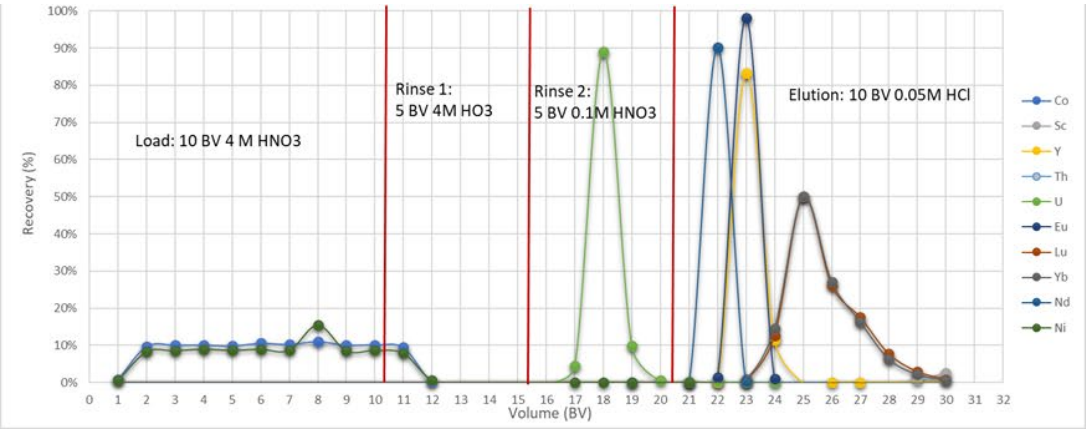
Elution of heavy lanthanides at as low volumes as possible

- small volume prefered => high activity concentration

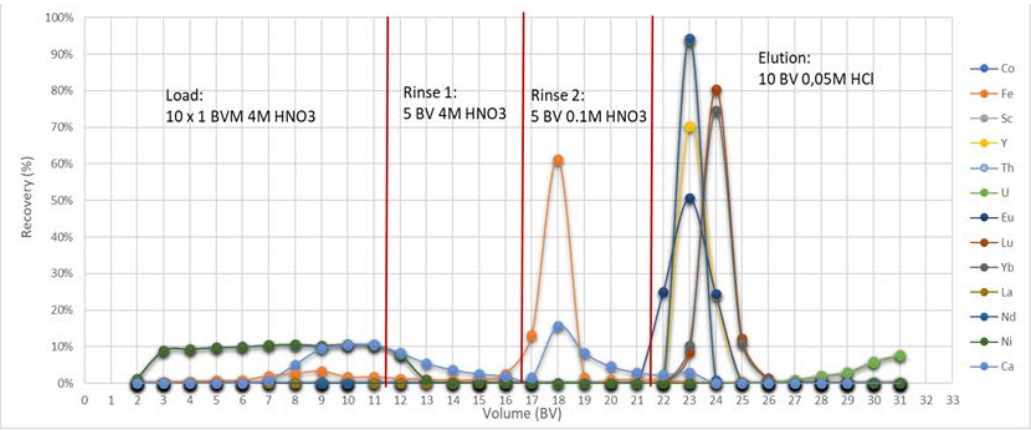
TK221 Resin

- DGA / phosphine-oxide,improved radiolysis stability (inert support, scavanger,…)
- Better La and U retention
- Lu & Tb eluted in small volume in dilute HCl => drawback, no group RE separation possible

DGA Resin



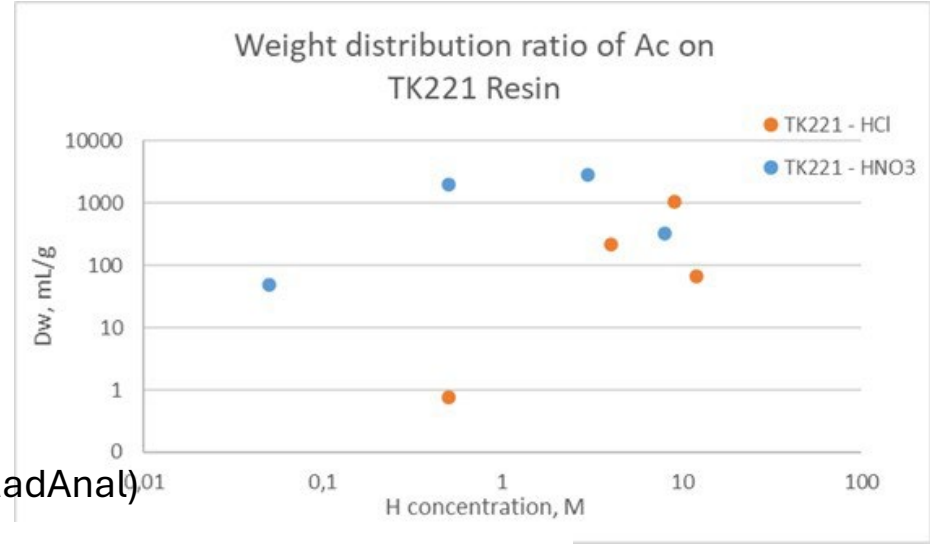
TK221 Resin



- **TK222 Resin => DGA, B/phosphine oxide**

TK221/2 Resins – Ac Dw values

- Ac Dw data determination on-going
- Work with several groups
- Upcoming publication



CONFIDENTIAL

Data courtesy of N. Vajda (RadAnal)

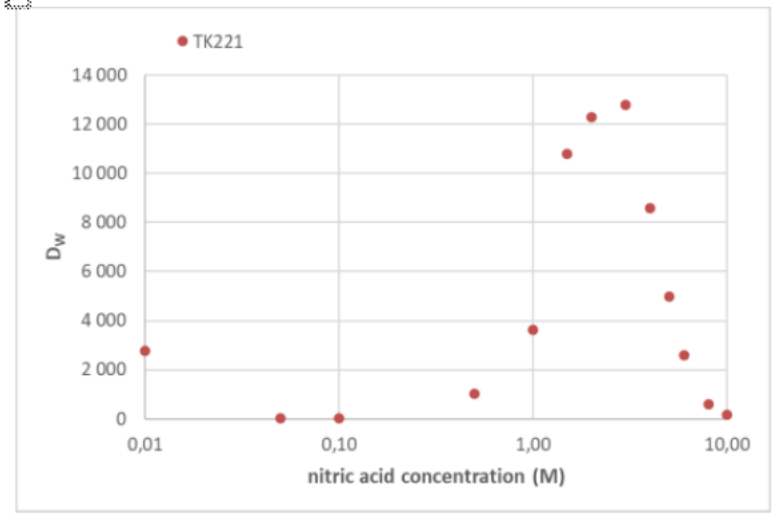


FIG. 1 The D_W values for ^{225}Ac between TK221 and nitric acid

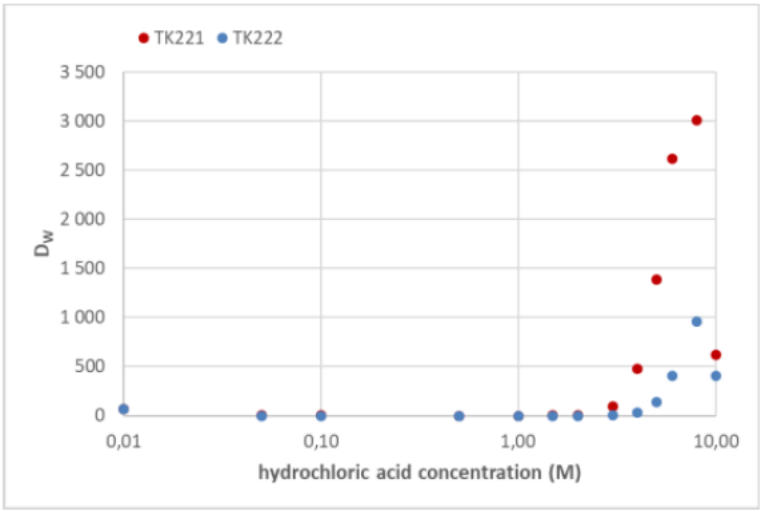


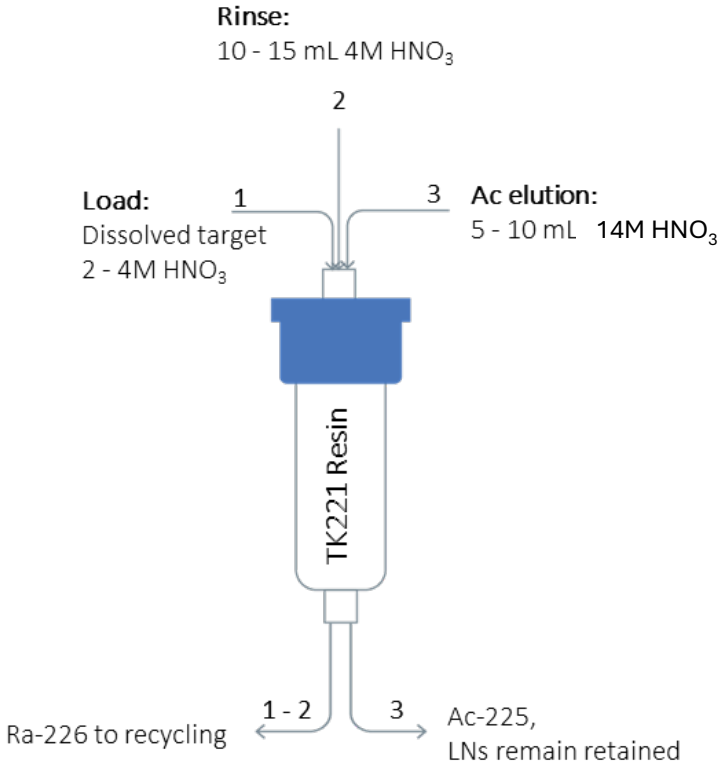
FIG. 2 The D_W values for ^{225}Ac between TK221 and TK222 and hydrochloric acid

Data courtesy of O. Lebeda (UjV Rez)

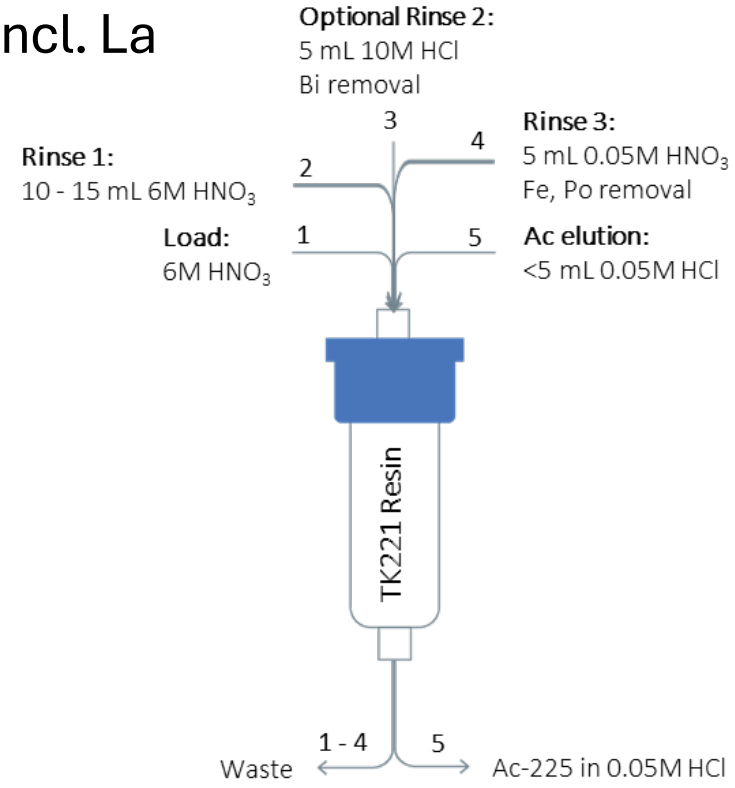
Ac-225 separation

Two TK221 cartridges for removal of impurities incl. La

- In case La can be excluded step 2 only

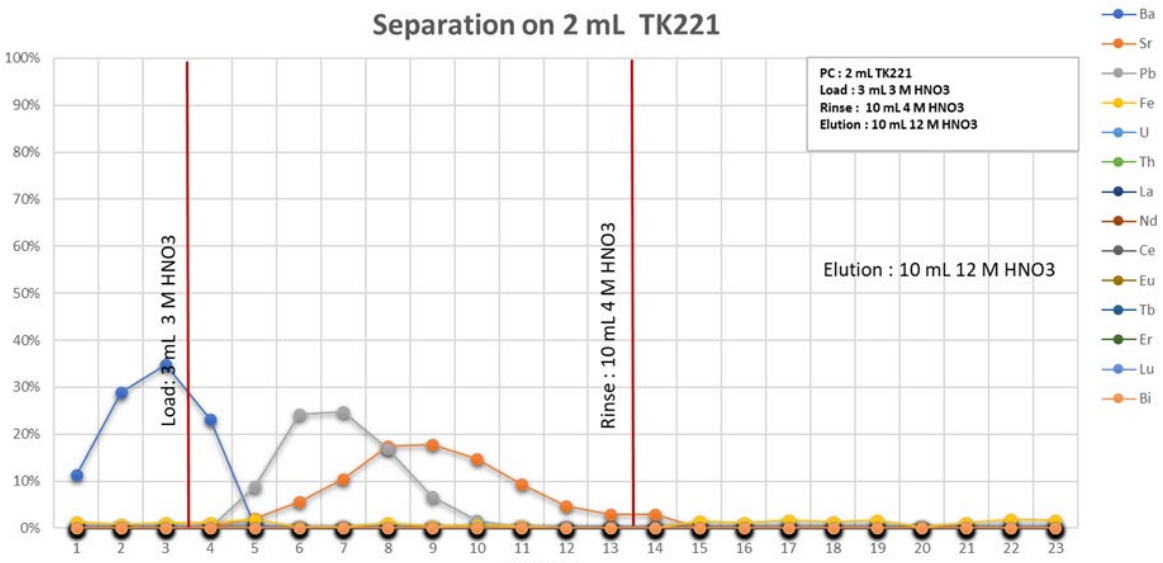


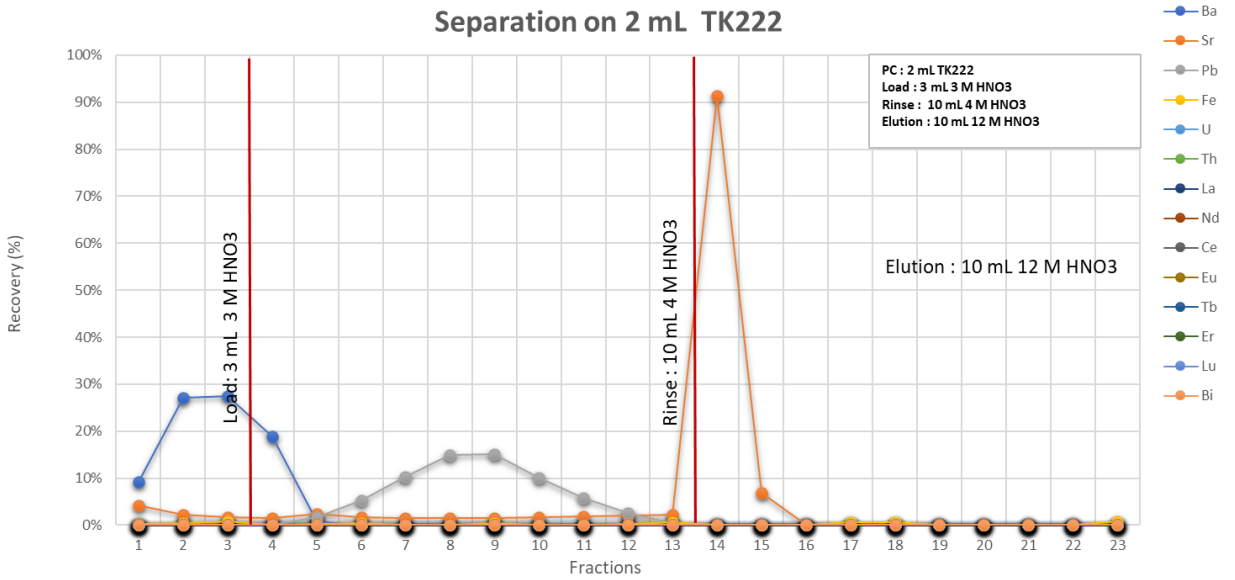
Step 1 TK221:
Target dissolved in 2 – 4M HNO_3 (2M prefered => Ra solubility)
Ra, Ba, Pb, Sr,... removal with 4M HNO_3
Ac elution in 14M HNO_3 (LNs retained)



Step 2 TK221:
2x diluted eluate from first TK221
Rinse with 6M HNO_3 and opional rinses with:
10M HCl => Bi removal and
0.05M HNO_3 (Fe, Po removal) => can be inverted
Ac elution in 0.05M HCl

TK221 Resin – Ac separation – step one





- In case LN need to be removed
- Two step procedure

First Ac / LN separation

TK221

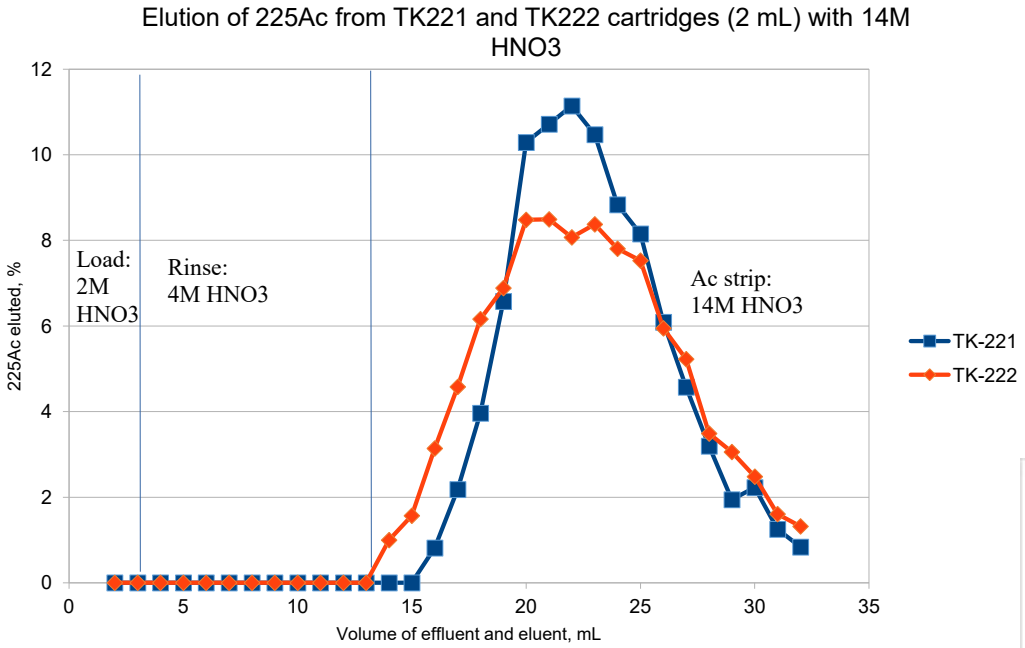
- Load from elevated HNO_3
- Ac elution in very high HNO_3
- LNs, U, Th retained
- Particular attention to Pb/Sr
  - Elution in 4M HNO_3

TK222

- Load from elevated HNO_3
- Ac elution in very high HNO_3
- LNs, U, Th retained
- Particular attention to Pb and Sr
  - Pb Elution in 4M HNO_3
  - Sr elution in 12M HNO_3

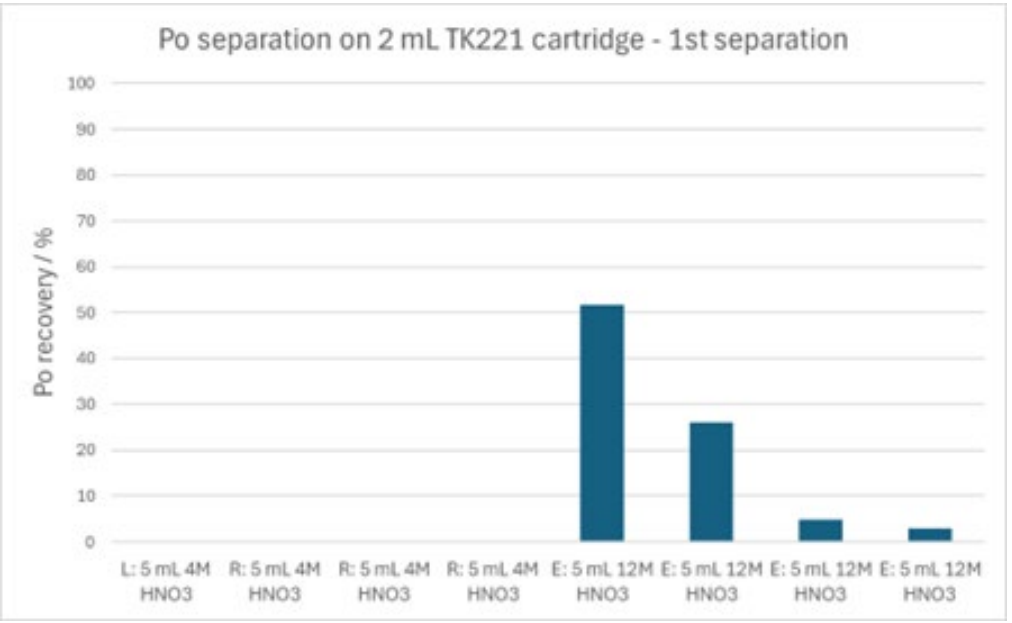
TK221 prefered option

Ac and Po behaviour – step 1



Data courtes N. Vajda

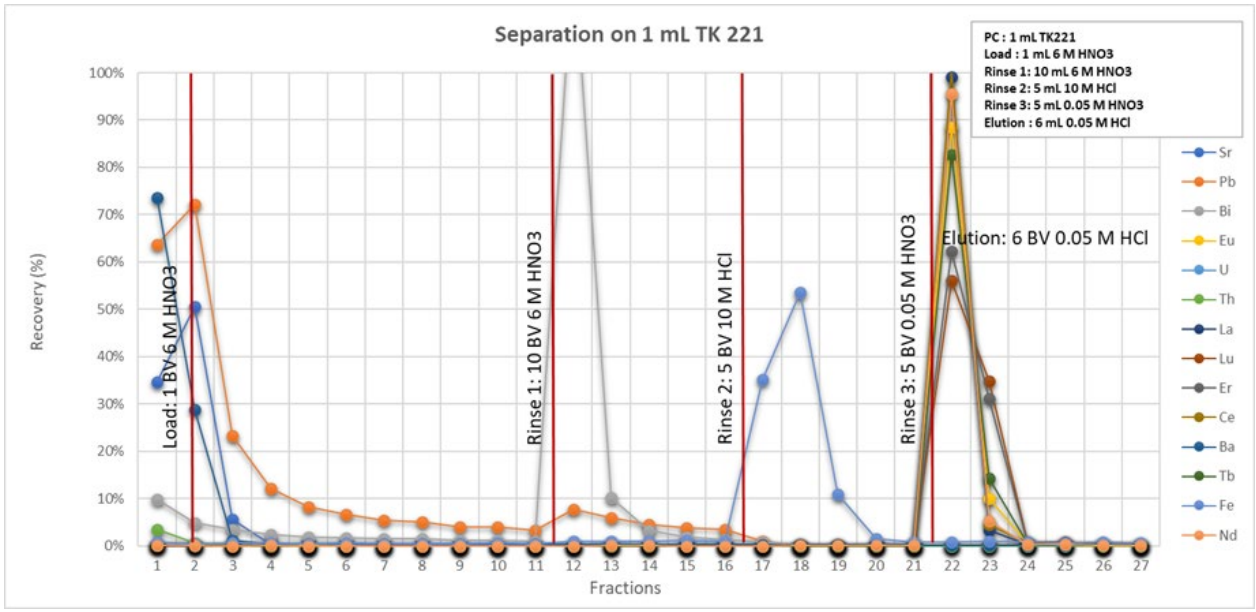
Ac elution in 14M HNO_3
Similar profiles for TK221 and TK222
Requires ~20 mL
Dilution by x2 before loading onto second TK221 or TK222

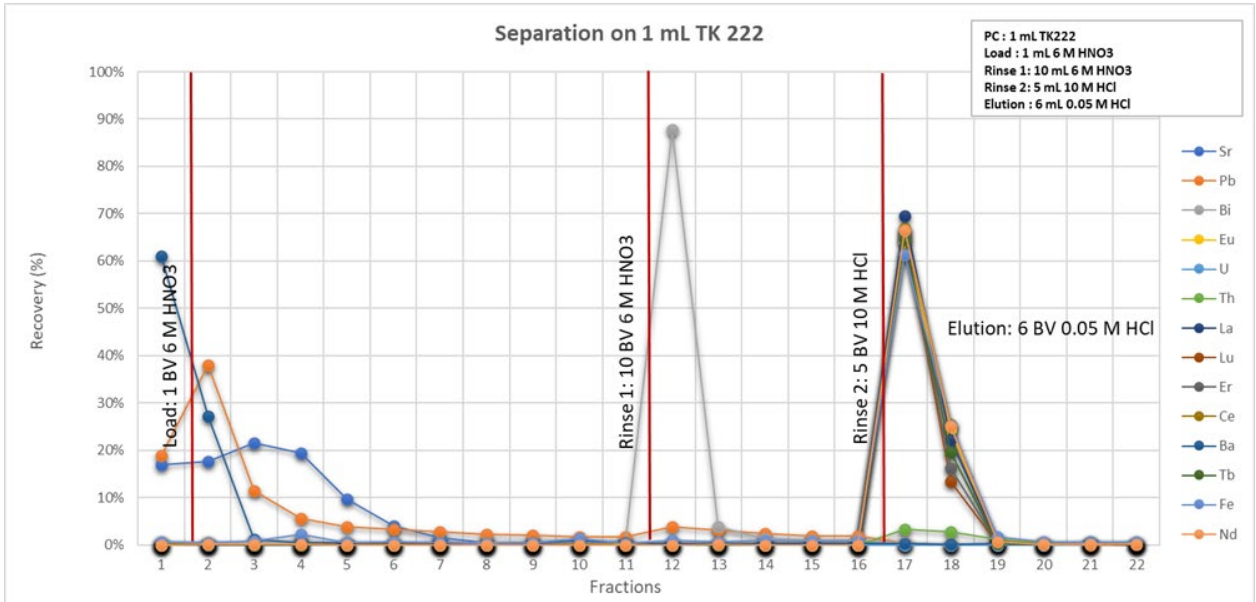


Po co-elutes with Ac
To be considered on second TK221/2

All data courtesy of Nora Vajda (Radanal)

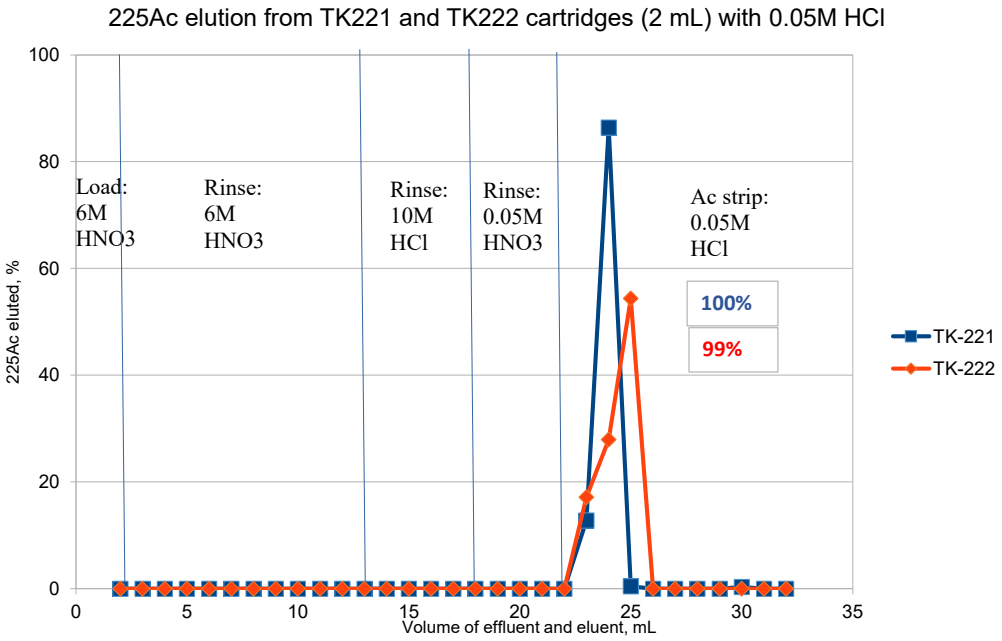
TK221 Resin – Ac separation – step two





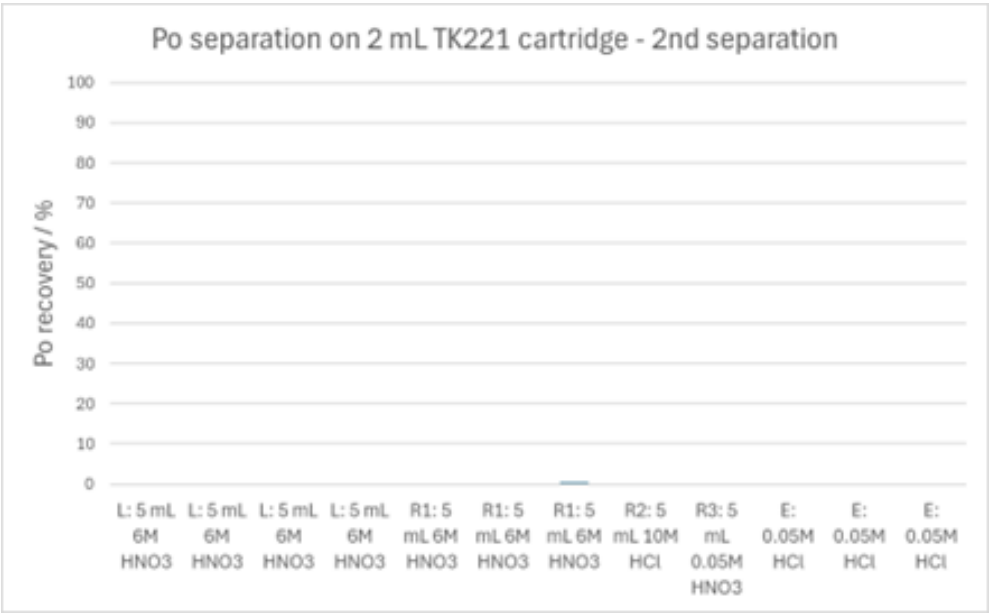
- Second separation
- TK221
  - Dilute x2 => load
  - Bi removal 10M HCl
  - Fe removal in 0.05M HNO_3
  - Ac elution in 0.05M HCl
  - Important: Lanthanides need to be removed upfront (1st TK221)
- Alternative: TK222
  - Sharper Ac elution
  - No rinse with 0.05M HNO_3
  - Only in case of absence of Fe
- TK221 prefered in case of presence of Fe

Ac and Po elution – step 2



All data courtesy of Nora Vajda (Radanal)

- Sharp Ac-225 elution from TK221 and TK222
- Note: 0.05M HNO_3 rinse only performed on TK221 (Fe removal not possible on TK222) so elution was performed directly after 10M HCl rinsing step => delays Ac elution.
- W/o this step Ac elution from TK222 very sharp



Po remains retained on TK221, no elution

Ac elution from TK221 and TK222

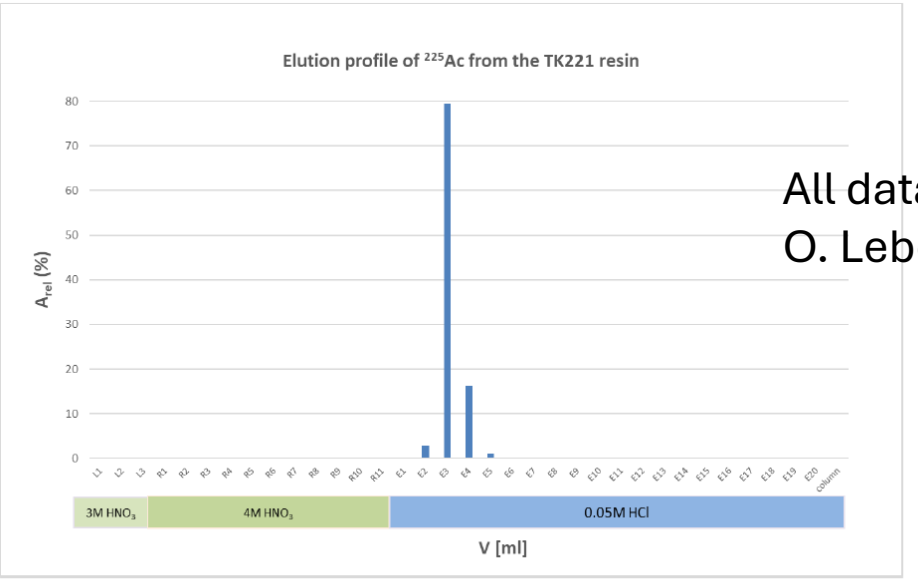


FIG. 3 Elution profile of ^{225}Ac loaded on the TK221 column in 3M nitric acid, rinsed with 4M nitric acid and eluted into 0.05M hydrochloric acid

All data courtesy of O. Lebeda, Rez

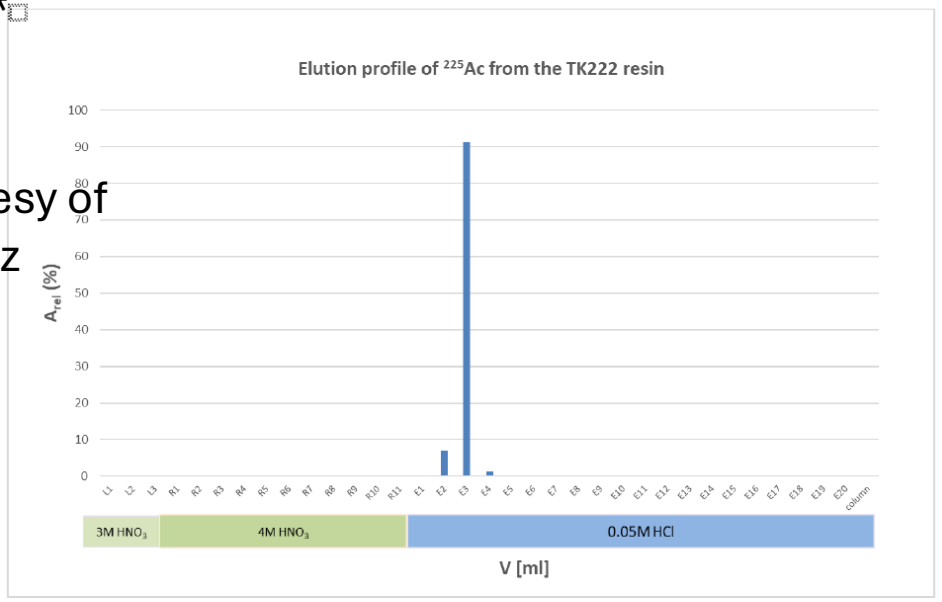


FIG. 4 Elution profile of ^{225}Ac loaded on the TK222 column in 3M nitric acid, rinsed with 4M nitric acid and eluted into 0.05M hydrochloric acid

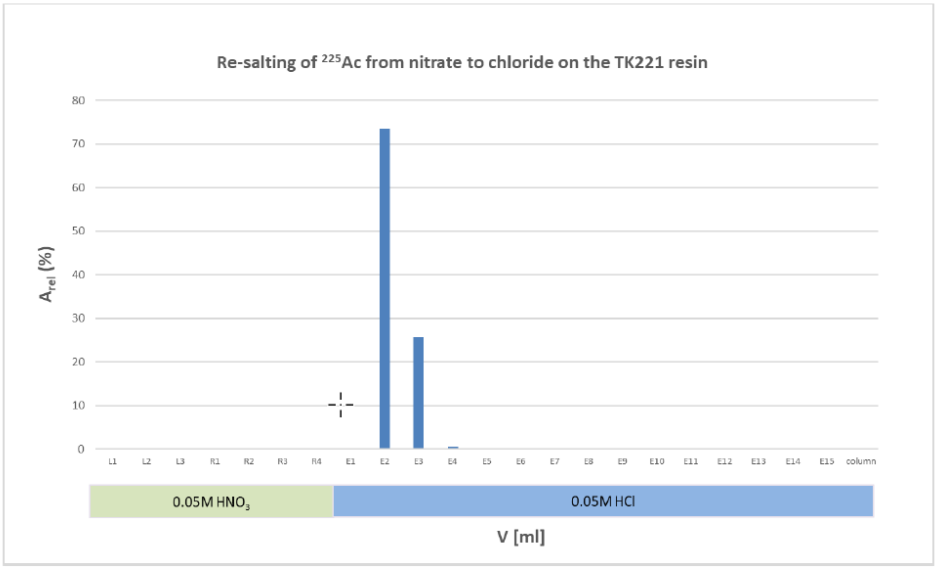
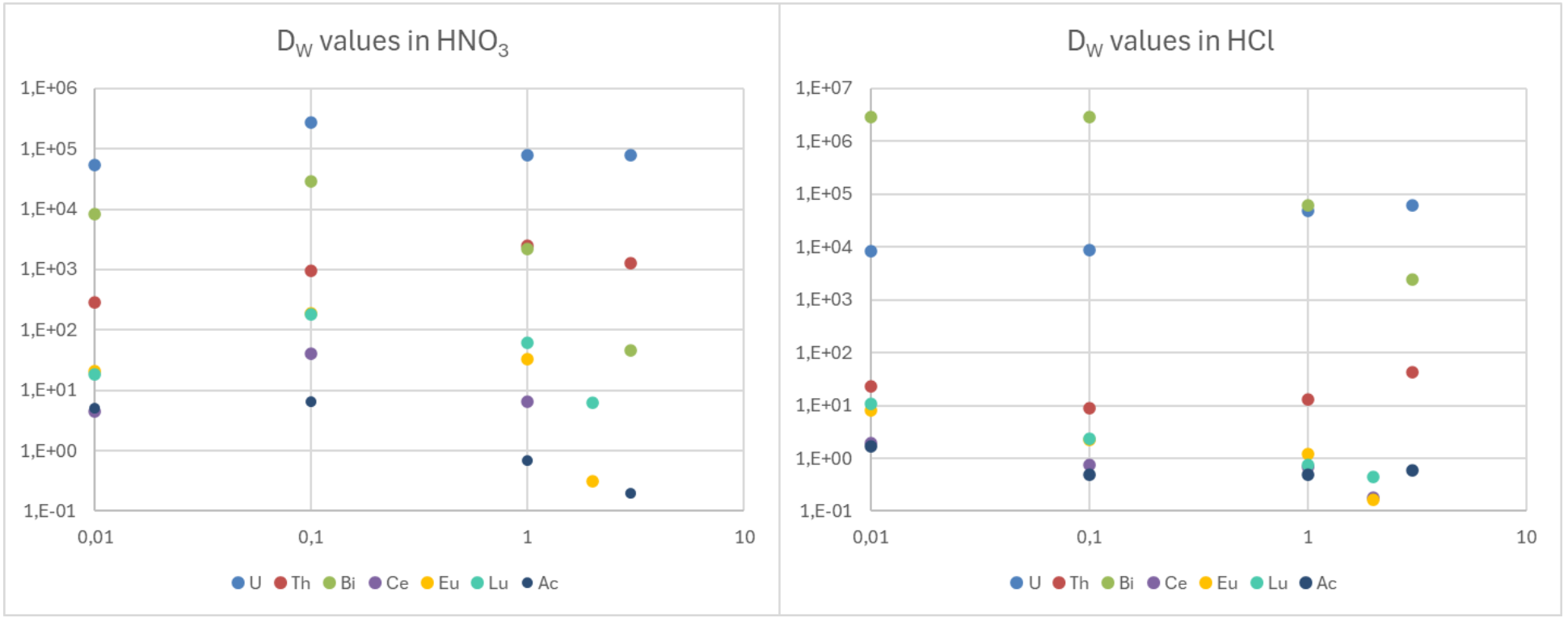


FIG. 5 Re-salting of ^{225}Ac loaded on the TK221 column in 0.05M nitric acid and eluted into 0.05M hydrochloric acid

- Sharp Ac elution from TK221, even sharper from TK222
- 'Resalting' from Ac nitrate to chloride form possible on TK221 (not TK222)
  - Load from 0.05M HNO_3, elution in 0.05M HCl
  - Further purification and concentration possible

Removal of lanthanides and actinides from Ac
TK200 Resin – D_W values



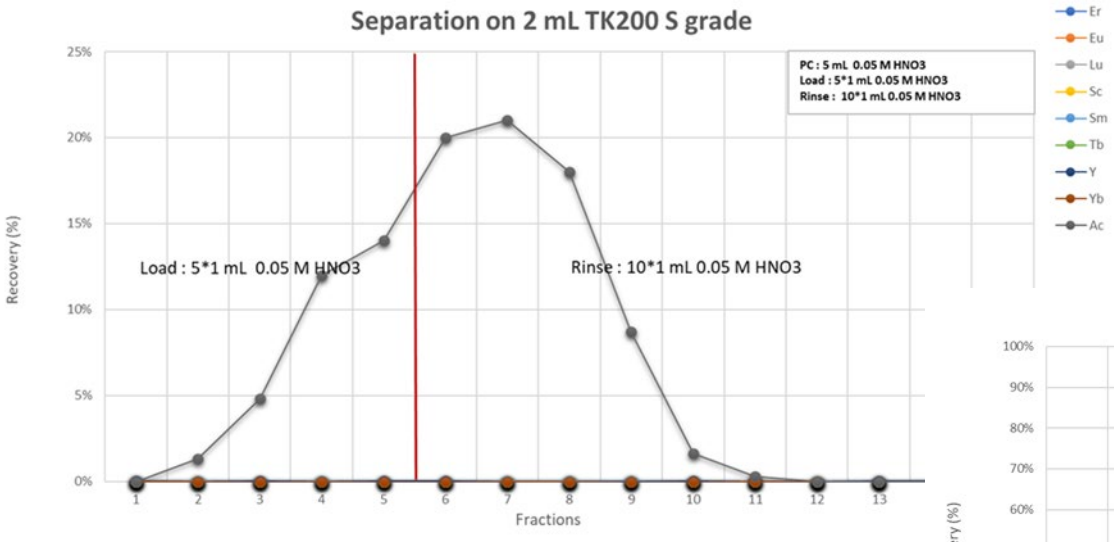
Ac data courtesu N. Vajda

Original context: removal of Ac from lanthanides (mining tailings, fertiliser,…)

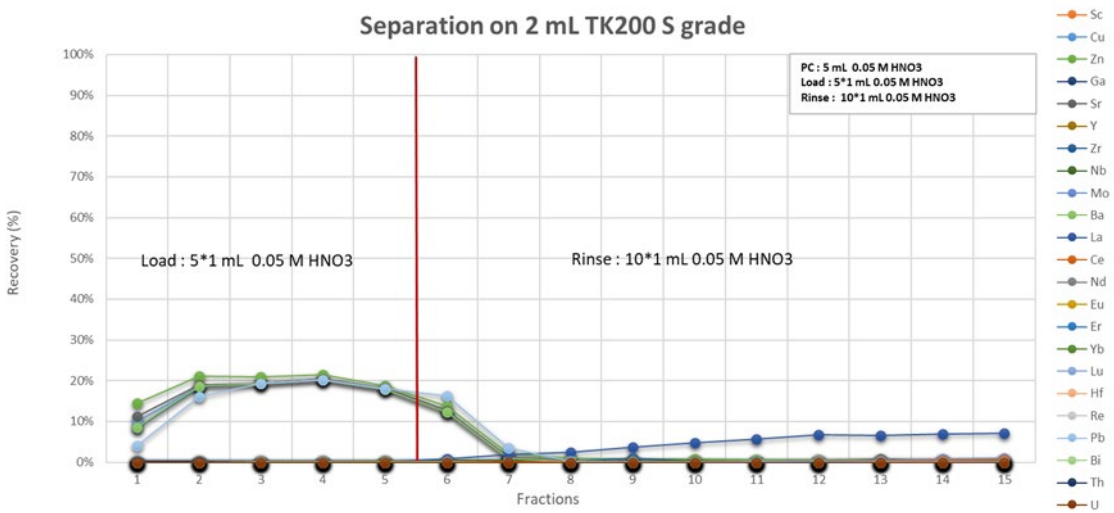
HNO_3: strong retention of U, Th and Bi, good retention of lanthanides, no Ac retention

HCl: strong retention of U and Bi, no retention of Ac, lanthanides and Th up to 3M HCl

TK200 Resin – Ac elution studies



Ac data courtesy N. Vajda



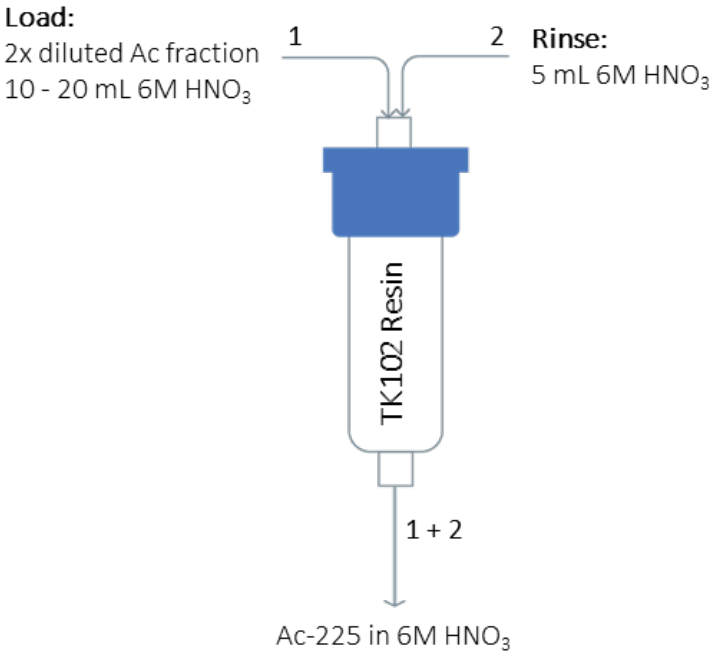
Ac not retained in 0.05M HNO_3, U, Th, Bi and lanthanides retained, slow La breakthrough => removal of alpha emitters and lanthanides

Most other impurities (Ca, Pb, Fe,… not retained, need to be eliminated upfront)

Under testing: TK200 Discs for determination of alpha emitters in Ac-225 by alpha spectrometry after filtration

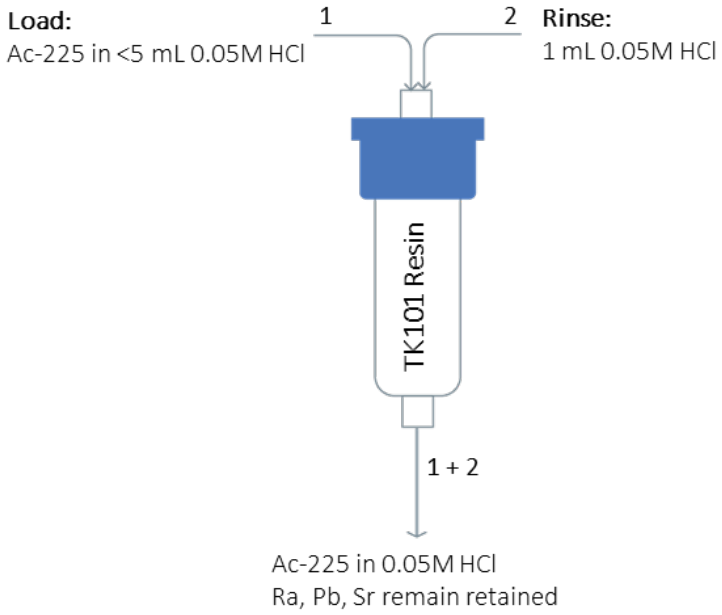
Ac-225 separation – Optional additional purification

Optional:
Pb removal on TK102



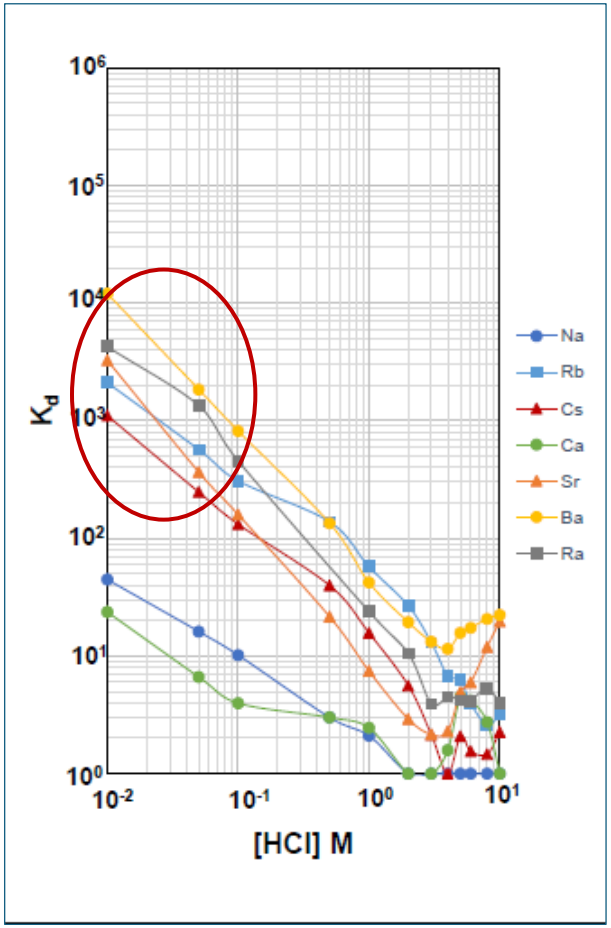
Optional Pb and Sr removal step (TK102)
Eluate of step 1 dilute by x2
Load through TK102
Pb and Sr retained, Ac passes through

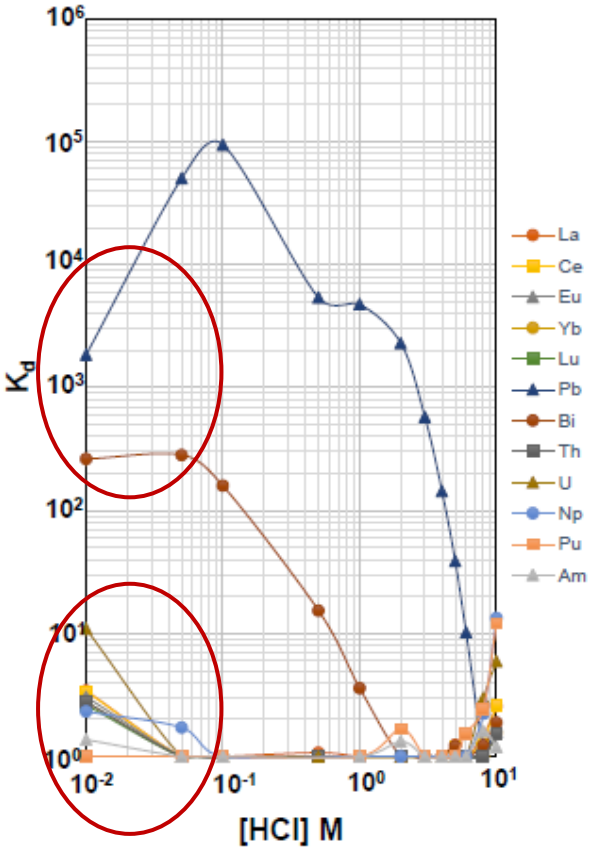
Optional:
Ra, Pb, Sr, Ba removal on TK101



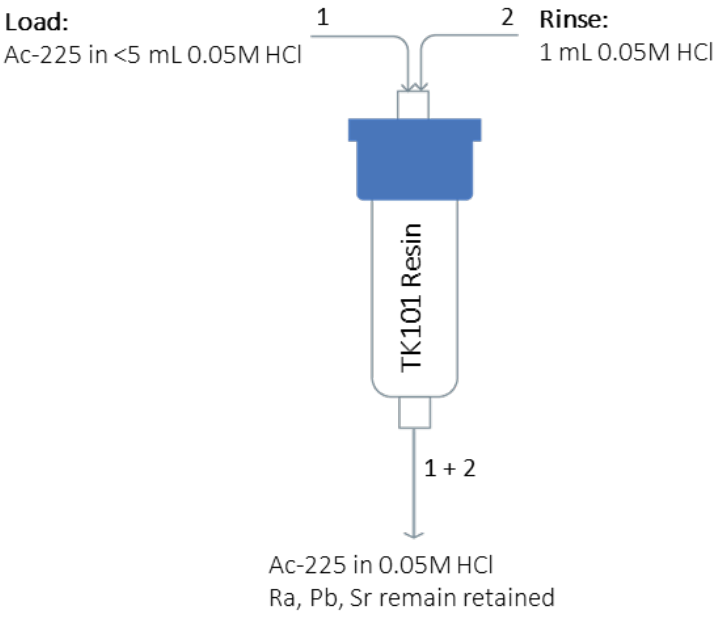
Optional Pb, Ra, Sr,... removal step (TK101)
=> removal of Ac daughters
Pass Ac fraction (0.05M HCl) through TK101
Ac passes through, Ra, Pb, Sr, Bi,... retained

Optional: TK101 purification step





Optional:
Ra, Pb, Sr, Ba removal on TK101



Data courtesy of B. Russel (NPL)

Optional Pb, Bi, Ra, Sr,... removal step (TK101)
Pass Ac fraction (0.05M HCl) through TK101
Ac passes - Ra, Pb, Sr, Bi,... retained

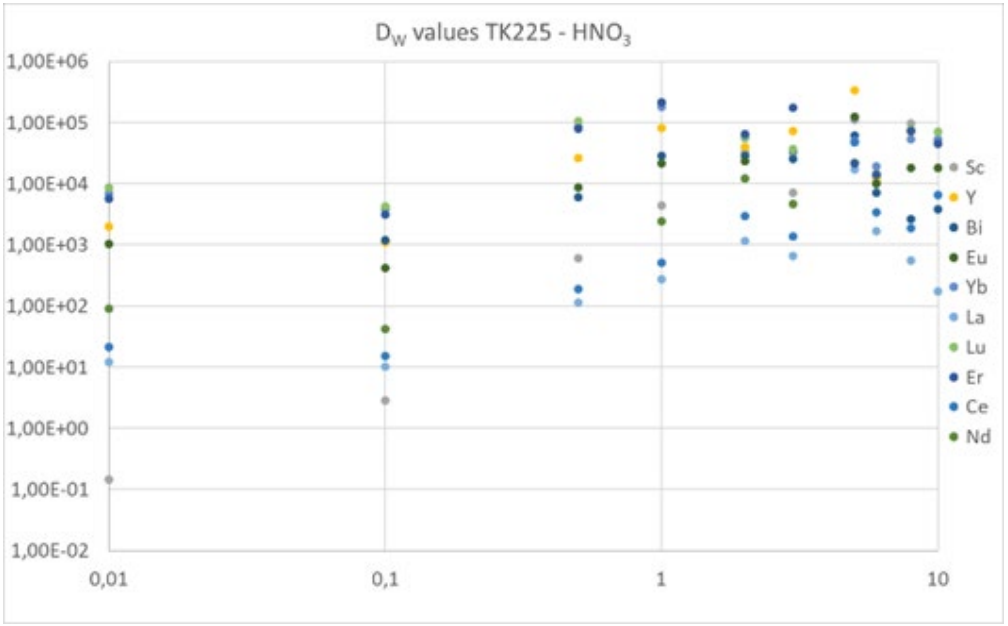
TK225 Resin

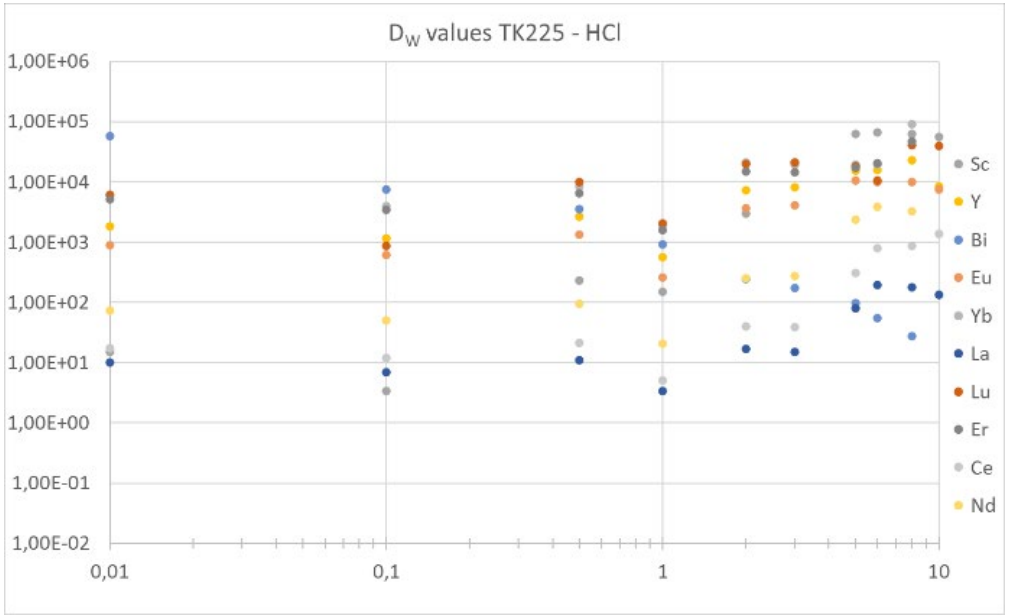
TO-DGA plus ionic liquid => originally failed experiment

Very high retention of lanthanides at medium to high acid

Especially heavy lanthanides also very well retained at low acid concentrations

Main application: Removal of radiolanthanides from effluents





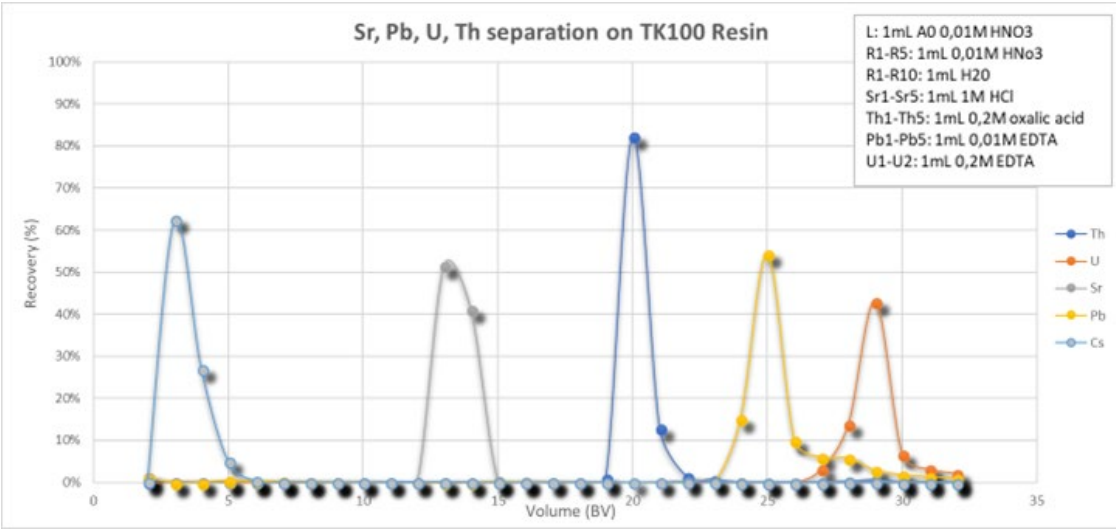
TK100/1

- In case Ra needs to be purified on-column (e.g. dissolved Ra needles)
  - Use of TK101 for Ra retention / purification => test against Chelex, CEX, TK100
- TK100: HDEHP facilitates phase transfer at dilute HNO_3 but also extracts various elements
  - High Ra/Ba retention from dilute HCl / HNO_3
  - preconcentration and sequential separation of U, Th, Pb, Sr, Ba, Ra on-going
- TK101 => similar to TK100 but ionic liquid replaces HDEHP

  Both based on same crownether as SR Resin

  TK100 developed for Sr and Pb uptake also between pH 2 and 7 (DGT)

  ⇒ Wagner et al. TK100 discs



- Replacing HDEHP by ionic liquid (=> TK101 Resin) allows for retention of Pb, Sr, Ba, Ra,… form pH 2 – 7 without extensive extraction of other elements

Ra purification / recycling

Needles and other Ra sources often contain Pt, Ir, Au, Ba besides Ra.

Ra generally present as $RaSO_4$

Suggestion: Work-up following Matyskin et al.

Destruction of the needle, generally cutting (higher losses) or dissolution in aqua regia

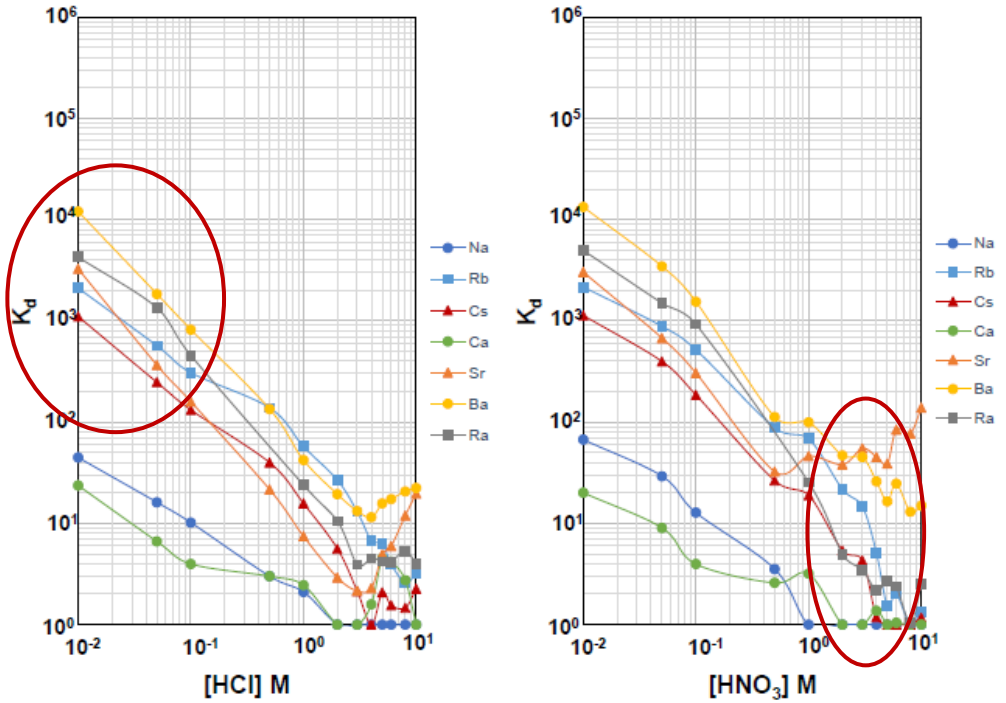
Conversion of $Ra(Ba)SO_4$ via heating with Na_2CO_3 solution

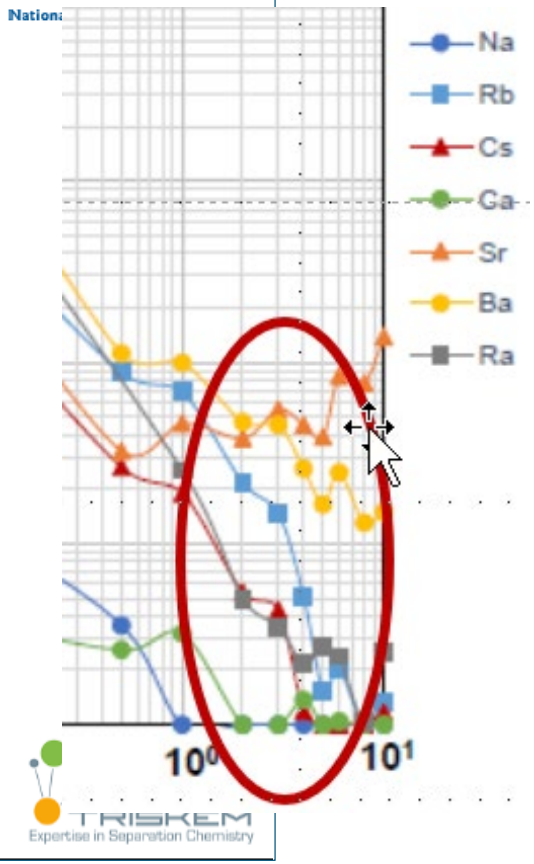
- $RaCO_3$ recovered as solid
- Soluble in dilute acid => dilute HNO_3 final acidity <0.1M HNO_3
- Alternative: EDTA => use of e.g. AC Resin to pull Ra out of EDTA at pH4

Ra purification on TK101/2 possible

TK101 - Radium

TK101 Group 1 and 2

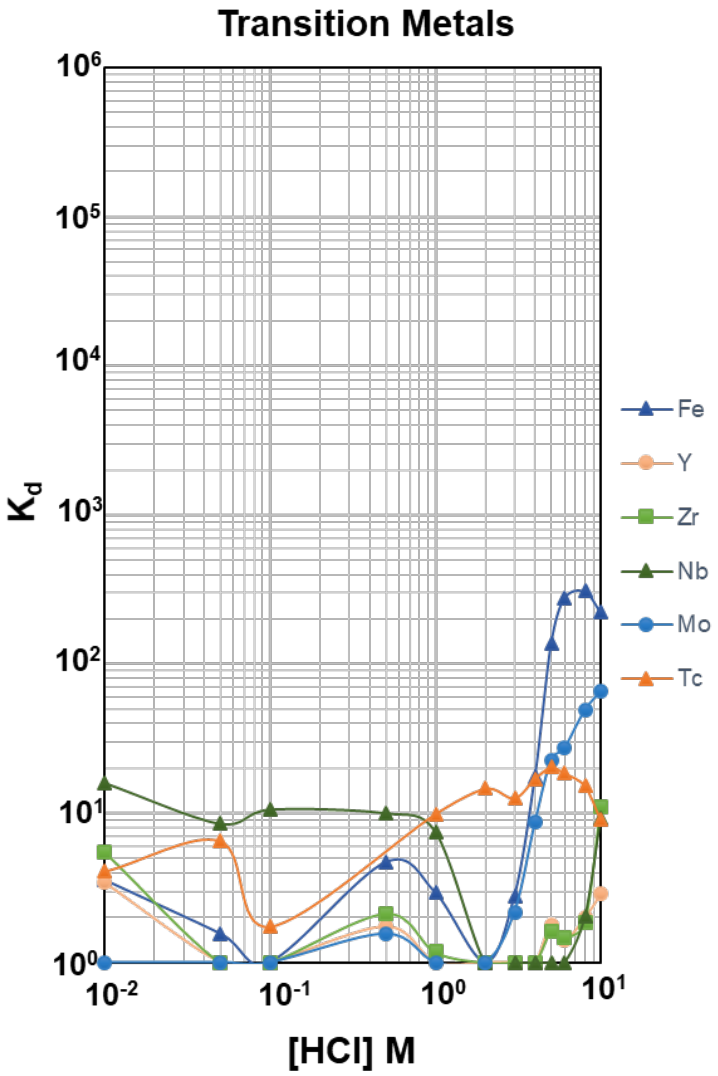


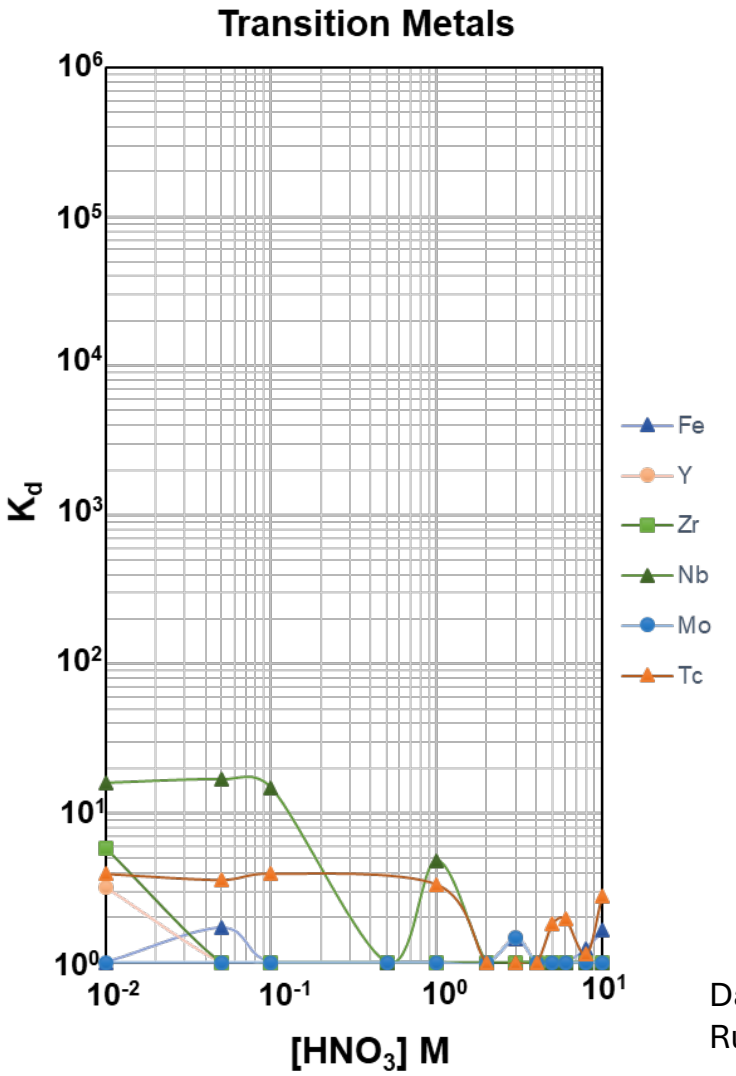


Data provided by Russel et al. (NPL)

- Ra retention from water/dilute acid up to ~0.5M HNO_3/HCl
- At higher conc. selectivity closer to SR Resin/TK102 Resin

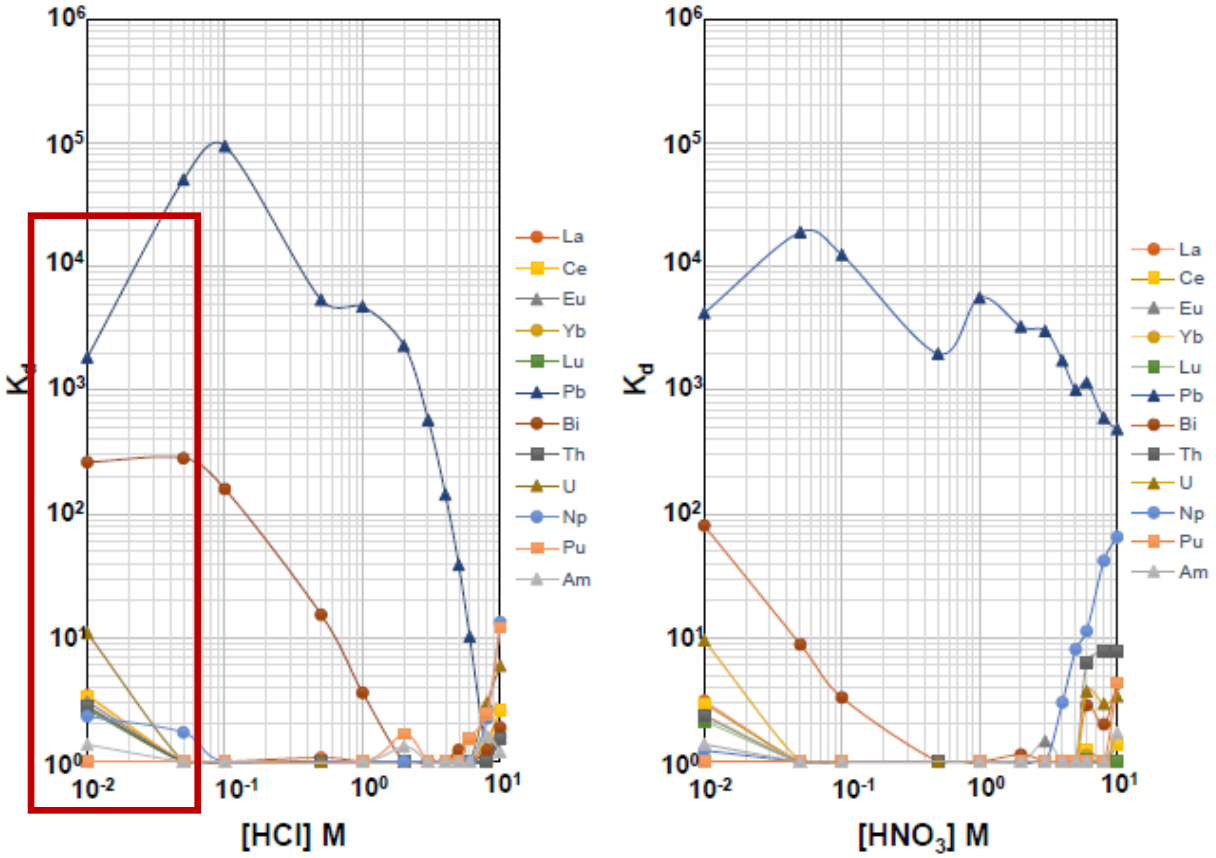
TK101 Transition Metals





Data provided by Russel et al. (NPL)

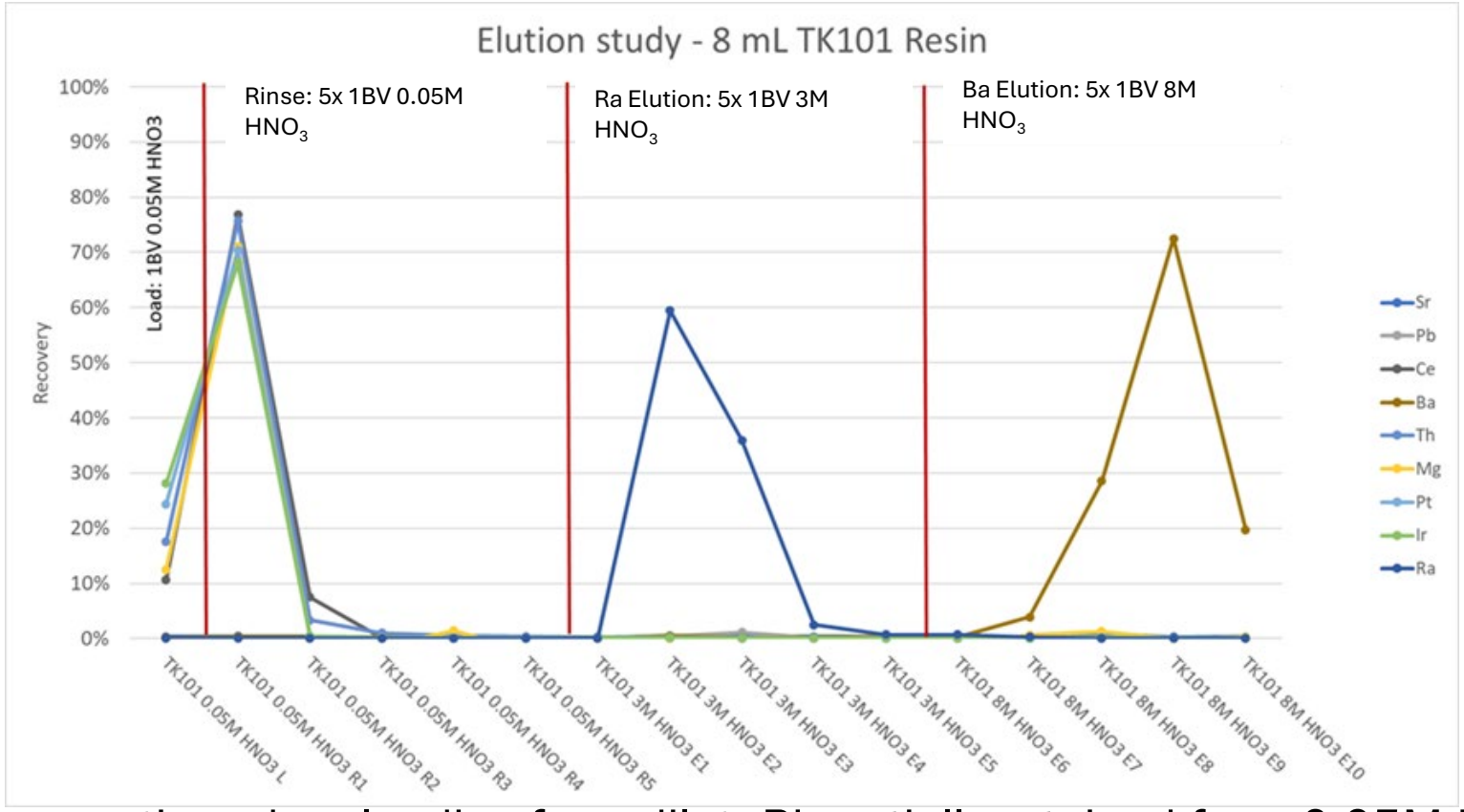
TK101 - Ra



Data provided by Russel et al. (NPL)

- No / extremely low selectivity for Th/U
- Very strong Pb retention => elution in high HCl or citrate

Ra separation on TK101



Good Ra separation when loading from dilute HNO_3/HCl

When eluting Ra in 3M HNO_3, Ba, Pb, Sr remain retained

No retention of U, Th, Pt, Ir,...

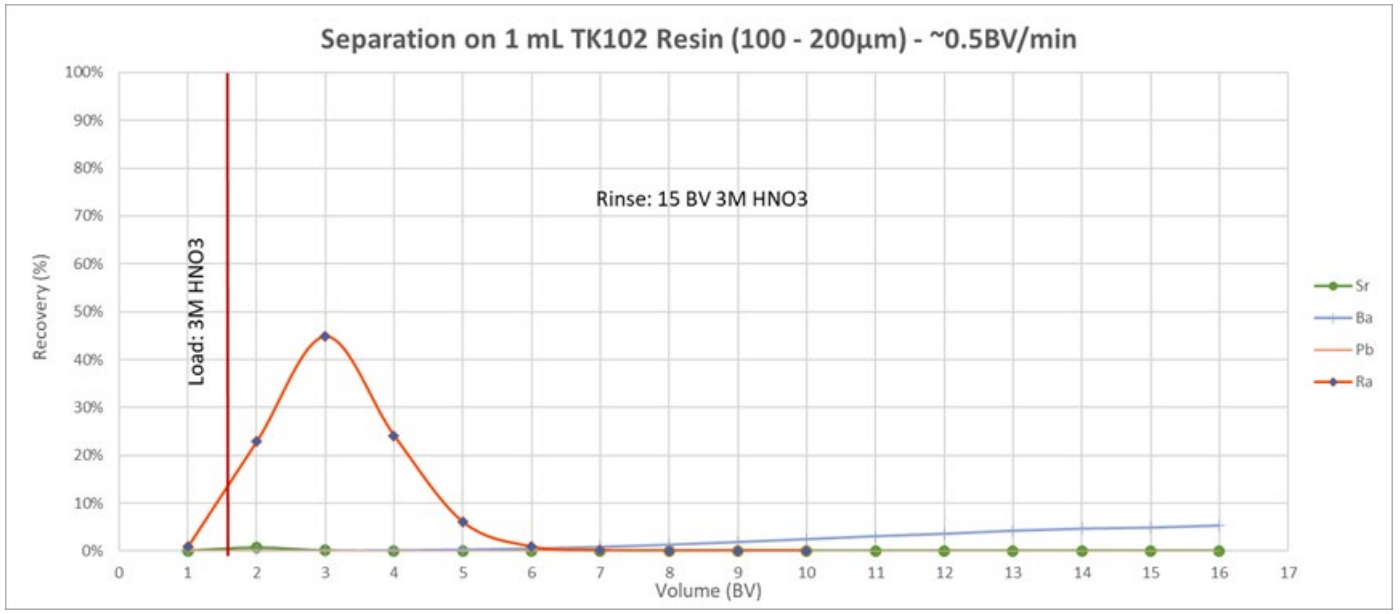
Bi partially retained from 0.05M HNO_3/HCl

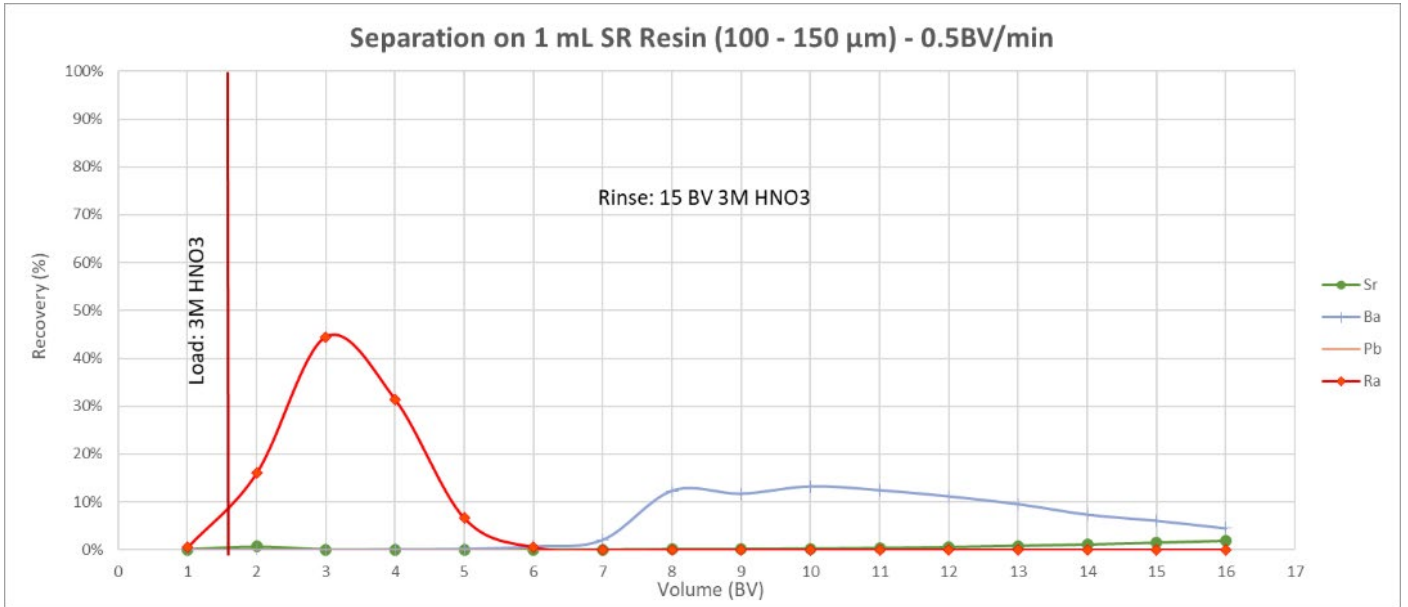
Ra eluted in 3M HNO_3

Further Ba removal via TK102 possible

Tl and Ba eluted in 8M HNO_3

TK102 - Ra purification / recycling

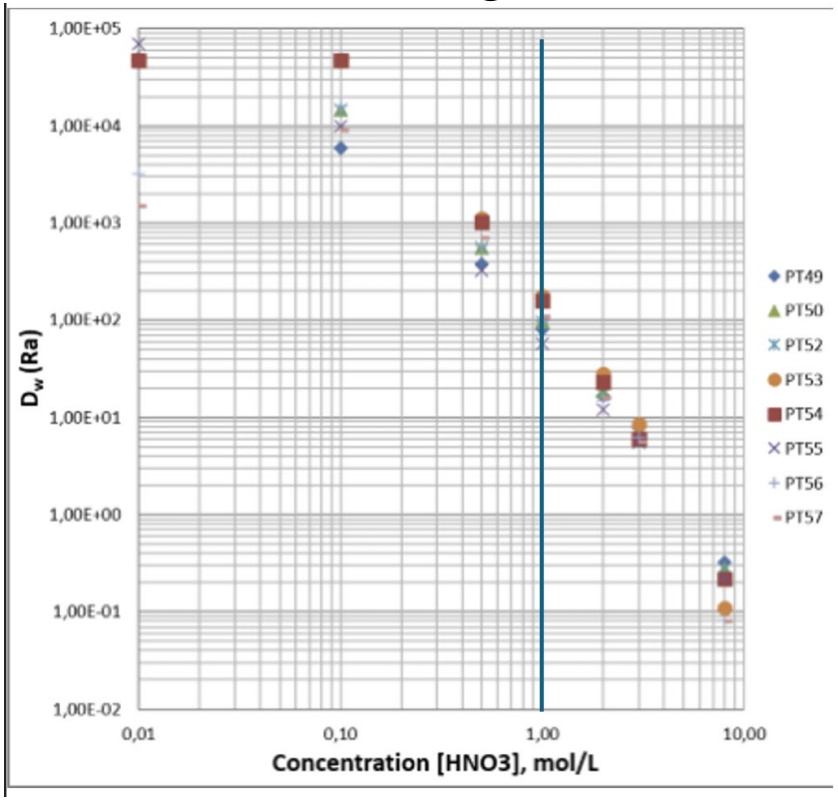




- SR Resin: high Ba breakthrough starts after 7 – 8 bed volumes
- TK102 Resin: significantly lower Ba breakthrough
- TK102 shows less bleeding than SR Resin

Under development: TK103 Resin

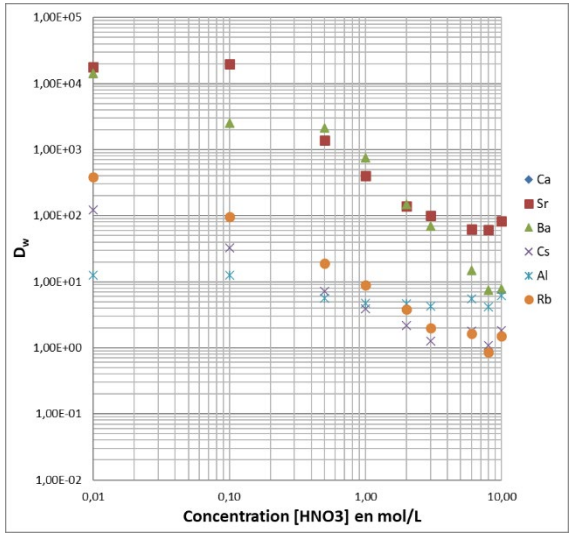
Several PT being tested



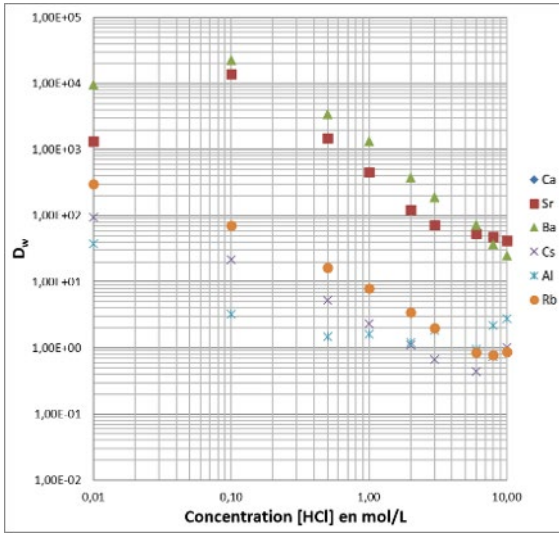
Ra Dw values PT under testing, HNO_3

Improved Ra retention at 1M HNO_3 compared to TK101 Resin

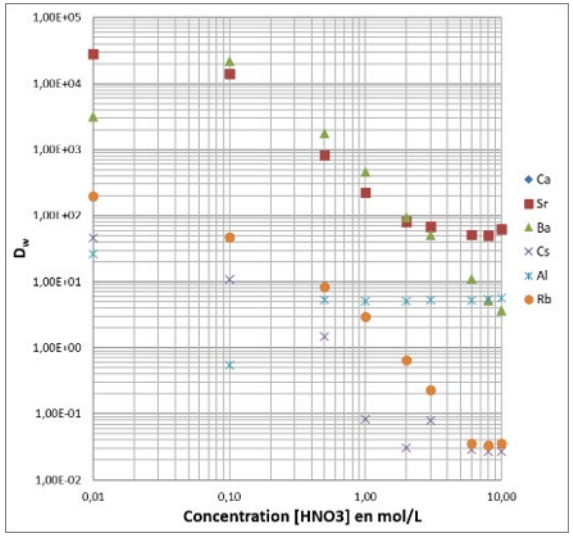
2 PT under further testing (PT 52 and 56), one containing a fluorinated compound, the other does not



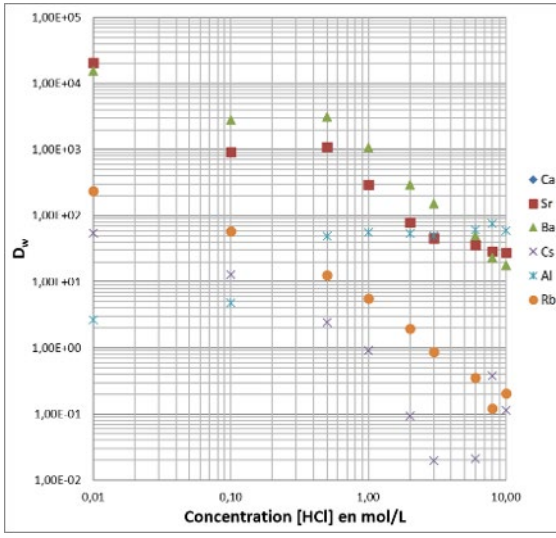
Dw values PT52, HNO_3



Dw values PT52, HCl

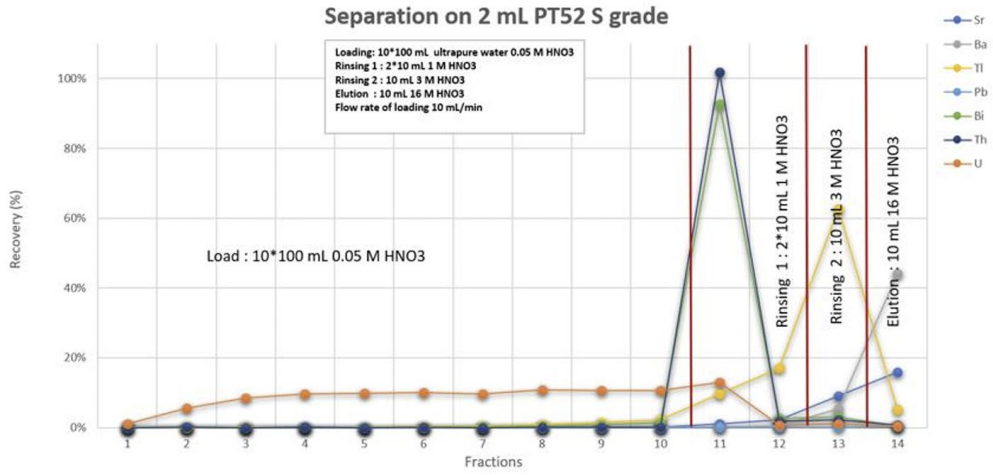


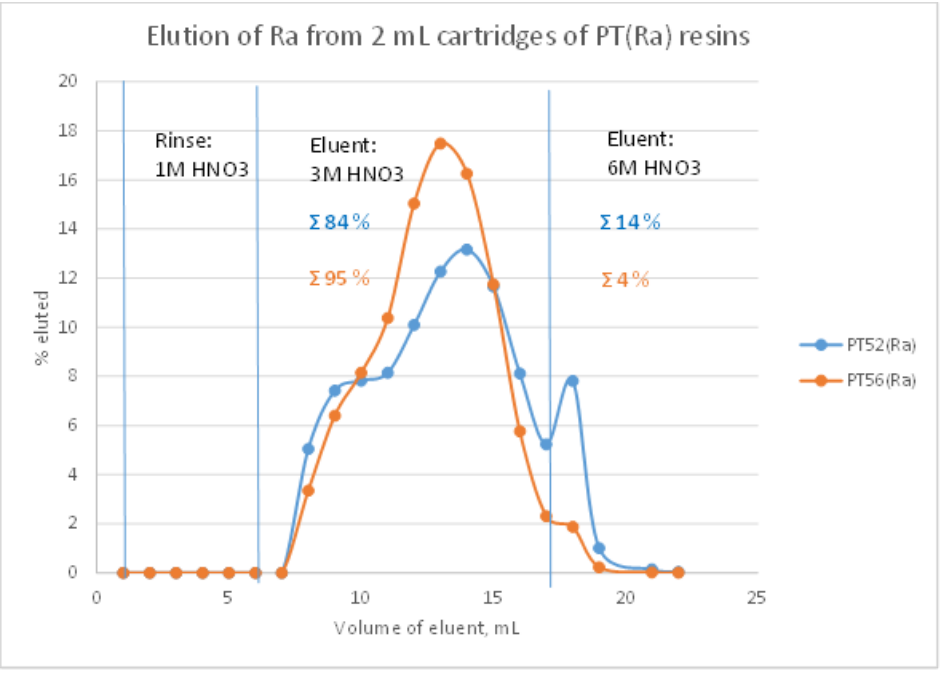
Dw values PT56, HNO_3

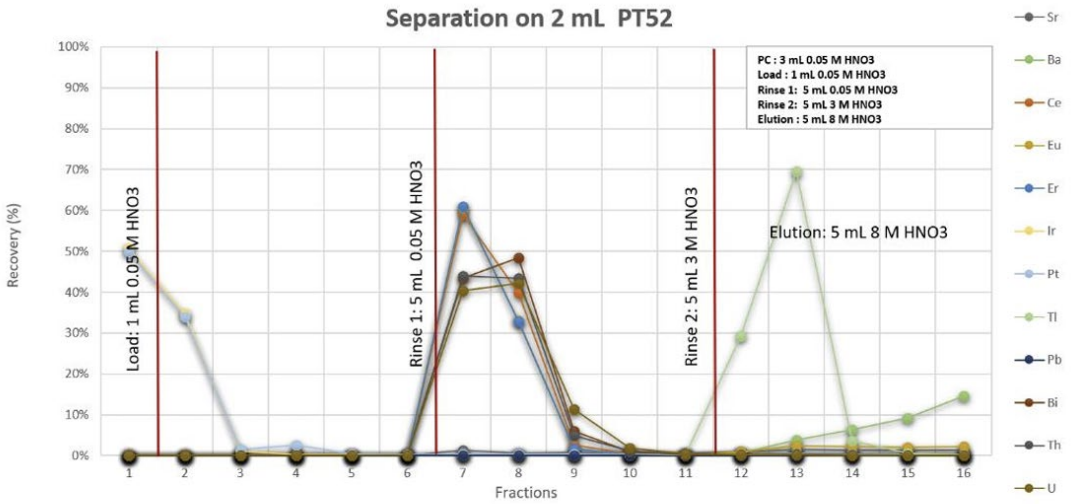


Dw values PT56, HCl

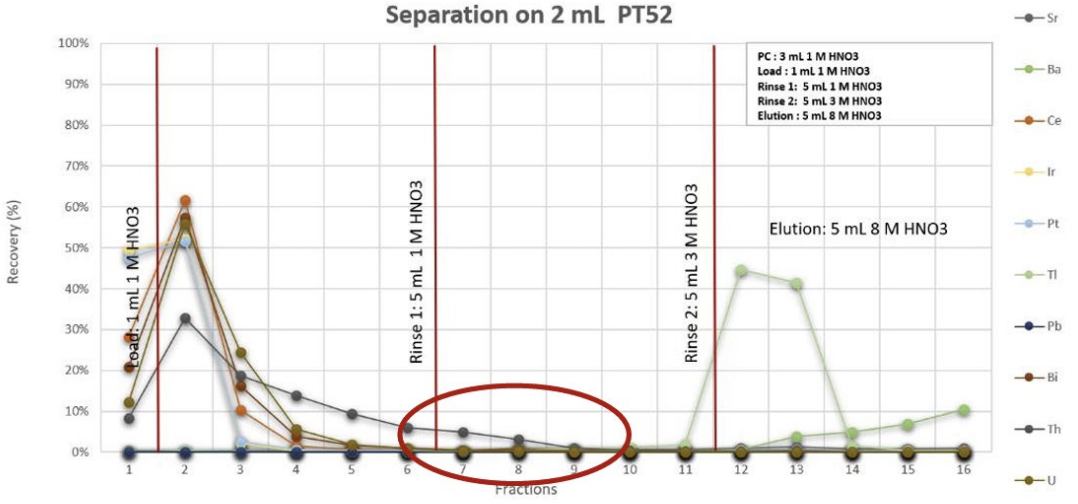
TK103 Resin – elutions studies







PT52



PT52

TK103 Resin

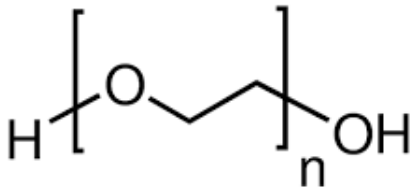
- Choice between 2 PT, probably PT w/o fluorinated compound
  - With fluorinated compound better Ra retention in 1M HNO_3
  - But elution in 3M HNO_3 less sharp
  - PFAS…
  - No difference in selectivity
- Ra uptake from dilute acid to 1M HNO_3
- 1M HNO_3 better than TK101
- High Sr uptake even in low to medium HCl
- In dilute acid it is possible to load 1L of water through a 2mL cartridge
- In dilute acid several RN retained, rince with 1M HNO_3 for RN removal (special attention to Th)
- Ra elution in 10 - 15mL 3M HNO_3 (sharper in higher HNO_3)
- Ba elution requires conc HNO_3 or complexant (e.g. EDTA)
- Next step: TK103 Disc and real samples

Tc-99m - TK202 Resin

Based on Polyethylene Glycol (PEG)

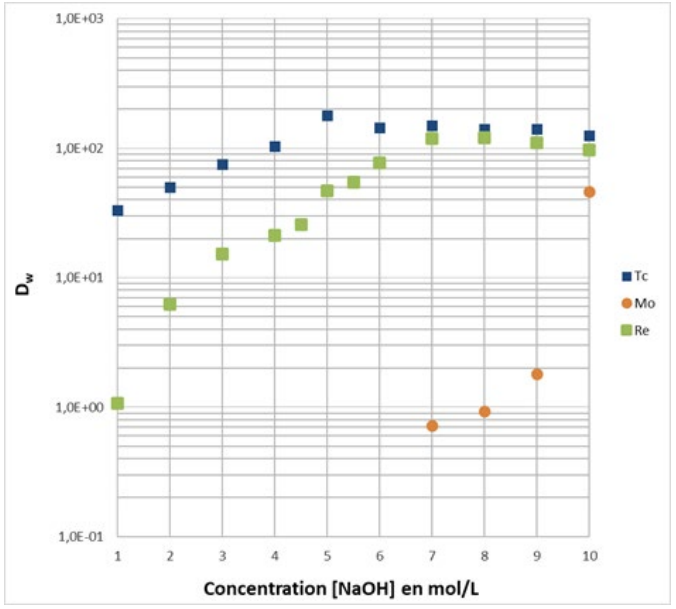
Less swelling/shrinking than crosslinked PEG

Aqueous Biphasic System (ABS)

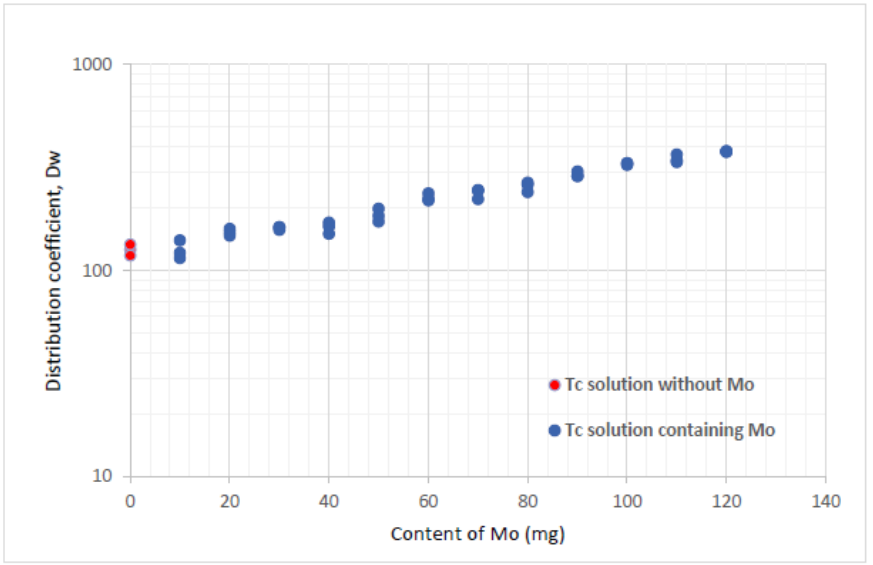


Retention of chaotrophic anions like TcO_4^- in presence of kosmotrophic anions (SO_4^{2-}, CO_3^{2-}, OH^-, MoO_4^{2-},…)

- Separation of Tc-99m from high masses of Mo
- Separation of Re from W (and Ta) possible, too

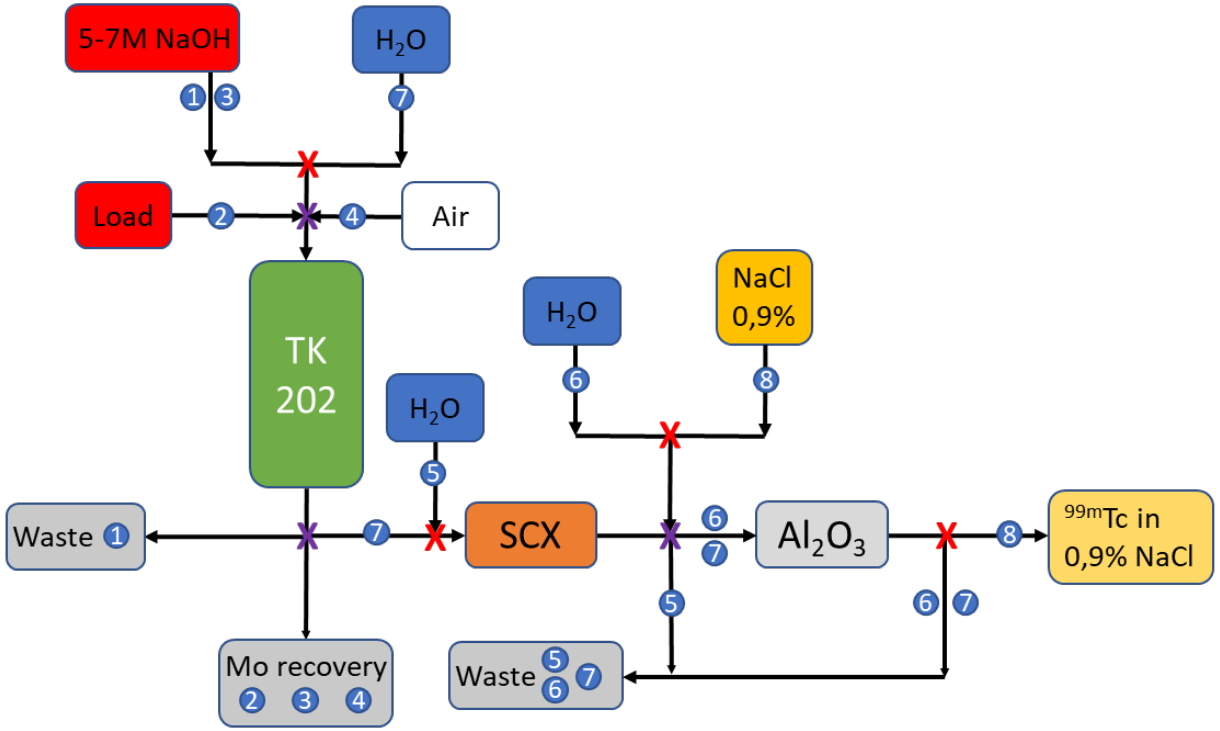


Dw values for Tc, Re and Mo on TK202 Resin, at varying NaOH concentrations. Tc data taken from Cieszykowska et al.(2).



Dw values for Tc in 5M NaOH using 40 mg TK202 Resin, increasing amounts of Mo. Data taken from Cieszykowska et

Tc-99m separation from Mo targets – suggested scheme (similar to Zeisler et al.)



1. Pre-cond. TK202 – 5-7M NaOH ➔ alkaline waste
2. Load Mo/Tc on TK202 ➔ Mo recovery
3. Rinse TK202 – 5-7M NaOH ➔ Mo recovery
4. Purge TK202 – Air ➔ Mo recovery
5. Pre-cond. SCX – HCl then H_2O ➔ Aq. waste
6. Pre-cond. Al_2O_3 – H_2O ➔ Aq. waste
7. Elute Tc from TK202 on SCX and load on Al_2O_3 – H_2O
8. Elute Tc from Al_2O_3 – NaCl 0,9% ➔ Tc recovery

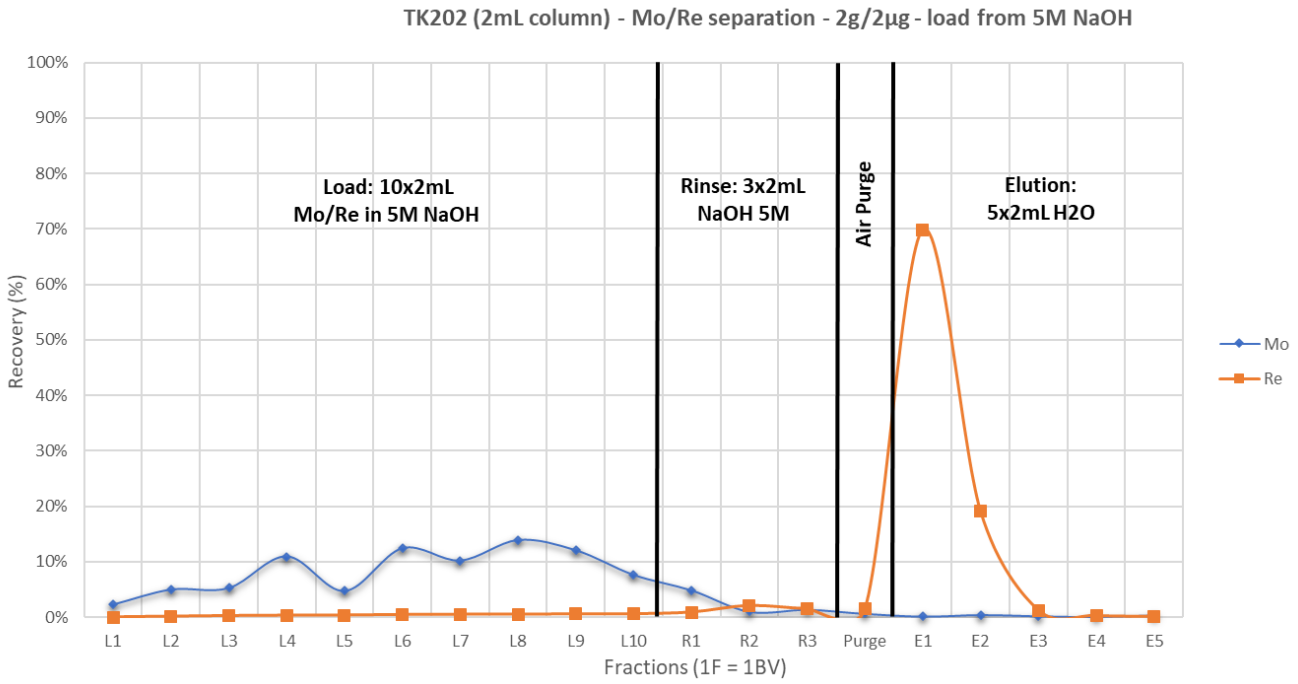
TK202 : 35-75 or 75-150µm
X : 3-ways valve
X : 4-ways valve
SCX : Strong Cation Exchange
Al_2O_3 : Acidic Alumina

Developed with ReO_4^- as TcO_4^- surrogate

Re recovered on saline solution from alkaline

Separation with 2g Mo ➔ From 20mL to 2mL
Separation with 200g Mo ➔ From 3L to 20mL

Tc-99m via cyclotron route

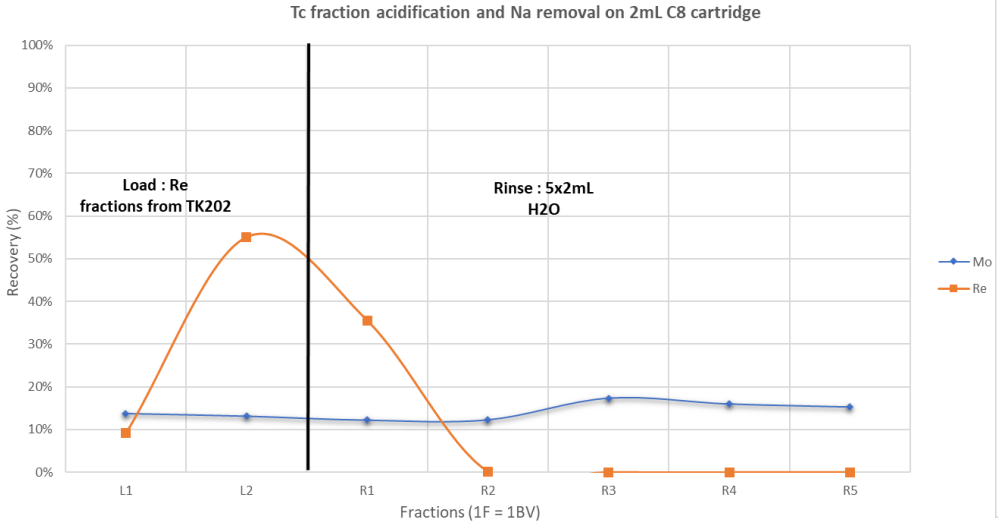


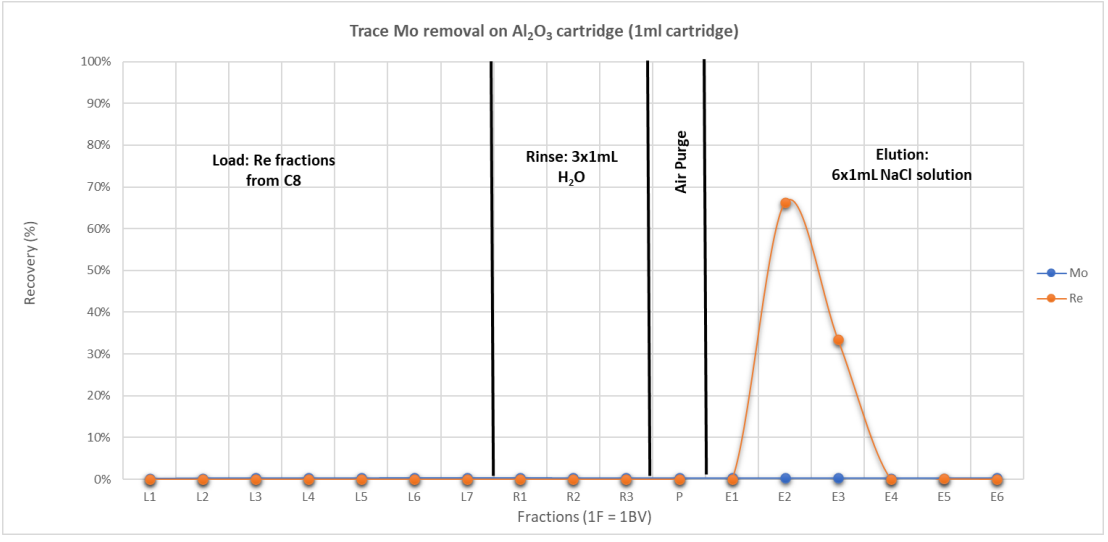
Tests performed cold with 2g Mo and 2 µg Re

- 2 mL TK202 cartridge
- 2 mL C8 cartridge
- 1 mL AlOxA cartridge

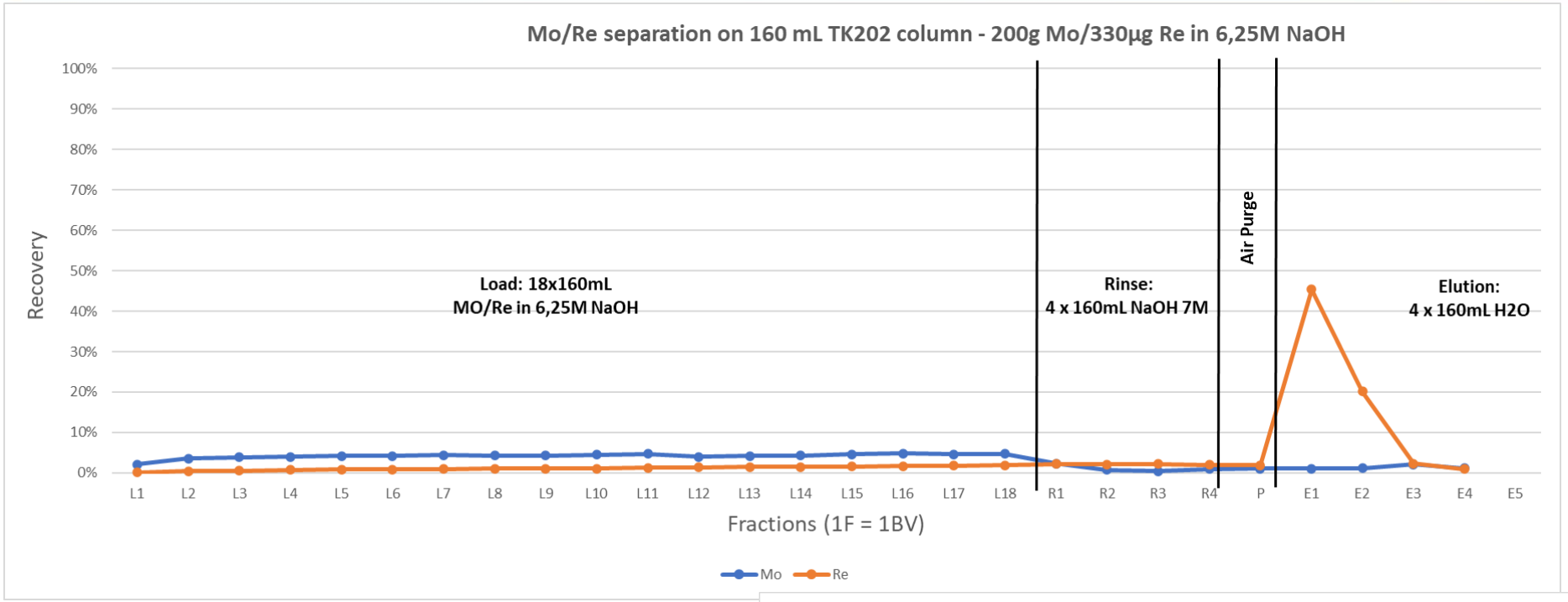
Method similar to Zeisler et al.

High Re yield (~90%) in 2 – 3 mL 0.9% NaCl solution





Tc-99m from large Mo targets



Test with 200g Mo

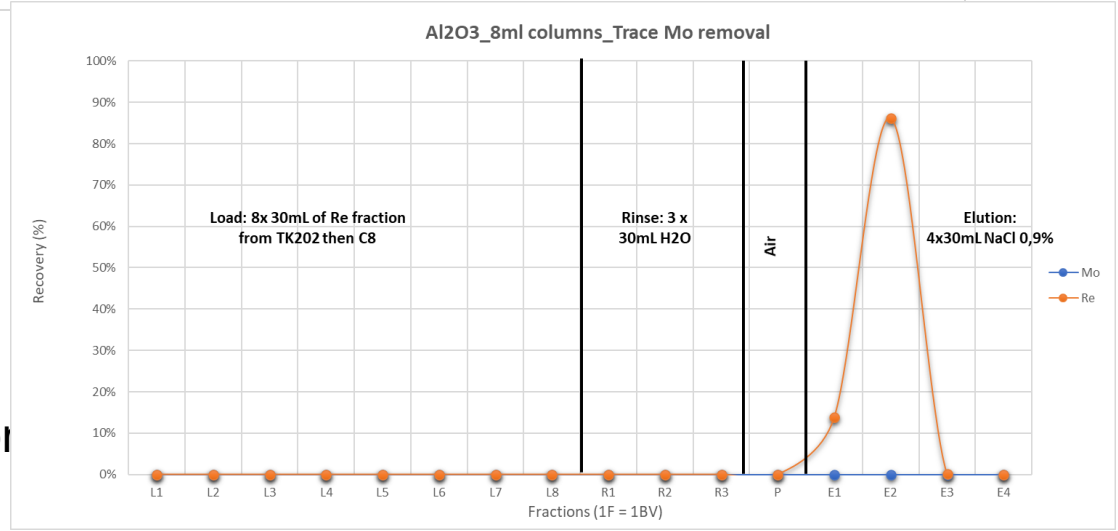
~160 mL TK202 column

Load from 6 - 7M NaOH - elution in water

Pass through C8 cartridge for acidification and Na removal

Final concentration/conversion to 0.9% NaCl or

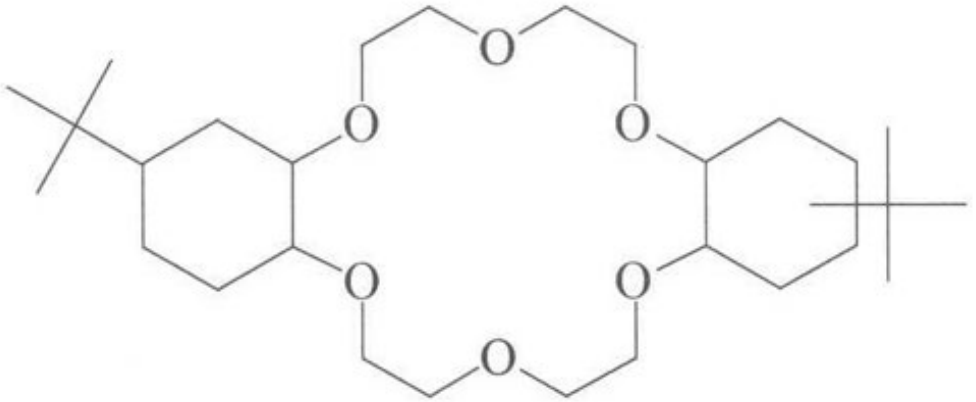
8 mL AlOxA cartridge



Pb-212

- Several fabrication paths
- Generator approach e.g. OranoMed (US patent) from Th:
  - Ra-228 retention from Th nitrate via Ra selective resin
  - Th-228 retention from eluate via e.g. DGA Resin
    - Alternatives: TK221, TK200, UTEVA, LN,… some with higher radiation stability
    - Elution of Ra-224
  - Preparation of Ra-224/Pb-212 generator (CEX)
    - Elution in 2M HCl onto PB Resin => elution in acetate solution
    - Radiomedix: use of TK201 instead of PB Resin
  - Alternative: direct Pb-212 extraction via PB Resin
- Direct extraction form Ra or Th via PB Resin e.g. Perspective (US patent):
  - Typically PB Resin for direct retention of Pb-212 from Th-228
  - Nowadays several suppliers of Th-228 (e.g. DOE)
  - Followed by WEX
- Rn generator
  - Source: Th-228
  - Capture of emanated Rn-220
  - Final purification e.g. on PB Resin

PB Resin



Extractant: 0.75M crown-ether (same crown ether as in SR Resin)

Diluent: Isodecanol

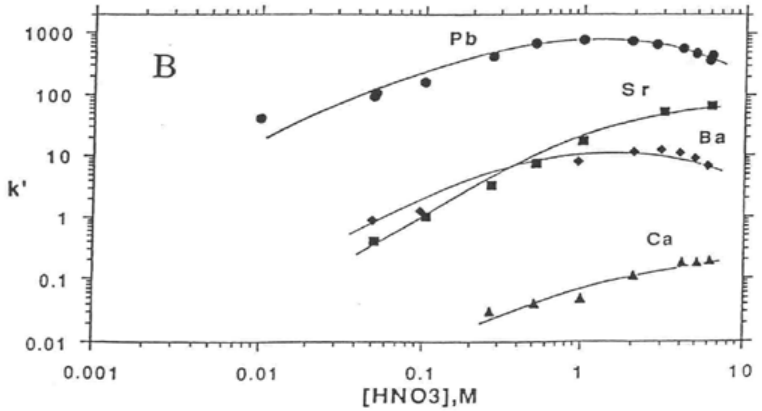
(longer carbonated chain for easier removal of Pb)

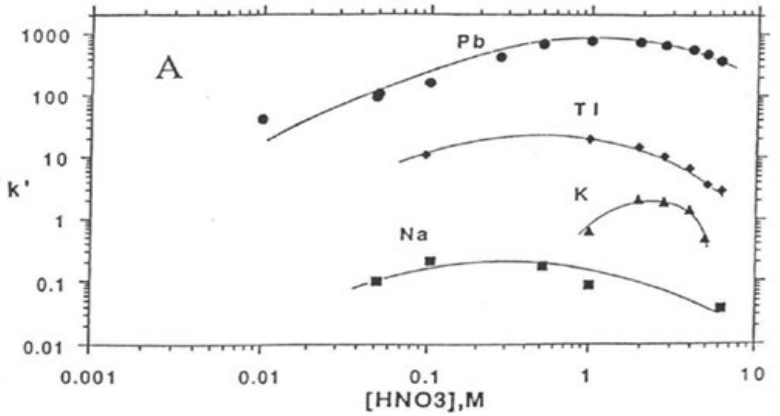
- **Pb capacity:** 29 $mg.g^{-1}$ PB resin (lower than SR Resin)
  Main application: Pb-210 in water

Less bleeding than SR Resin (lower solubility of Isodecanol in aqueous solutions)

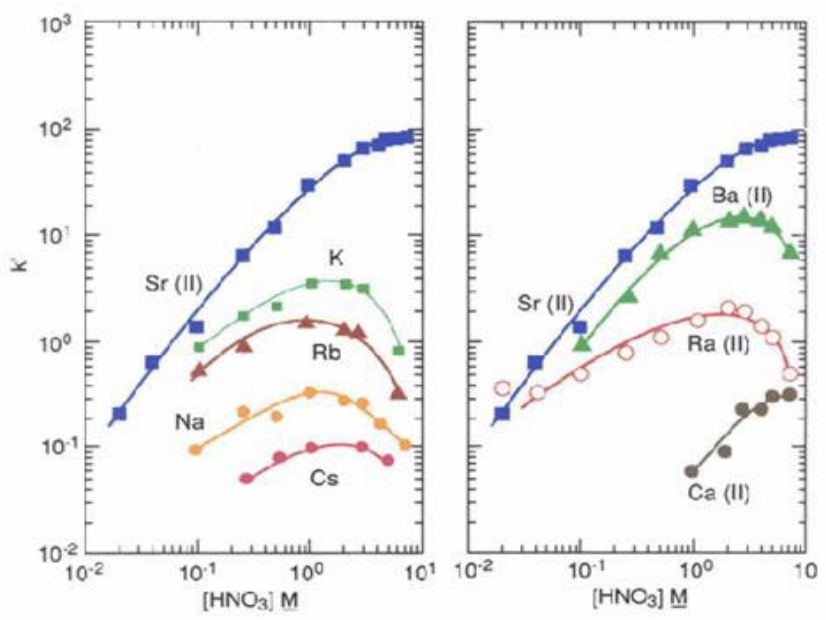
Comparison PB vs SR

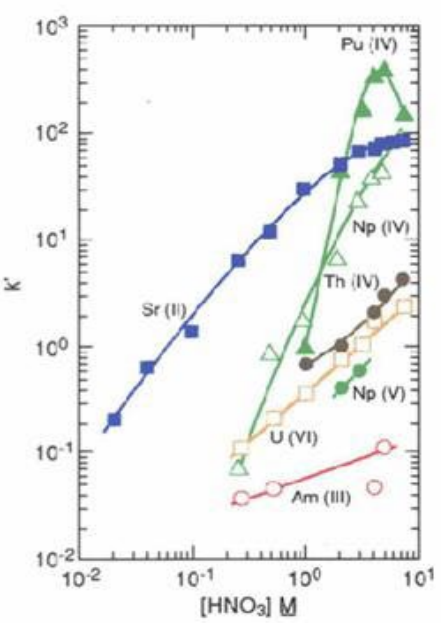
Dw values PB Resin:

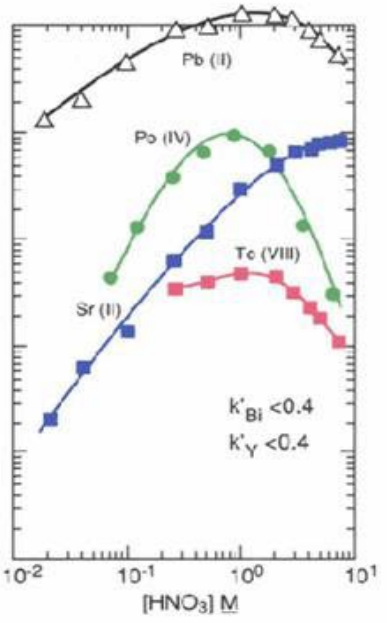




- Dw values SR Resin:







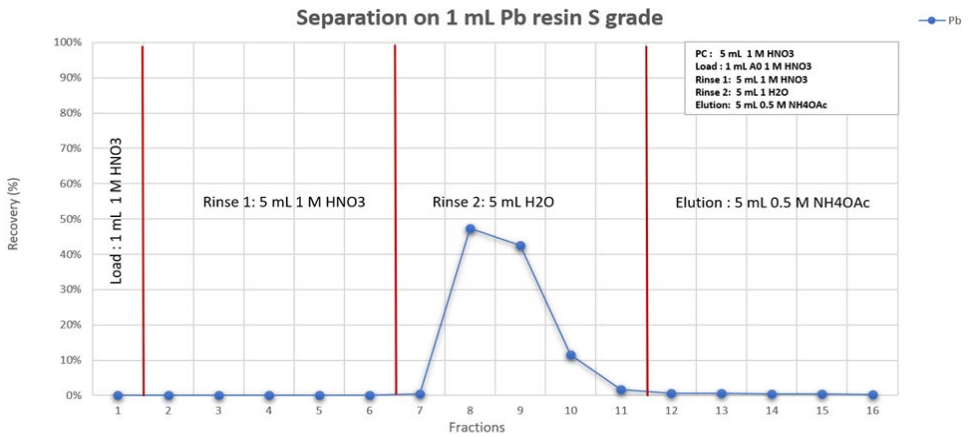
Differences SR and PB Resin

PB Resin:

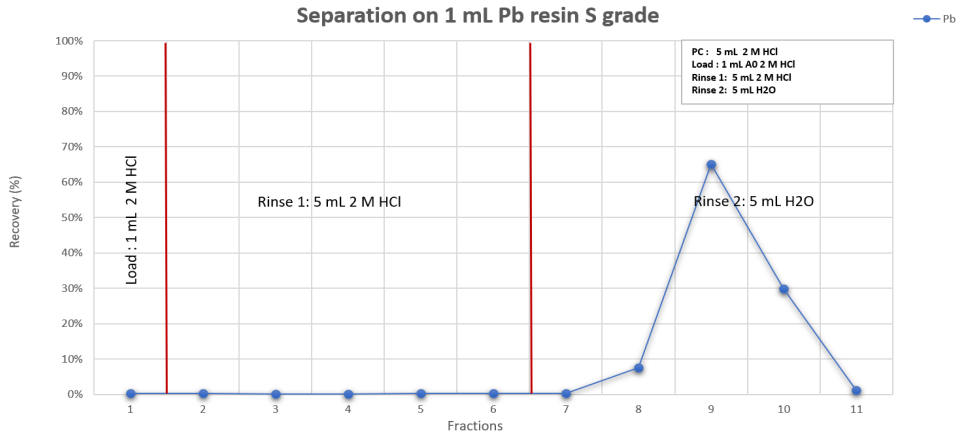
- Lower concentration (and thus amount) of crown-ether
- Use of isodecanol instead of octanol
  - Horwitz et al showed that solutions of crown-ether in alcohols with longer chains show lower Dw
  - Shorter-chain + fluorinated alcohol (TK102 Resin) => higher retention than SR Resin
  - Less bleeding
- Deliberate choice:
  - Pb retention on PB Resin remains high
  - PB Resin allows Pb elution in water or aceate

On-going: TK104 Resin

TK104 Resin

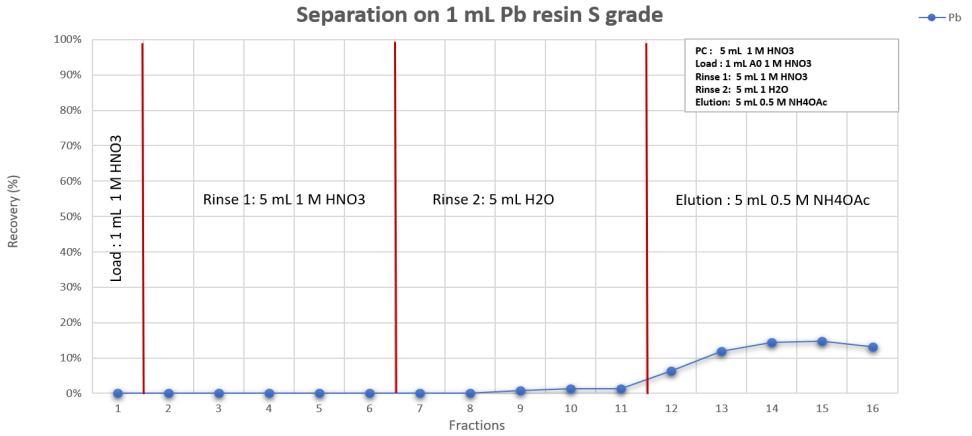


Elution on 1 mL RDPBS261001

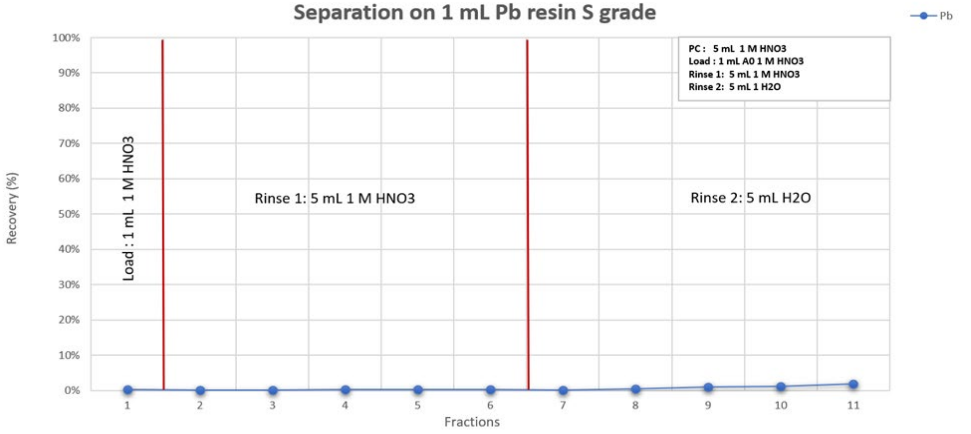


RDPbS261013 = same composition as RDPBS26101 (upscale)

PB Resin



Elution on 1 mL FPBS240522



Elution on 1 mL FPbS240522.

Pb-212 - QC

- Generally check for Th-228 and Ra-224
- Frequently alpha spec
- Th-228
  - Th separation on e.g. TEVA/TRU, TK200, TK201,…
  - Sample prep via microprecipitation
  - Yield often via Th-230, may be Th-229
  - Ongoing work: use of Discs
    - Separation and sample prep for alpha spec in one step (TK-GA Discs, TK221 Discs or TK201 Discs)
- Ra-224
  - Combined with Th: use of TEVA/TRU (Th retention) and SR (Pb-212 retention)
  - Microprecipitation of eluates with $BaSO_4$ for alpha spec
  - Yield mainly Ba-133, may be Ra-225 (rare)
  - Ongoing: combination of TK102 and Discs (e.g. TK103 Disc)

At-211

- Requests for cartridge based separation of At from Bi targets in HNO_3. Resin approach already used by Burns et al. (3-octanone)
- Eriksen et al. showed At separation from Bi possible in HNO_3 via LLX using Octanol (=> TK400 Resin)
- Tereshatov et al. tested several extraction chromatographic resins for At separation from Bi incl. TK400
- At elution via alcohol (removal of org. phase + At from resin)
- TK400 and five additional resins currently being tested ("TK401" - "TK404", TK200) – standard and new support => improvements possible?
    - Gagnon et al. PEG Resin (=> TK202?)
- Elution via NaOH possible?
- At still active in labelling reactions?
- Currently shipping samples
- Also working on resins for Rn-211/At-211 gen.



DGA Sheets

TO-DGA (normal DGA) and TEH-DGA (branched DGA) impregnated Whatman TLC paper

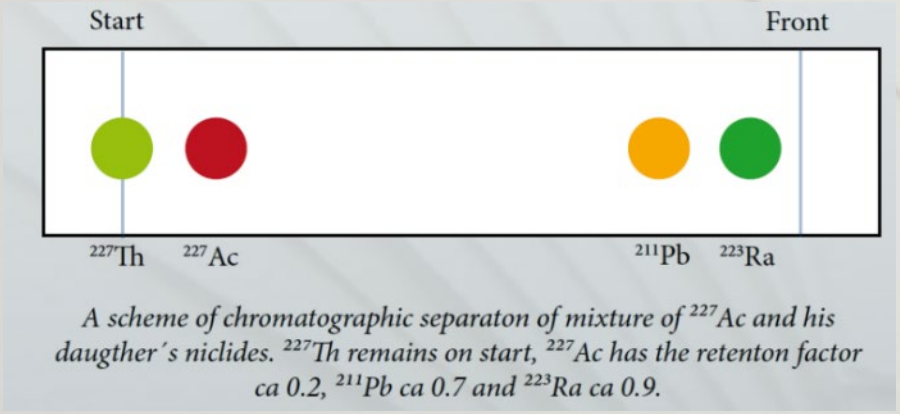
- Developed at CVUT (Kozempel et al.)
- Now also iTLC based (iSheets)

QC of radionuclides and generator eluents

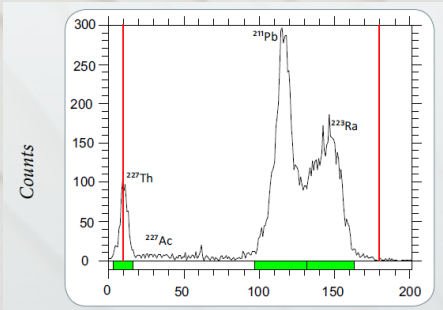
(p.ex. Ra-223, Ac-225/Bi-213, Pb-212, Ge-68/Ga-68 …)

- TLC scanner or radiometer/LSC or HPGe after cutting

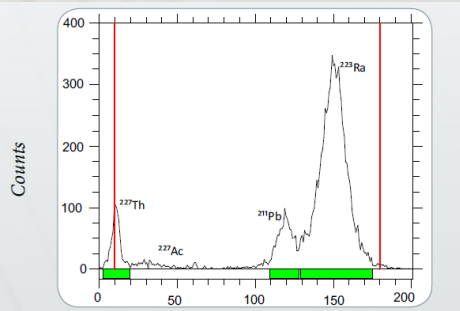
Run under acidic conditions => radionuclidic purity



A scheme of chromatographic separaton of mixture of ^{227}Ac and his daugther´s niclides. ^{227}Th remains on start, ^{227}Ac has the retenton factor ca 0.2, ^{211}Pb ca 0.7 and ^{223}Ra ca 0.9.



Radiochromatogram measured immediately after separaton. Low abundant radiatons of ^{227}Ac were not detected.



Radiochromatogram measured one hour afer separaton. Decay and ingrowth of ^{211}Pb is clearly visible.

More types of sheets under development (selectivities, geometry, support)

- ZR, TK201,...
- 2D TLC for radionuclide screening ?

DGA Sheets - Ra

DGA-SHEETS technical note - Quality control of labelled Ra compounds

Radio-instant thin layer chromatography (radioTLC) can be used to assess complex formation of Ra isotopes with a stable ligand such as biologically stable radiocomplex with macropa, which can stably chelate $[^{223}Ra]Ra^{2+}$ with a radiolabelling efficiency of >95%.
The complexation is carried out at room temperature in metal-free ammonium acetate buffer (0.1 M, pH 6). Aliquots from these radiolabeling reactions were collected at various time points and analyzed by radioTLC to evaluate complex formation.
The TLC is performed using DGA impregnated TLC sheets (DGA Sheets) as the stationary phase and **0.1 M NaOH** as the mobile phase. Under these conditions, free $[^{223}Ra]Ra^{2+}$ remained at the baseline (R = 0), while the complexed species migrated with the solvent front (R = 1) [1].

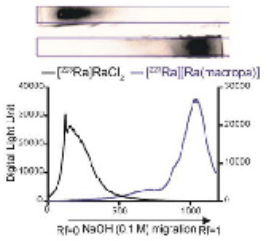


Fig. 1 Formation of $[^{223}Ra][Ra(macropa)]$ under migration of $[^{223}Ra]RaCl_2$ (top) and $[^{223}Ra][Ra(macropa)]$ (bottom) on DGA-coated chromatographic strips. [1]

Buffered solutions

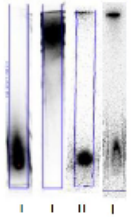


Fig. 2 TLC autoradiographic readings of $[^{223}Ra][Ra(macropa)]$ (10 mM), DOTA (10 mM) and EDTA (5mM) migrated on DGA-coated TLC using a NaOH (0.1 M) mobile phase.
I. $[^{223}Ra]RaCl_2$ migration (Rf≈0)
II. $[^{223}Ra][Ra(macropa)]$ (Rf ≈ 1)
III. ^{223}Ra tentatively chelated with DOTA showing unsuccessful radiolabeling (85% remained unchelated)
IV. ^{223}Ra partially chelated with EDTA (65% remained unchelated). [1]

Serum

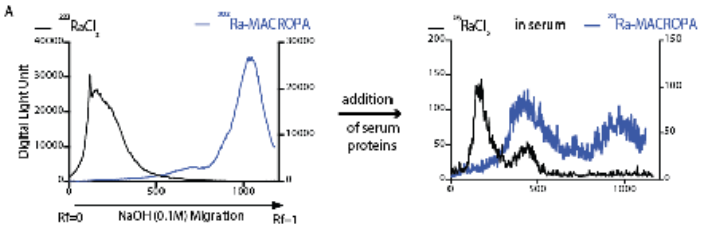


Fig. 3 TLC profiles of pure $[^{223/224}Ra]RaCl_2$ and labeled macropa in PBS (left) and in human serum (right). $[^{223}Ra]RaCl_2$ (black trace) and $[^{223}Ra][Ra(macropa)]$ (blue trace) mixed in serum were poorly separated, questioning the suitability of the DGA sheets to detect Ra decomplexation in serum. Weak ionic interactions of $[^{223}Ra]Ra^{2+}$ or $[^{223}Ra][Ra(macropa)]$ with proteins may occur and result in the inability of TLC to clearly separate each species. [1]

[1] Abou, D. S., Thiele, N. A., et al (2021). Towards the stable chelation of radium for biomedical applications with an 18-membered macrocyclic ligand. Chemical Science, 12, 3733-3742

TrisKem International, 3 rue des Champs Géons, 35170 BRUZ
www.triskem.com

Based on publication by Abou et al.

Free Ra vs macropa labelled Ra

0.1M NaOH

Ra remains fix (R_f=0), labelled compound moves (R_f=1)

CU iSheets

Poster presented at Terachem 2022 (Svedjehed et al.)

QC of Cu radiolabeled peptides (labeled vs free Cu)

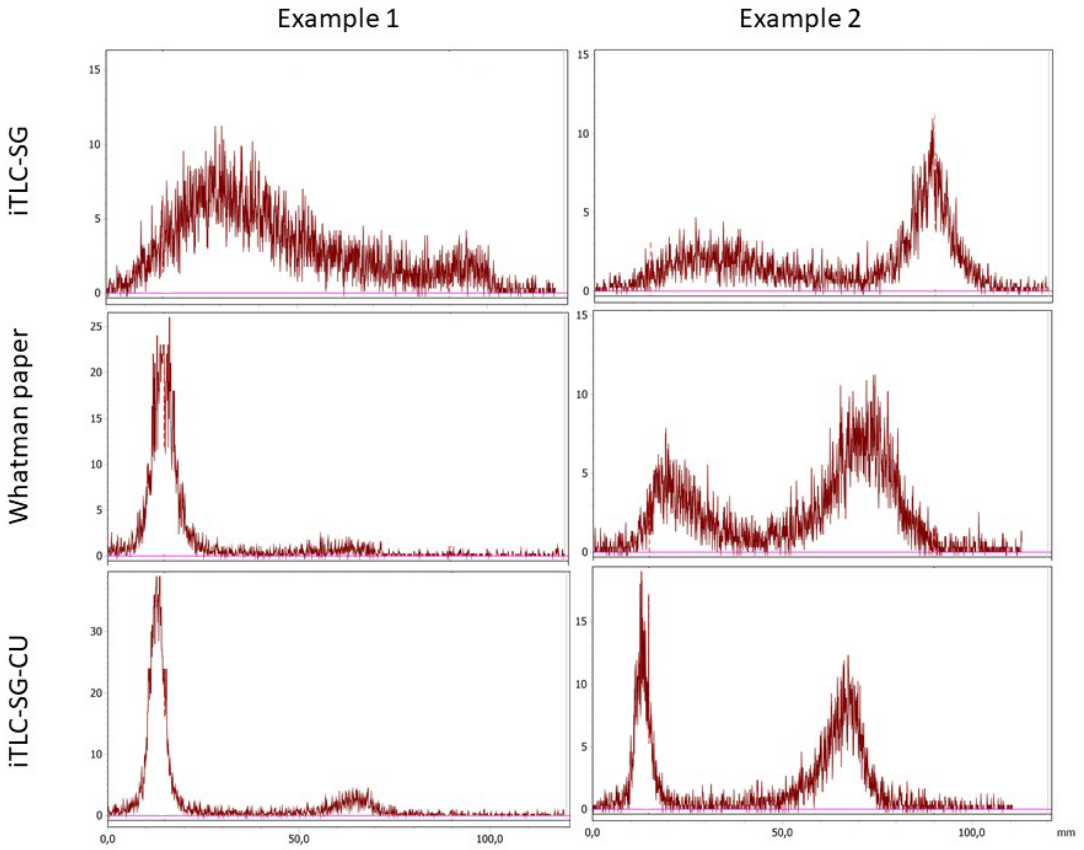
- Shown: [^{61}Cu]Cu-NOTA-octreotide

Spotting/run on three different papers after labeling:

- Whatman and iTLC without modification and
- CU extractant impregnated iTLC paper.

Both iTLC paper (impregnated/non-impregnated) developed in less than 10min, Whatmn took 25 – 30 min.

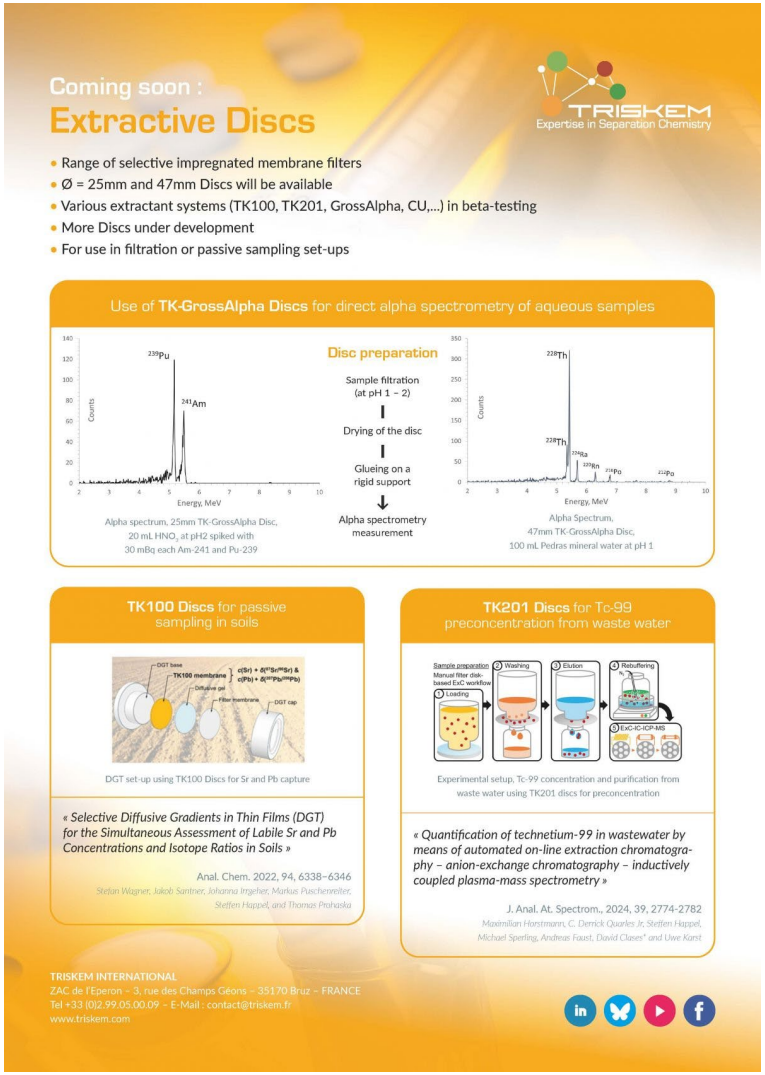
CU extractant impregnated iTLC paper showed superior resolution



- Other systems under development/testing

New/under development impregnated membrane filters

Tesmarac
joint research laboratory



Special membrane filters impregnated with extractant(s)

25mm and 47mm Discs available

Commercialized:

- TK-GA Discs (Gross Actinide)

Beta Testing:

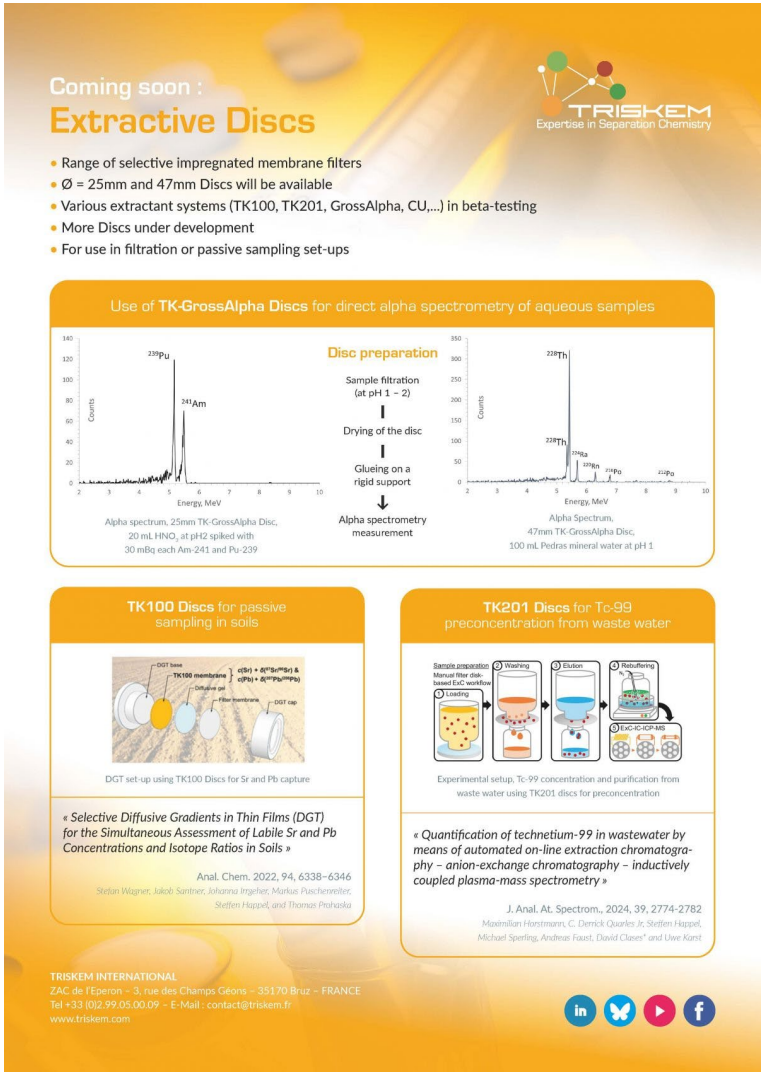
- TK100 & TK201 (both published), CU,...
- TK200 (U, Th, Pu) and TK221 (U, Th, Am, Pu) => sequentila separation (evtl. TK201 (Pu, Th) => rapid screening?
- QC of Ac-225 and Pb-212 (presence of Th, Ra,...)
- Alphaspec: Retention vs. Retention on the surface (70 - >90%)

Under development:

- TK102/TK227 - Rapid methods for Sr, TK101 (Pb, Ra),...
- TK101 – Ra separation

New/under development: impregnated membrane filters

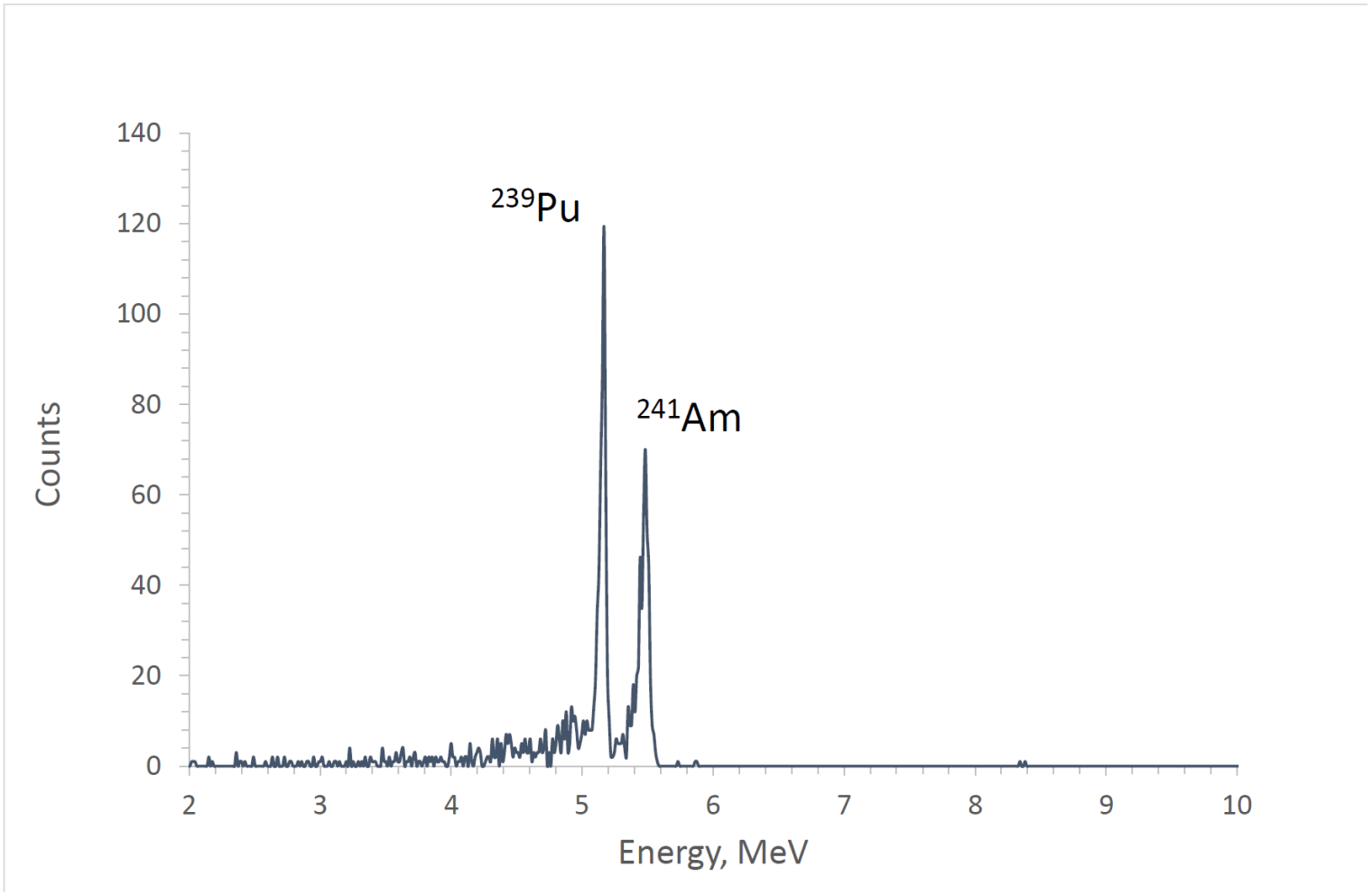
Tesmarac
joint research laboratory



Typical applications of TK-GA Disc:

- pH 1 – 2 (for some actinides up to 3M HNO_3)
- Preconditioning of the disc: 20% EtOH:water, water, then loading medium
- Loading of the sample, flow rate: 1 - 10mL/min,
- Lower flow rates seem to favor better resolution
- 25 mm Discs typically up to 100mL samples,
- 47 mm Discs typically up to 1L (higher volumes possible depending on extractant system)
- Rinse with water and 20% EtOH:water
- Drying and glueing onto steel disc => alpha spectometry.
- Optional: subsequent Alpha/Beta via LSC

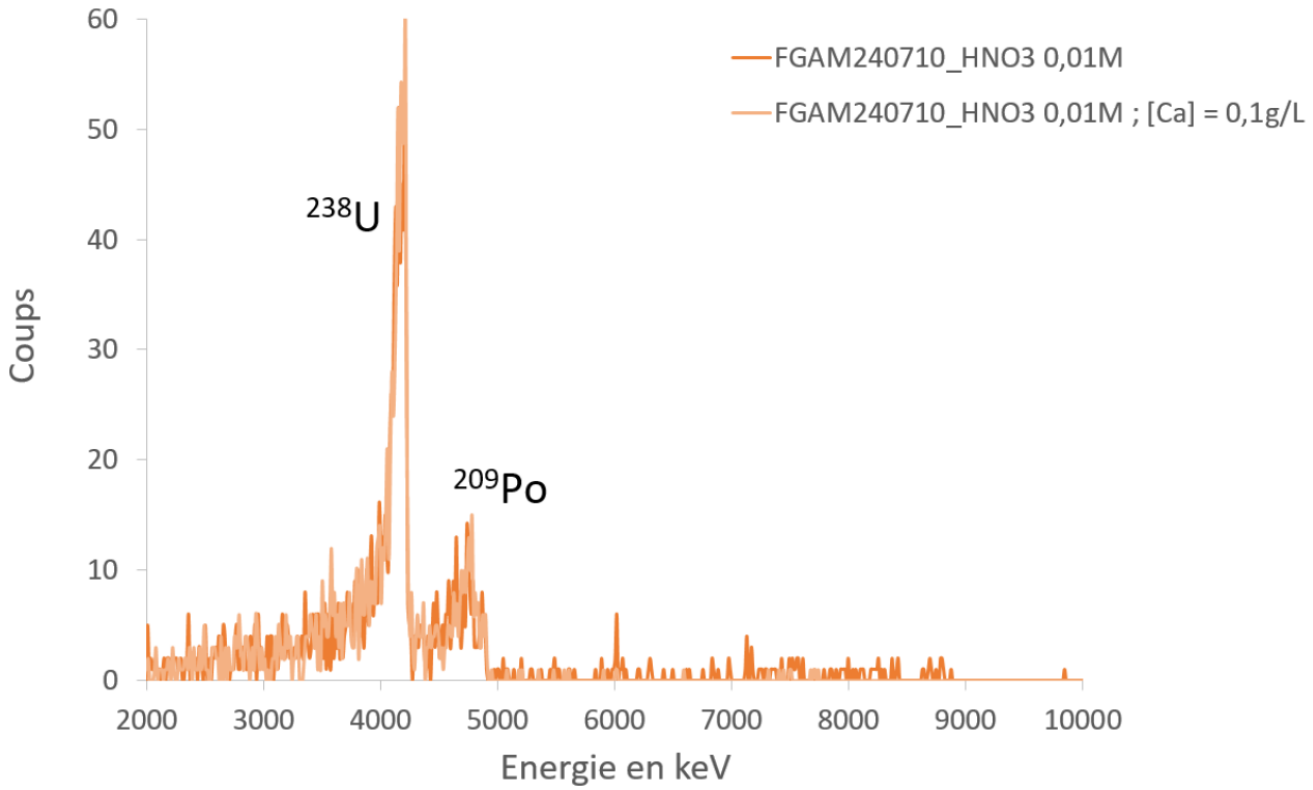
TK-GA Disc – Am/Pu in spiked acidified water



Alpha spectrum, Am-241 & Pu-239, each ~50mBq, 100mL pH2 HNO_3

TK-GA Disc – U/Po in spiked acidified water

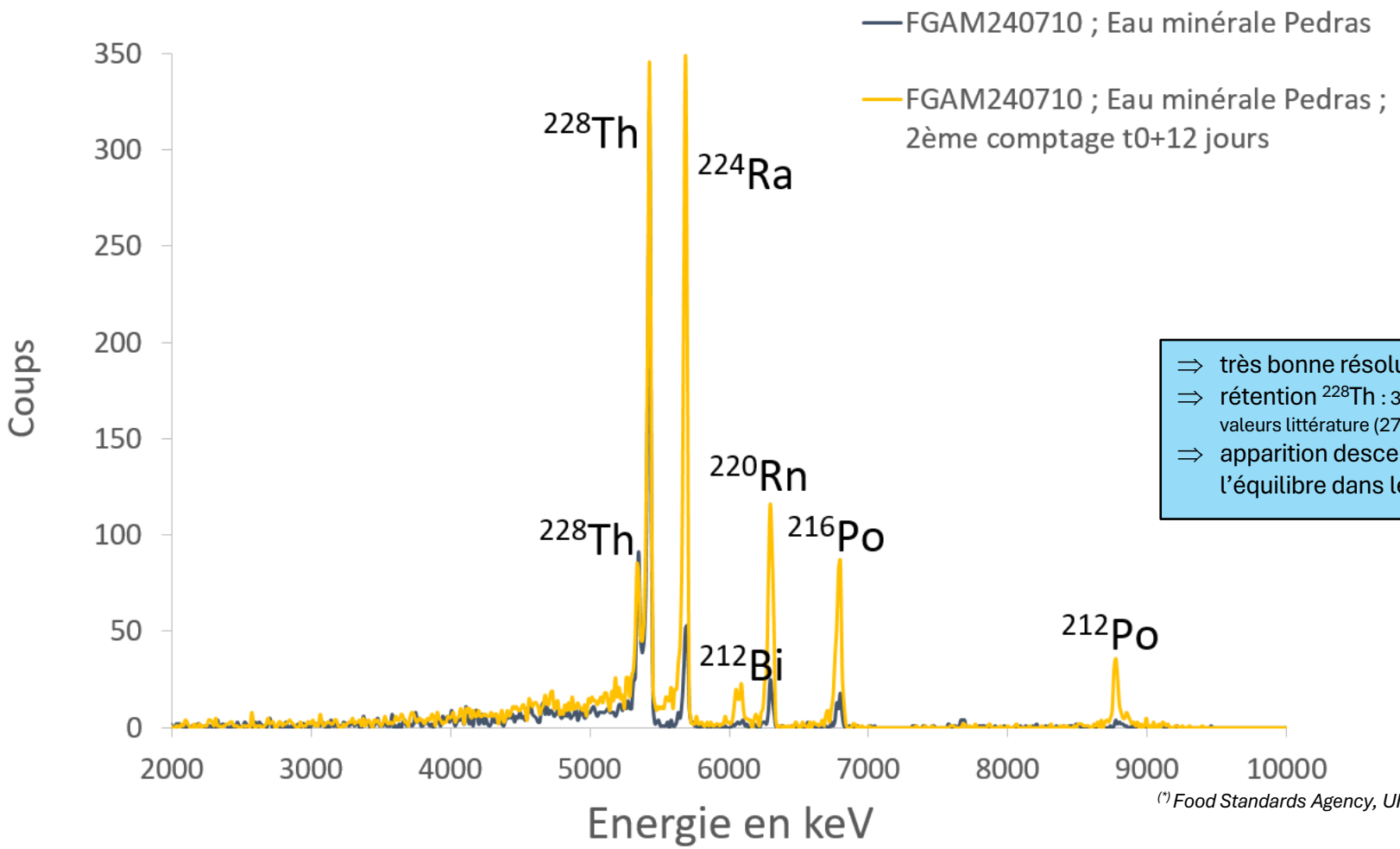
→ Solution synthétique simple dopée en ^{238}U et ^{209}Po
(100mL HNO_3 0,01M ; sans ou avec Ca à 0,1g/L ; 30mBq soit <u>0,3Bq/L</u>)



Tesmarac joint research laboratory

Résultats :

→ Eau minérale naturelle : Pedras (100mL)



⇒ très bonne résolution

⇒ rétention ^{228}Th : 320mBq/L mesuré = cohérent avec valeurs littérature (270mBq/L (*))

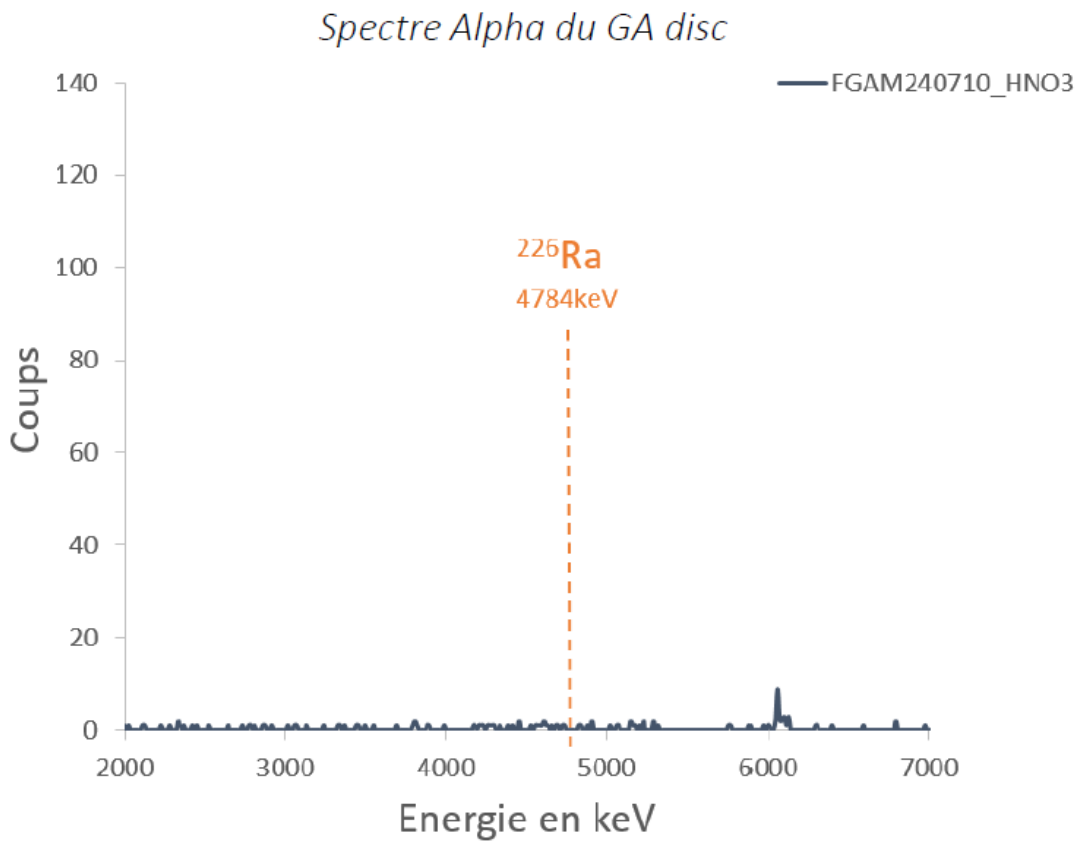
⇒ apparition descendants du ^{228}Th puis mise à l'équilibre dans le temps

(*) *Food Standards Agency, UK, Report 67/04 September 2004*

No Ra Retention in pH1 , Th very well retained. Good resolution

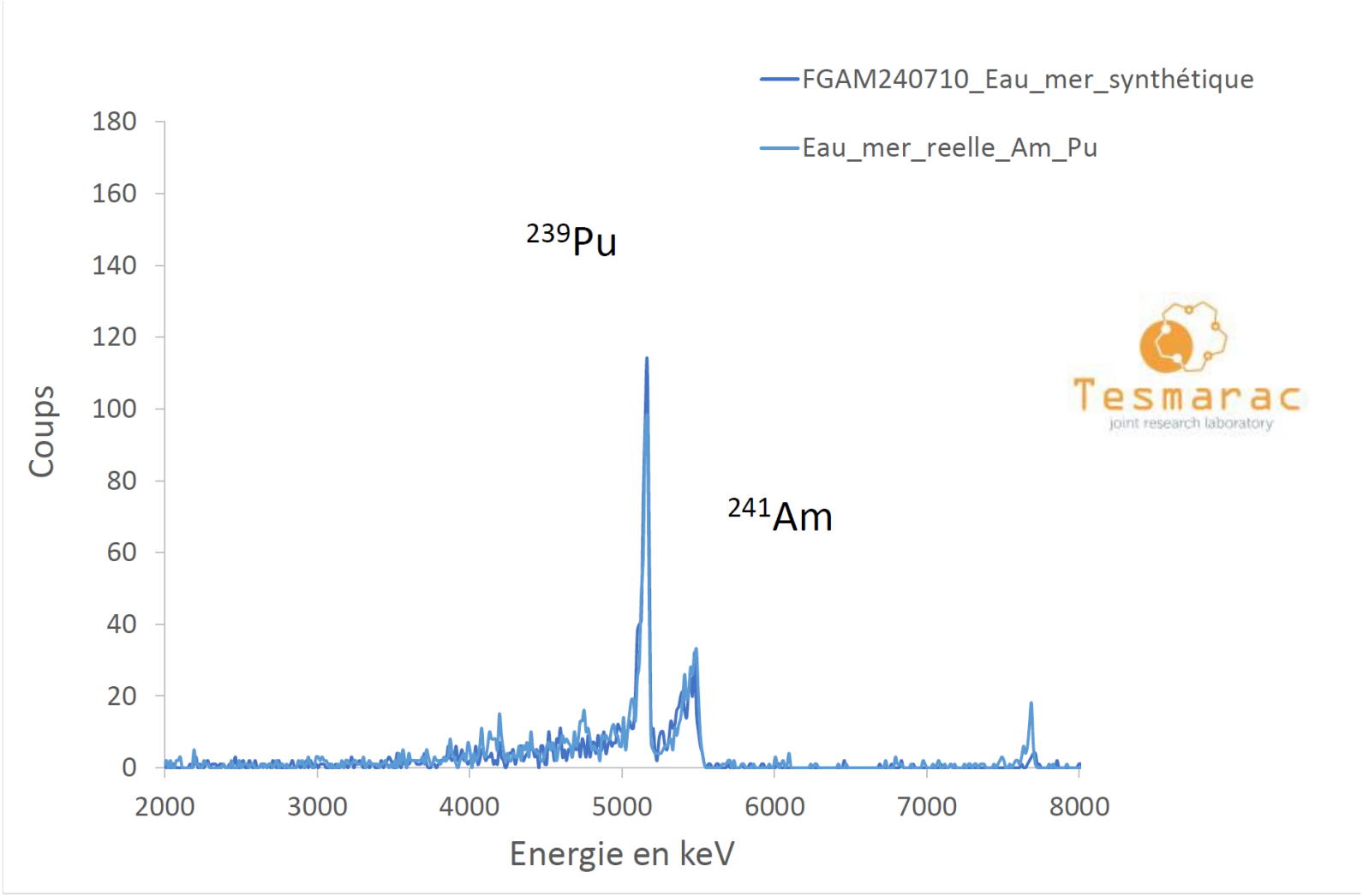
TK-GA Disc – Ra in spiked acidified water

→ Solution synthétique simple HNO_3 (100mL) 0,01M dopée en ^{226}Ra (30mBq soit 0,3Bq/L) *(résultats octobre 2024)*



No Ra retention at Ph 1 and 2. Ra retained at higher pH but no spectrum

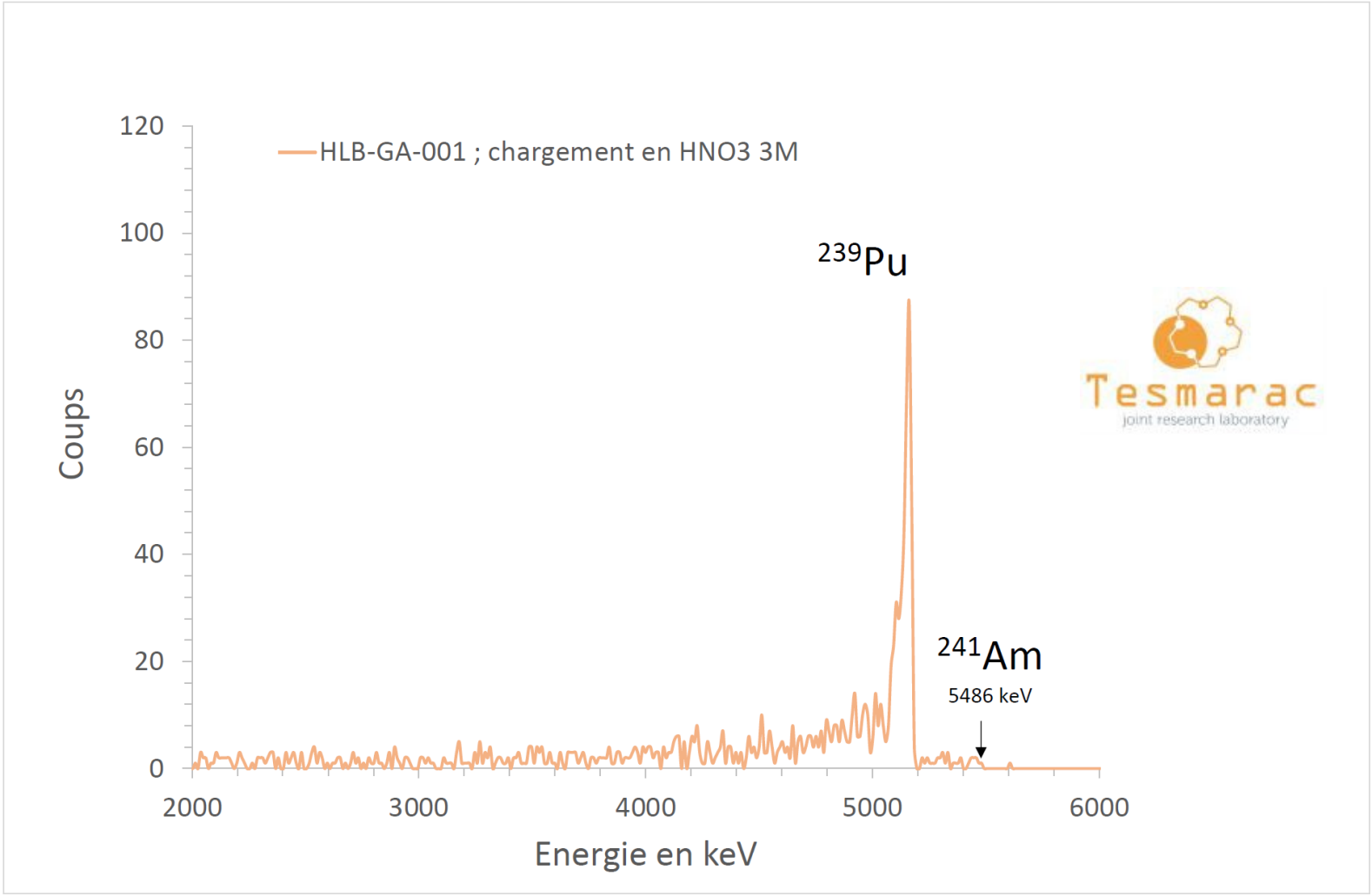
TK-GA Disc – Am/Pu in sea water



Alpha spectrum, Am-241 & Pu-239, each ~30mBq, 100mL sea water, pH2 HNO_3

Higher yields for Pu

TK-GA Disc – Am/Pu in 3M HNO_3



Alpha spectrum, Am-241 & Pu-239, each ~50mBq, 100mL 3M HNO_3

High yields for Pu, no Am retention

Next steps

TK-GA Discs:

- Publication upcoming
- Other matrices (e.g. primary cooliant) and acid concentrations
- Spectrum deconvolusion => Subatech
- More data on other alpha emitters
- Behaviour of Ra
  - Retention at pH3-4 but no alpha spectrum
  - Migration into the disc?

TK221 and TK200 Discs in 3M HNO_3

- Stacking for AC screening? => rapid screening methods
- Will require 6M $NaNO_3$ rinse before drying for acid removal…
- => looks good cold, alpha spectra?

TK201 and TK101 Discs and methods optimisation

Sr via TK102 and/or TK227 Discs? LSC? GPC?

More discs…

Passive sampling

- Wagner et al.
- Passive sampling via DGT (Diffusive Gradiant in Thin films) => ‘bio-availability’
- TK100 Discs for Sr, Pb, Zn and Sr-90
- CU Discs for Cu

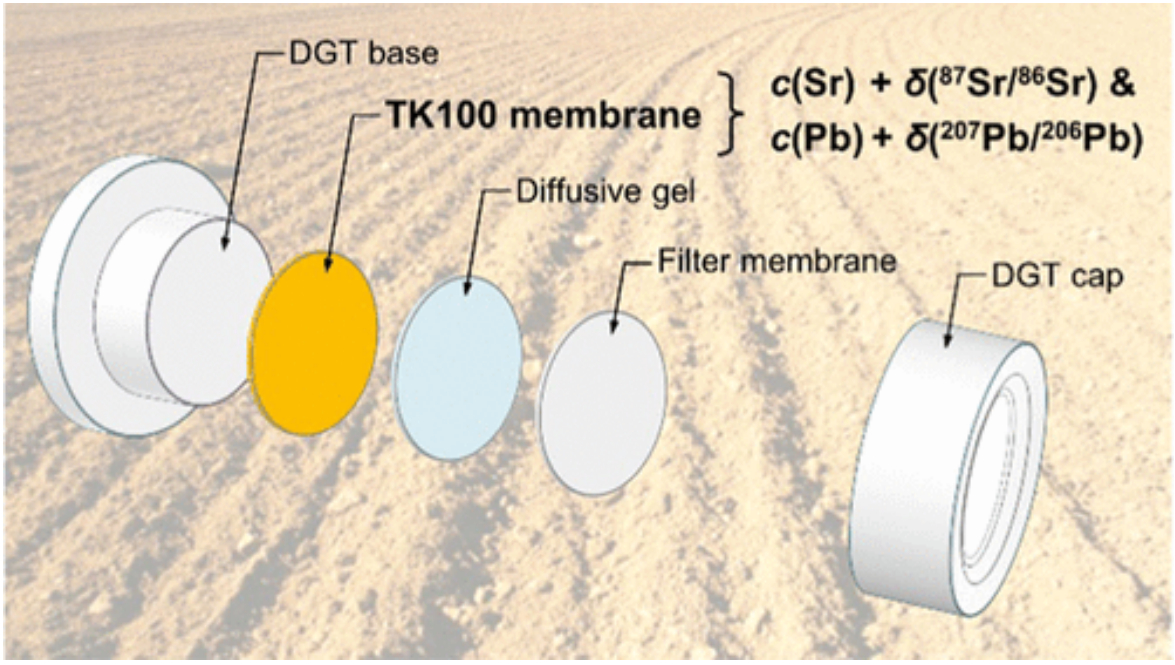
analytical chemistry

pubs.acs.org/ac Article

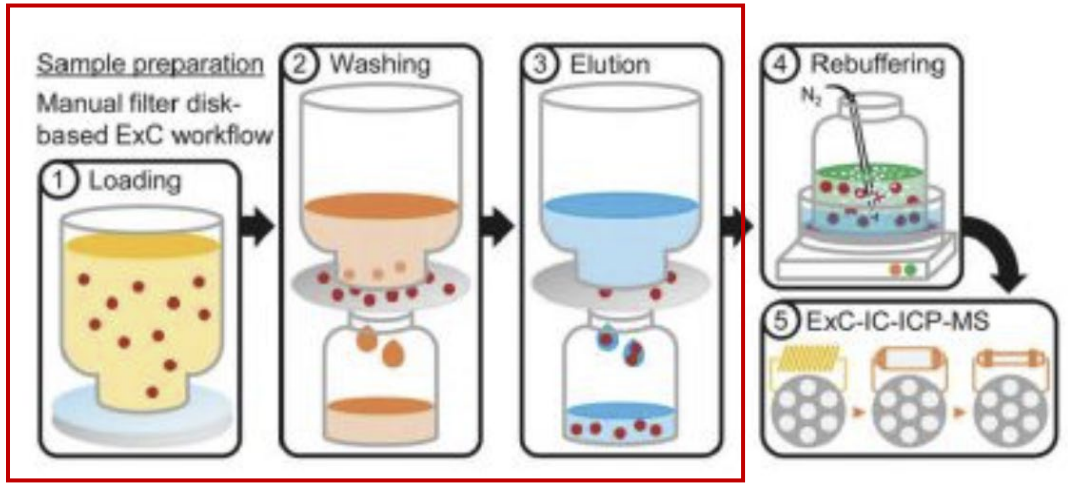
Selective Diffusive Gradients in Thin Films (DGT) for the Simultaneous Assessment of Labile Sr and Pb Concentrations and Isotope Ratios in Soils

Stefan Wagner, Jakob Santner, Johanna Irrgeher, Markus Puschenreiter, Steffen Happel, and Thomas Prohaska*

Cite This: *Anal. Chem.* 2022, 94, 6338–6346 Read Online



Tc Reconcentration



Experimental setup, Tc-99 concentration and purification from waste water using TK201 discs for preconcentration

- 1L hospital waste water
- Preconcentration on 47mm TK201 Disc
- Elution in 0.5M NH_4OH
- Readjustment of pH to allow loading onto TK201 column (PrepFast)
- Elution in 0.5M NH_4OH concentration/purification step)
- Load onto IC column
- Elution in 0.15M NH_4NO3 in very small volume
- ~100% chemical yield
- LoD < 1fg/kg

« Quantification of technetium-99 in wastewater by means of automated on-line extraction chromatography – anion-exchange chromatography – inductively coupled plasma-mass spectrometry »

J. Anal. At. Spectrom., 2024, 39, 2774-2782

Maximilian Horstmann, C. Derrick Quarles Jr, Steffen Happel, Michael Sperling, Andreas Faust, David Clases and Uwe Karst*

CL Resin – Iodine removal from effluents

Decamp et al.: Iodine removal from elevated sample volumes[§]

- Treatment of complex process effluents
  - > 10 L radioactive effluent (1M HNO_3)
- Issues with rad. waste storage
  - Storage as liquid waste challenging
  - Preferably stored as solid waste
- Use of mixed-bed columns
  - 3g Ag loaded CL resin (plus 4g XAD-4 resin)
- Flow rate up to 180 mL/min
- Radio-iodine retention: 89% - 98%
- Retention of up to 2000 GBq radio-iodine per 7g column

Example for decontamination of effluents

[§] C. Decamp (IRE), S. Happel: Utilization of a mixed-bed column for the removal of iodine from radioactive process waste solutions, Journal of Radioanalytical and Nuclear Chemistry, online April 2013, DOI: 10.1007/s10967-013-2503-1

CL Resin – other radionuclides

Chromatographic separation of the theranostic radionuclide ^{111}Ag from a proton irradiated thorium matrix

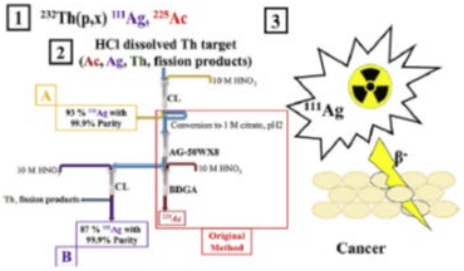
Tara Mastren [a], Valery Radchenko [a, 1], Jonathan W. Engle [a, 2], John W. Weidner [a], Allison Owens [b], Lance E. Wyant [b], Roy Copping [b], Mark Brugh [a], F. Meiring Nortier [a], Eva R. Birnbaum [a], Kevin D. John [a], Michael E. Fassbender [a, *]

[a] Chemistry Division, Los Alamos National Laboratory, P.O. Box 1663, Los Alamos, NM 87545, USA
[b] Nuclear Security and Isotope Technology Division, Oak Ridge National Laboratory, Oak Ridge, TN 37831, USA

HIGHLIGHTS

- Chromatographic recovery of medical isotope ^{111}Ag from proton irradiated thorium targets.
- First-time measured equilibrium distribution coefficients for silver and ruthenium on CL resin.
- ^{232}Th (p, fission) cross-section data for the formation of ^{111}Ag and ^{110m}Ag.

GRAPHICAL ABSTRACT



Anal. Chem., 2018, https://pubs.acs.org/doi/10.1021/acs.analchem.8b01380

Separation of protactinium employing sulfur-based extraction chromatographic resins

Tara Mastren[†], Benjamin W. Stein[†], T. Gannon Parker[†], Valery Radchenko[†#], Roy Copping[‡], Allison Owens[‡], Lance E. Wyant[‡], Mark Brugh[†], Stosh A. Kozimor[†], F. Meiring Nortier[†], Eva R. Birnbaum[†], Kevin D. John[†], Michael E. Fassbender[†*]

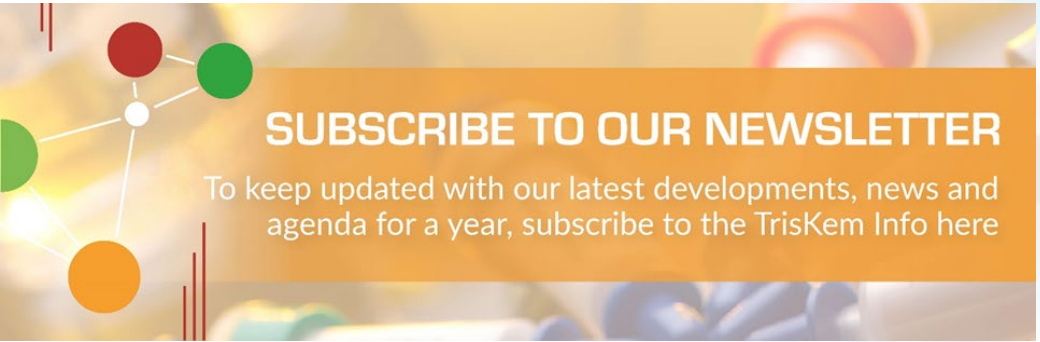
[†]Chemistry Division, Los Alamos National Laboratory, P.O. Box 1663, Los Alamos, NM 87545, USA
[‡]Nuclear Security and Isotope Technology Division, Oak Ridge National Laboratory, Oak Ridge, TN 37831, USA

[#]Current Address: Life Sciences Division, TRIUMF, 4004 Wesbrook Mall, Vancouver, BC, V6T2A3, Canada

Some other on-going projects

- Improvement of radiolysis stability
- Additional ‘Sheets’
- Removal of free RN from reaction mixtures
- Further upscale of radiolanthanide separations
- Other radiometals
  - Auger (Sb, Pd, Hg, Ag,…), Mn, V…
- At separation
  - Resin optimisation, Rn-211/At-211 generator,…
- Decontamination
  - Effluents and reaction wastes
- Other geometries
- Fate’ of RN in the environment and bioassay
  - Separation methods
  - Mainly longer lived RN (=> therapy)
    - Ac-225/7, Lu-177(m), radioiodine,…
  - Quantification

Thank you for your attention!



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