TrisKem International

Development of new extraction chromatographic materials for use in radioanalytical chemistry and isotope production

Steffen Happel

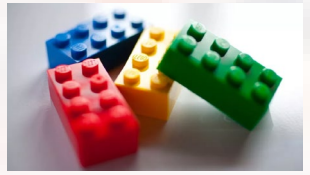
02/09/2022

6th-INCC 2022
6th International Nuclear Chemistry Congress

TRISKEM
Expertise in Separation Chemistry

Overview

- Overview new resins/applications/R&D cooperations
- Examples of new resins and methods: radioanalysis
  - TK200 for actinide preconcentration and separation
  - TK221 for actinide separation
  - TK400/ZR Resin for Fe separation
- Examples of new resins and methods: radioisotope production
  - Ga-68 from Zn targets (ZR/TK200 & TK400/TK200)
  - Cu-61/4 from solid Ni targets (TK201/TBP)
  - Tb-161 from Gd targets (TK221 & TK211/2)
- Other new resins and ongoing projects



Recently developed new products/applications

Product	Application
TK100/1 Resin	Sr, Pb direct separation, Ra separation
TK200 Resin	Actinides, Ga-67/8, Zn
TK201 Resin	Cu-61/4, Tc, Re, Pu
TK202 Resin	Tc, Re
TK211/2/3 Resin	Lanthanide separation (e.g. nca Lu-177, Tb-161,…)
TK221 Resin	Actinides, lanthanides
TK400 Resin	Ga-67/8, Pa-230/1, Fe, Nb, Mo, Po
ZR Resin	Zr-89, Ga-67/8, Ti-44/5, Ge-68, Fe
TK-TcScint	Tc-99 direct LSC measuement (with Uni Barcelona)
DGA Sheets	Functionalized TLC paper for RN QC (with CVUT Prague)

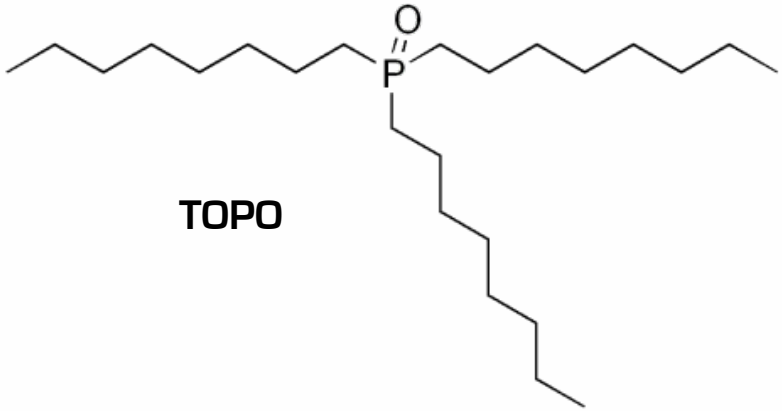
Upcoming products: **TK102 Resin** (Sr, Pb, Ra/Ba separation), **TK225 Resin** (lanthanide removal from acidic effluents), **TK300 Resin** (Cs and Rb separation), **impregnated membrane filters** (TK100, TK201,…)

Recently developed new products/applications

Product	Application
TK100/1 Resin	Sr, Pb direct separation, Ra separation
TK200 Resin	**Actinides, Ga-67/8, Zn**
TK201 Resin	**Cu-61/4, Tc, Re, Pu**
TK202 Resin	Tc, Re
TK211/2/3 Resin	**Lanthanide separation (e.g. nca Lu-177, Tb-161,…)**
TK221 Resin	**Actinides, lanthanides**
TK400 Resin	**Ga-67/8, Pa-230/1, Fe, Nb, Mo, Po**
ZR Resin	**Zr-89, Ga-67/8, Ti-44/5, Ge-68, Fe**
TK-TcScint	Tc-99 direct LSC measuement (with Uni Barcelona)
DGA Sheets	Functionalized TLC paper for RN QC (with CVUT Prague)

Upcoming products: **TK102 Resin** (Sr, Pb, Ra/Ba separation), **TK225 Resin** (lanthanide removal from acidic effluents), **TK300 Resin** (Cs and Rb separation), **impregnated membrane filters** (TK100, TK201,…)

TK200 Resin

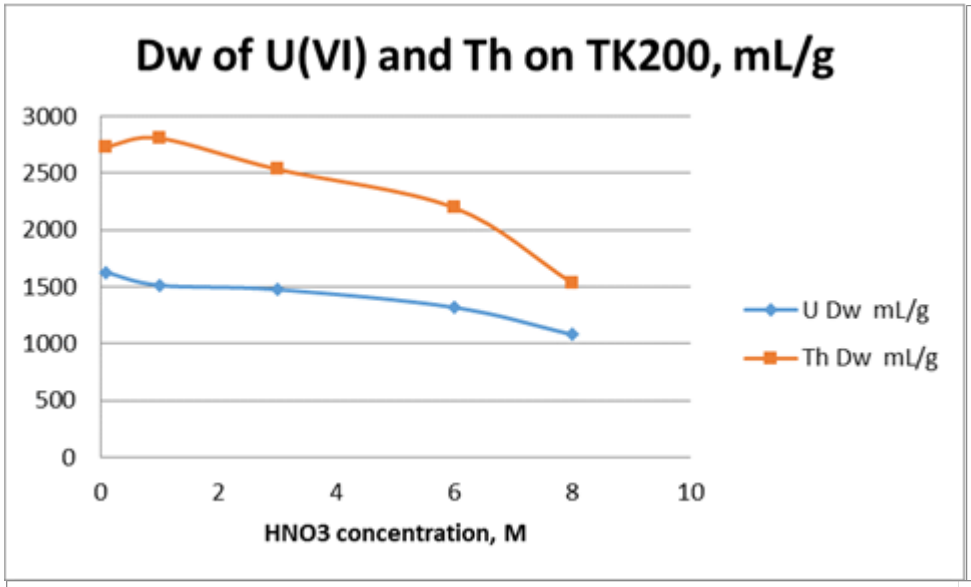


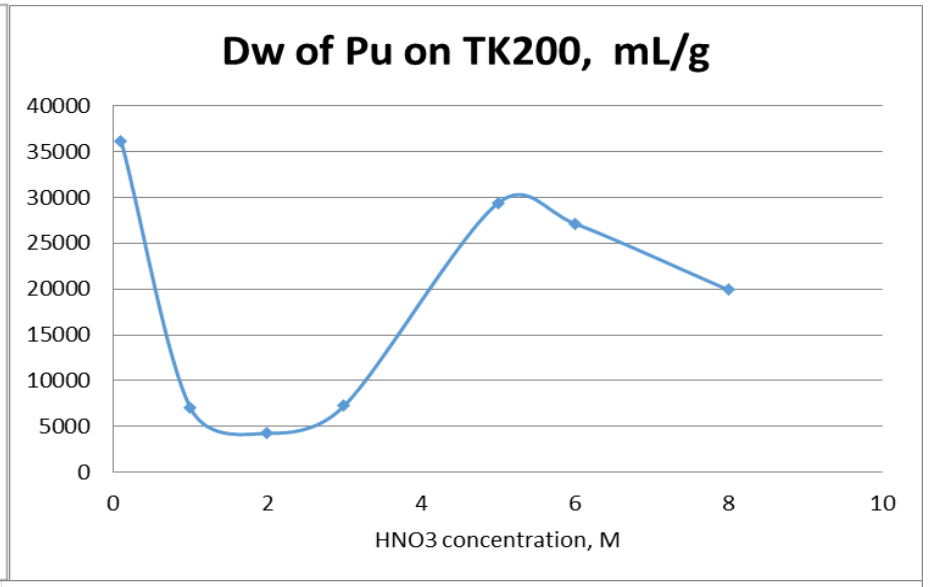
TOPO

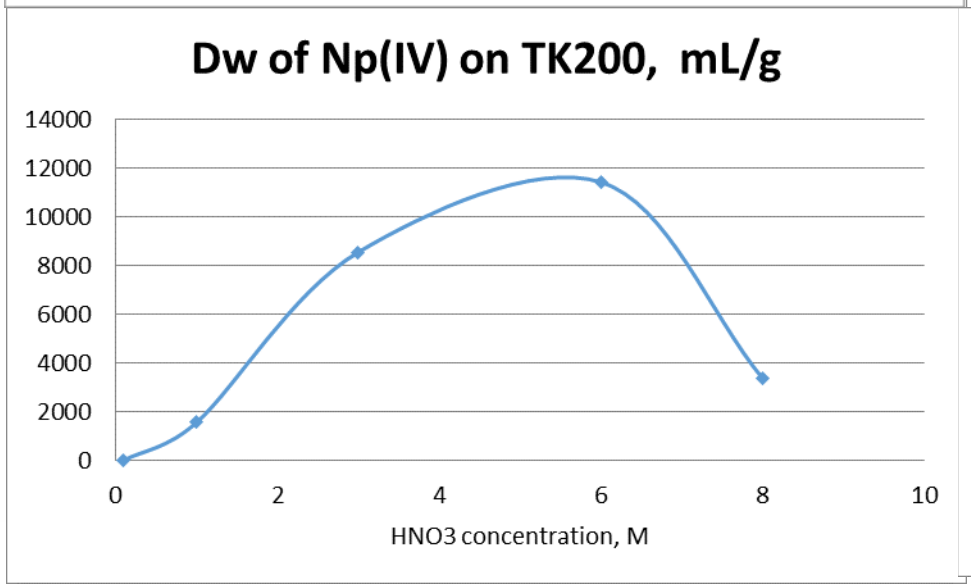
- Based on TOPO extractant
- High retention of actinides
- Applications:
  - Use for very efficient U removal from Pu (Wang et al.)
  - Determinaiton of Tc-99 in water samples (Ni Yuan et al.)
  - Ga-68 production (in combination with ZR Resin)
  - Actinide separation from water samples
- Extracts actinides even at pH 1 - 2 (nitric acid)
  - Preconcentration and purification of selected actinides on same column
  - ‘In the field’?

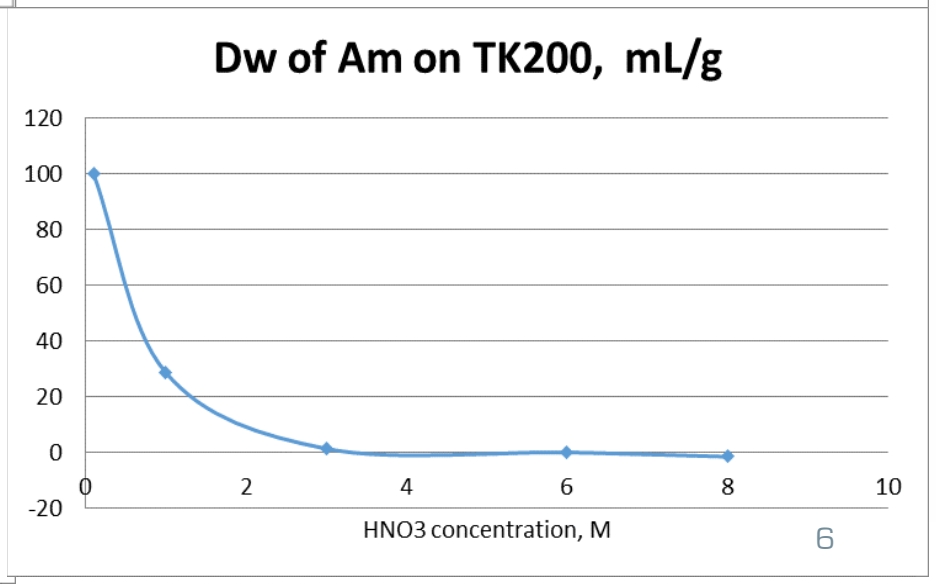
Actinides on TK200 – HNO_3
(all data N. Vajda et al)

TRISKEM
Expertise in Separation Chemistry



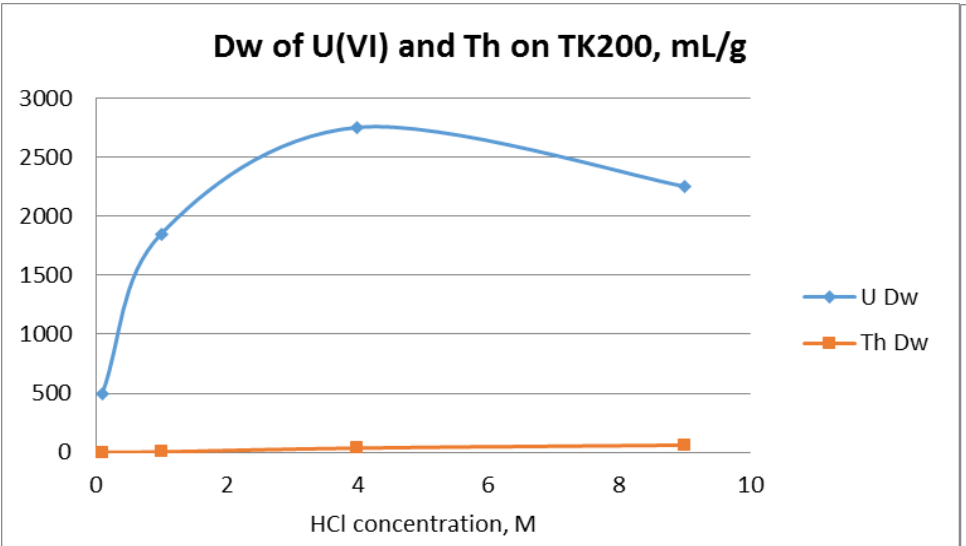


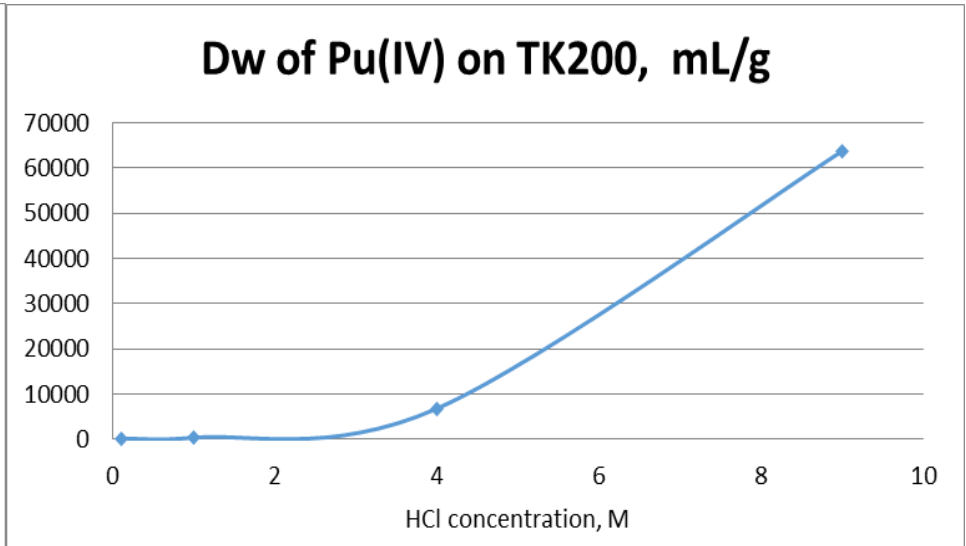


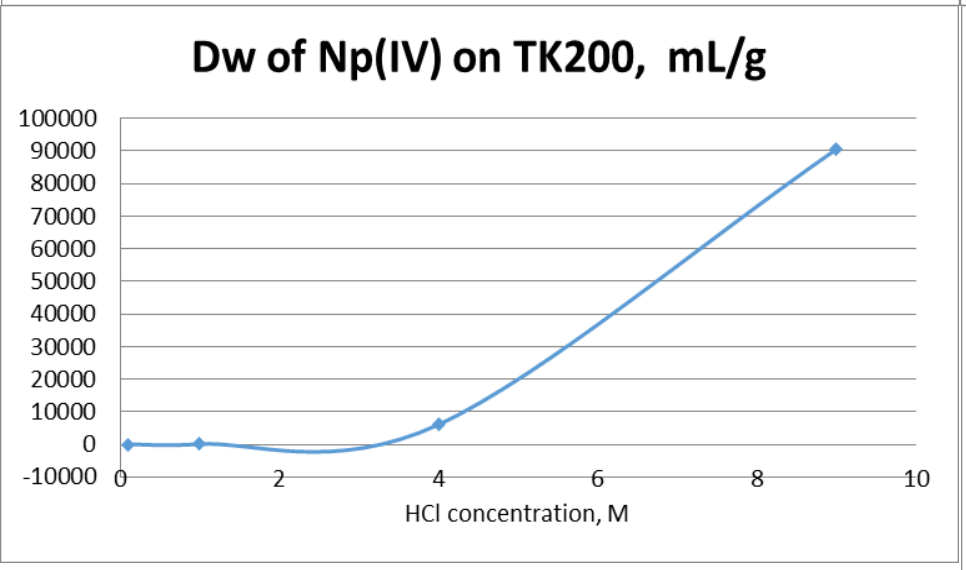


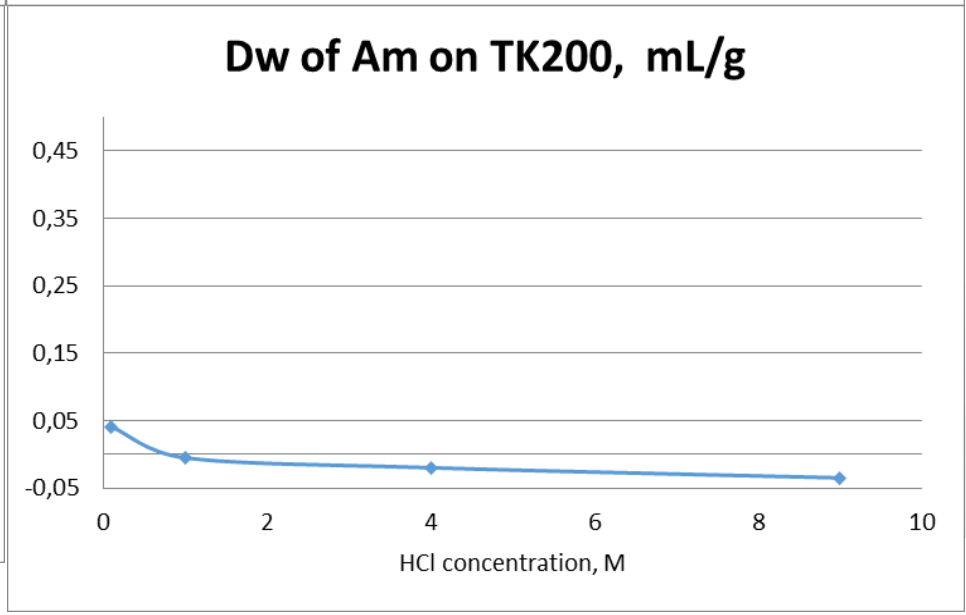
Actinides on TK200 – HCl
(all data N. Vajda et al)

TRISKEM
Expertise in Separation Chemistry

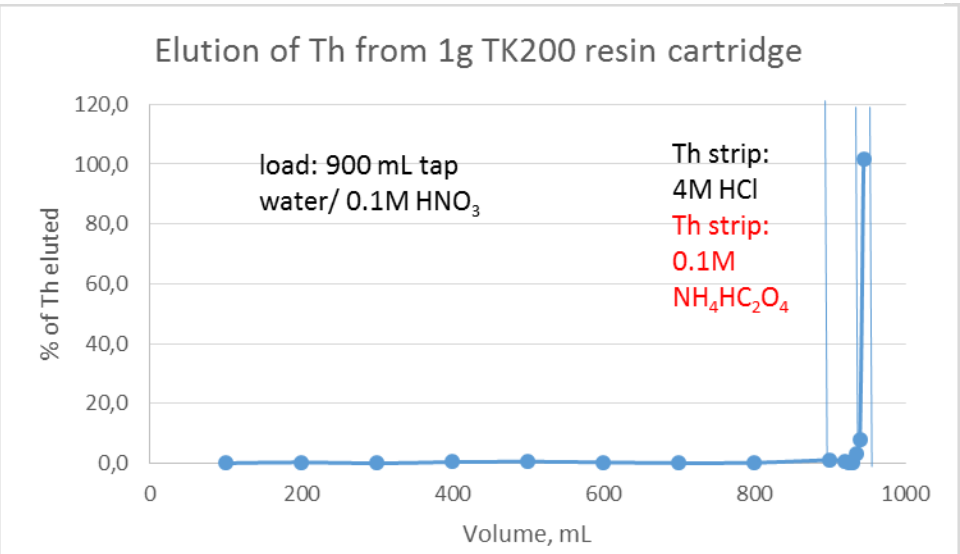


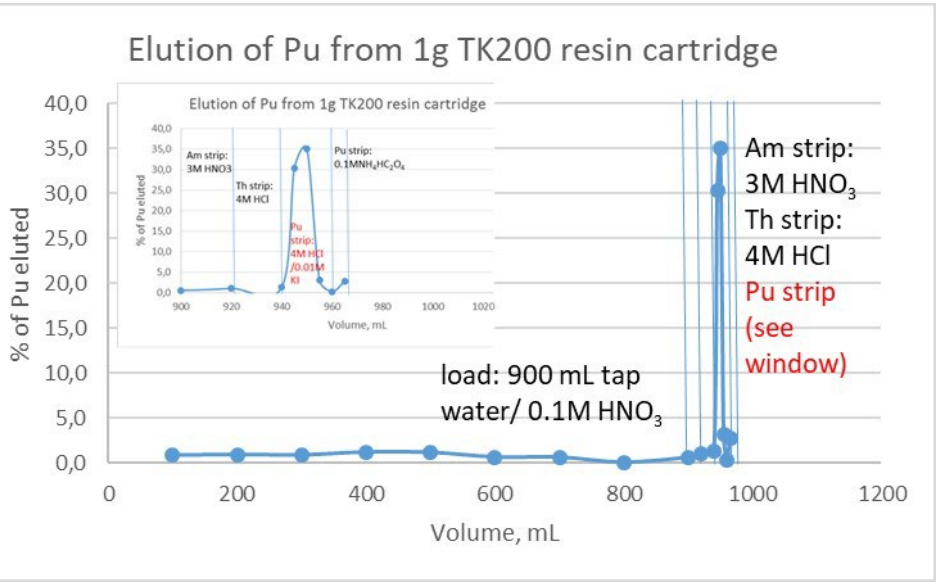


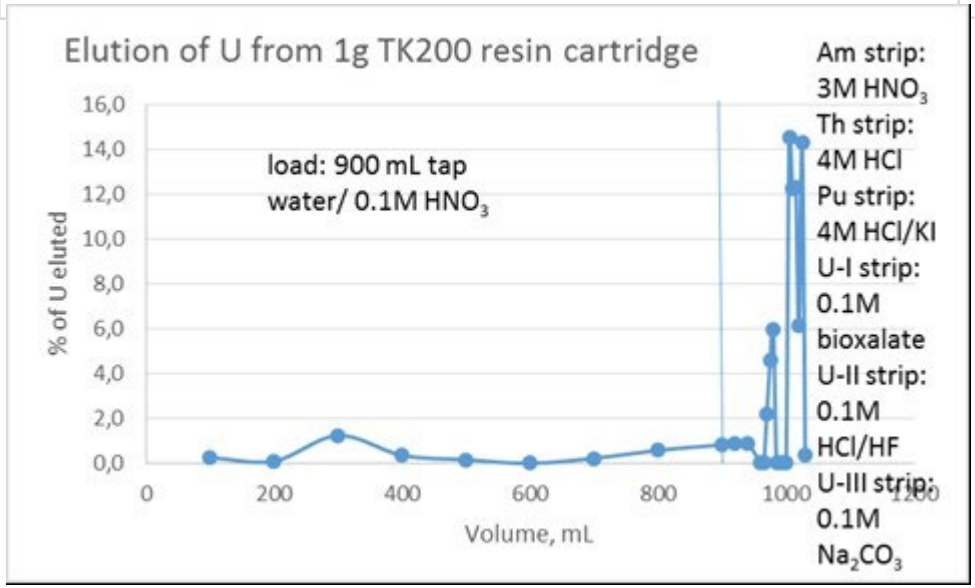




Actinides on TK200 – Application



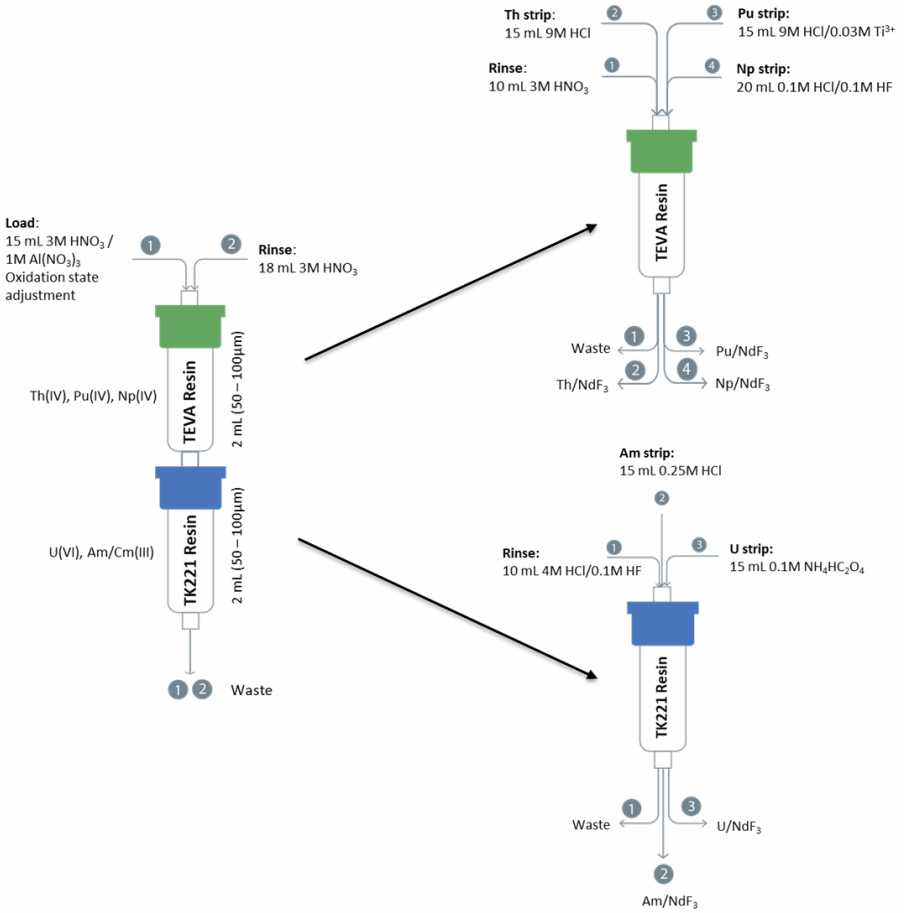




- Data by N. Vajda (RadAnal)
- Method development on-going
- Direct load of U, Th and Pu from acidified water samples (here 900 mL on 2 mL TK200)
- Sequential separation on TK200
- Automatisation & 'in the field' preconcentration'?

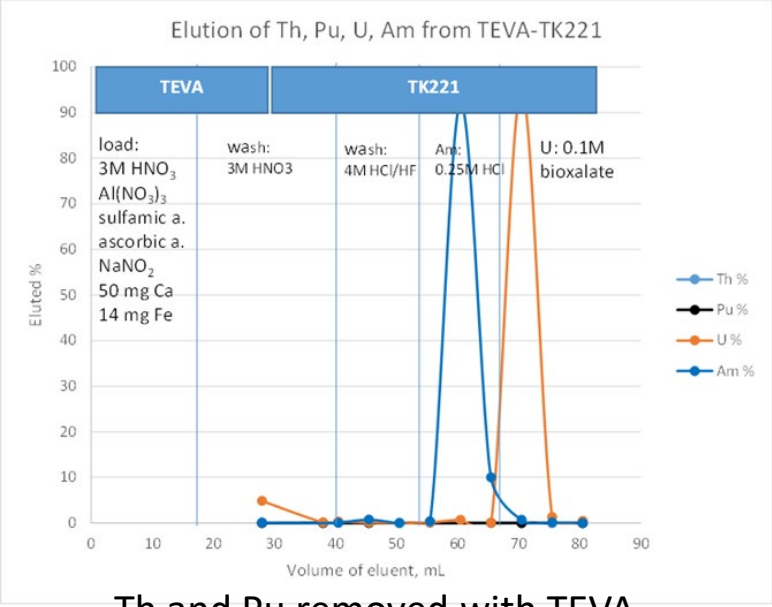
TK221 Resin

- Optimisation of DGA Resin
  - Contains TO-DGA / phosphine-oxide
  - higher load and more radiolysis stable inert support
- Main application: Lu, Tb concentration from high acid and elution in small volume of dilute HCl
- Higher U retention than DGA
- Higher Am retention than TRU
  - Potential interest for Actinide separation, particularly Am
- Cooperation with Nora Vajda
- Method development for water samples
  - TEVA/TK221 method
  - Ideally later also soil and decommissioning samples



Papp, I., Vajda, N. & Happel, S. *J Radioanal Nucl Chem* (2022). https://doi.org/10.1007/s10967-022-08389-9

TK221 Resin



Th and Pu removed with TEVA.

Am and U separation on TK221 Am elution before U

Table 3 Recovery of actinide tracers from spiked water samples

	Actinides determiantion	
	Without Np separation	With Np separation
	Yield	Yield
	%	%
TAP water		
^{230}Th	90 ± 8	86 ± 7
^{239}Pu	108 ± 7	95 ± 7
^{237}Np	–	91 ± 9
^{241}Am	103 ± 7	97 ± 6
^{233}U	103 ± 7	70 ± 7
SEA water		
^{230}Th	71 ± 7	61 ± 6
^{239}Pu	91 ± 7	87 ± 6
^{237}Np	–	93 ± 8
^{241}Am	89 ± 7	92 ± 6
^{233}U	88 ± 7	59 ± 6

Analyte	Target values		Measured values			Relative bias	MARB[a]	Z-score[b]	Test evaluation
	Mean activity concentration	Standard deviation (sd)	Activity concentration	Standard uncertainty	Relative standard uncertainty				
	Bq/kg	Bq/kg	Bq/kg	Bq/kg	%	%	%		
^{239}Pu	5.93	2.27	5.09	0.24	4.7	14	25	0.37	Accepted
^{241}Am	4.85	0.57	4.73	0.15	3.2	2.5	30	0.21	Accepted
^{244}Cm	7.02	2	7.19	0.34	4.7	2.4	25	0.09	Accepted

[a]Maximum Acceptable Relative Bias

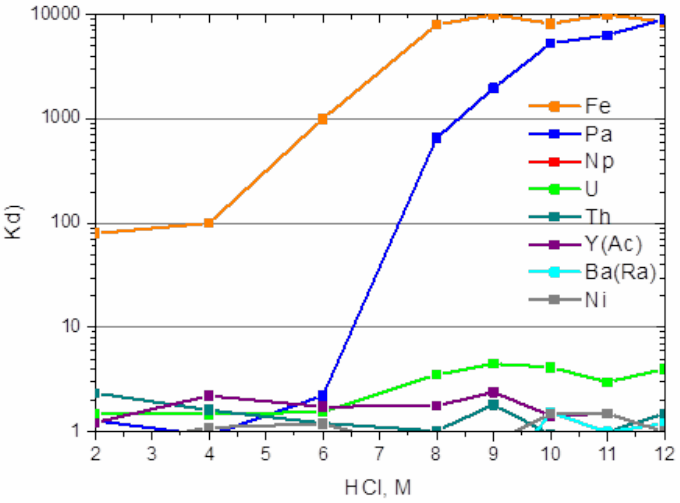
[b]Z = |Xreported—Xtargetl/sdtarget

- Method tested on spiked tap and sea water samples
- High yields (88+ for U and Am)
- Analysis of IAEA-TEL-2021–03 WWOPT succesful
- Next: use for solid samples?

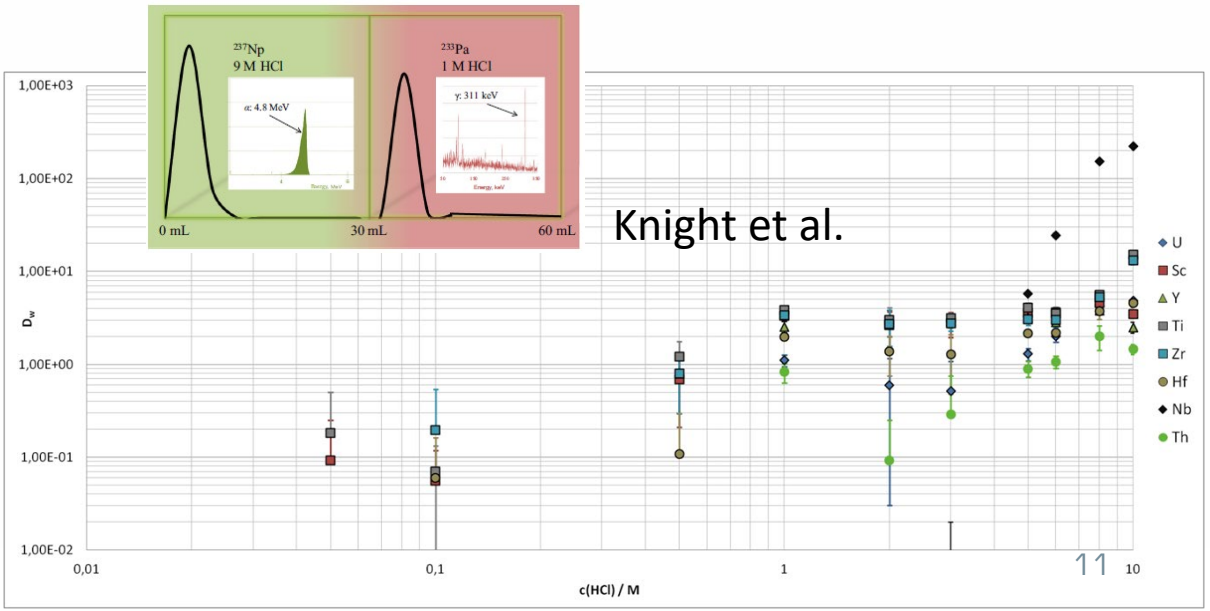
All data: Papp, I., Vajda, N. & Happel, S. *J Radioanal Nucl Chem* (2022). https://doi.org/10.1007/s10967-022-08389-9

TK400 Resin

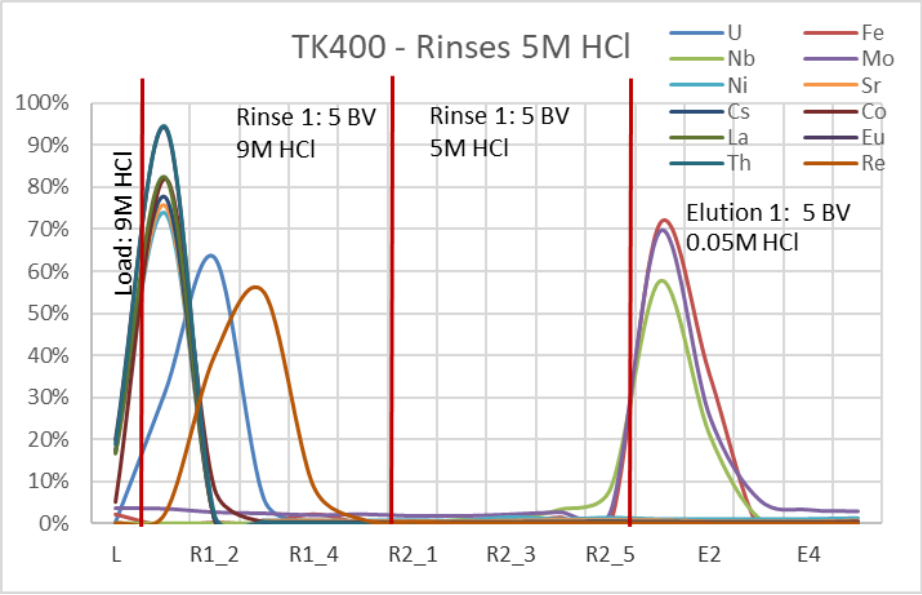
- Long chained alcohol
  - First work by Knight et al. on Np/Pa separation
- Retention only at high HCl concentration (>6M HCl), elution in low HCl, water,…
- Main application: Pa separation
- Also retains Mo, Fe, Po, Ga, Nb, Nb,…
- Higher Fe capacity than e.g. TRU Resin (~15mg Fe/g TK400)

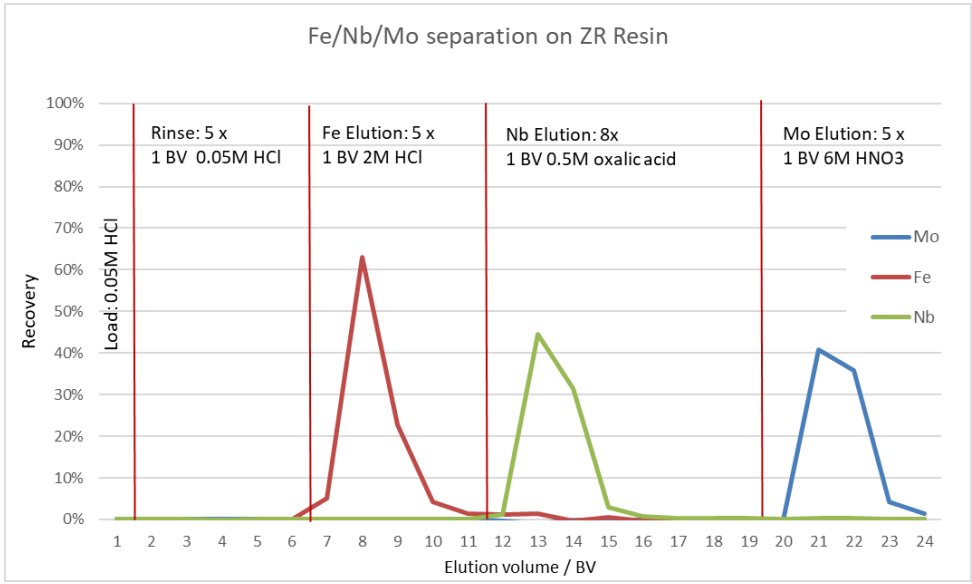


Data provided y B. Russel (NPL)



Fe/Mo/Nb separation

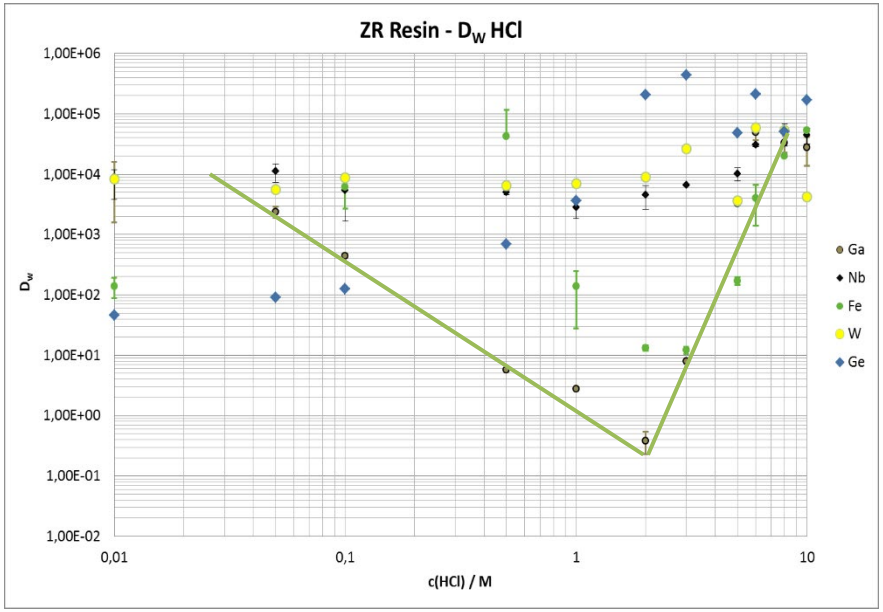


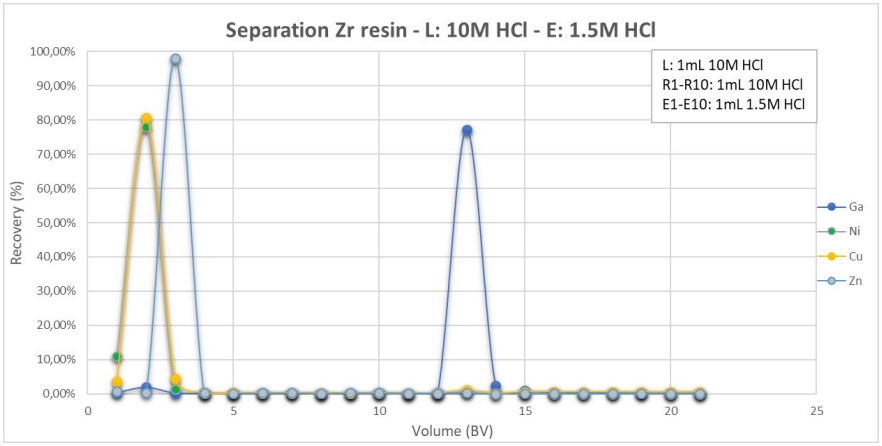


- Recovery of Fe/Nb/Mo from high HCl on TK400
- Majority of other elements removed during load and rinses (9M and 5M HCl)
- Fe/Nb and Mo eluted in dilute HCl => separation on ZR Resin
- Can also be used to remove Nb from Zr (e.g. stacked TK400/UTEVA) or Pu-241

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





- Conversion necessary
  - Evaporation & dissolution difficult to automize
- Easier => use of another resin
- TK200 Resin load from 1.5M HCl
- Rinse with 1.5M HCl
- Elution in 2 – 3 BV water, dilute acid,..

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*]

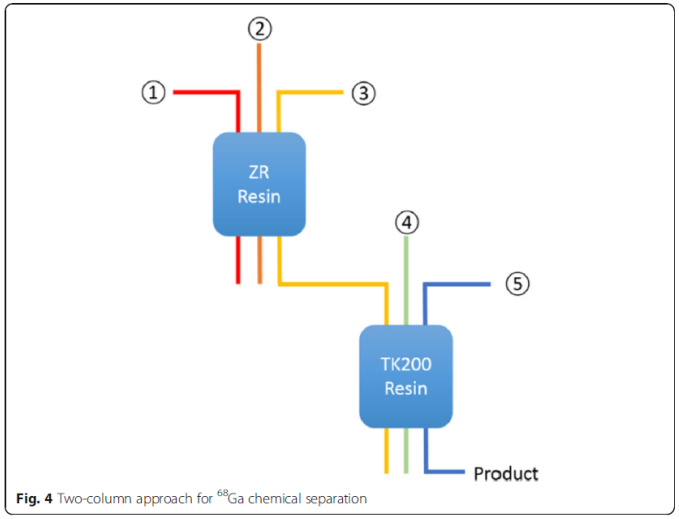


Fig. 4 Two-column approach for ^{68}Ga chemical separation

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

ORIGINAL RESEARCH

Multi-Curie Production of Gallium-68 on a Biomedical Cyclotron and Automated Radiolabelling of PSMA-11 and DOTATATE

Helge Thisgaard, Joel Kumlin, Niels Langkjær, Jansen Chua, Brian Hook, Mikael Jensen, Amir Kassaian, Stefan Zeisler, Sogol Borjian, Michael Cross, Paul Schaffer, Johan Hygum Dam

DOI: 10.21203/rs.3.rs-70698/v1 Download PDF

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

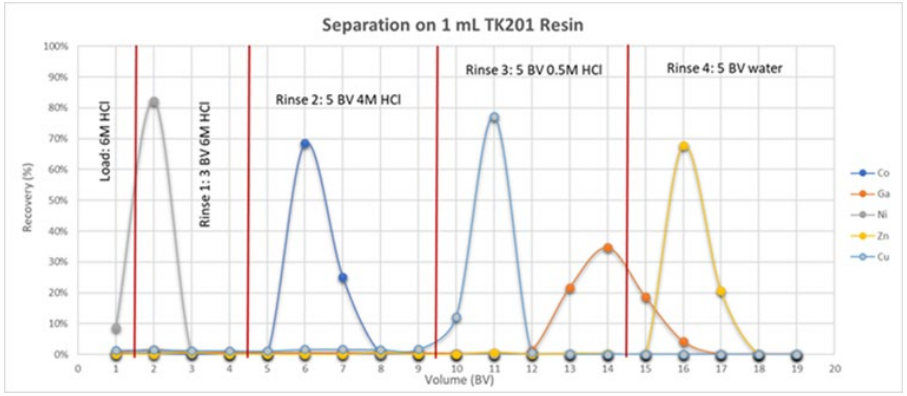
Demystifying solid targets: Simple and rapid distribution-scale production of [^{68}Ga]$GaCl_3$ and [^{68}Ga]Ga-PSMA-11

Johan Svedjehed, Martin Pärnaste, Katherine Gagnon

Cu-64 separation on TK201

- Cu-64 separation from solid Ni-64 targets
  - Original method development:
  - Target dissolution in high HCl
  - Load and rinse at 6M HCl
    - Ni removal and recovery/recycling
  - Co elution with 4 – 5M HCl
  - Cu elution with 0.5M HCl
    - Zn remains retained (Ga and Fe partially co-elute)

    => requires further treatment



- Improvements:
  - Preferred alternative: Use of TBP (or TK400) upfront for Fe/Ga removal

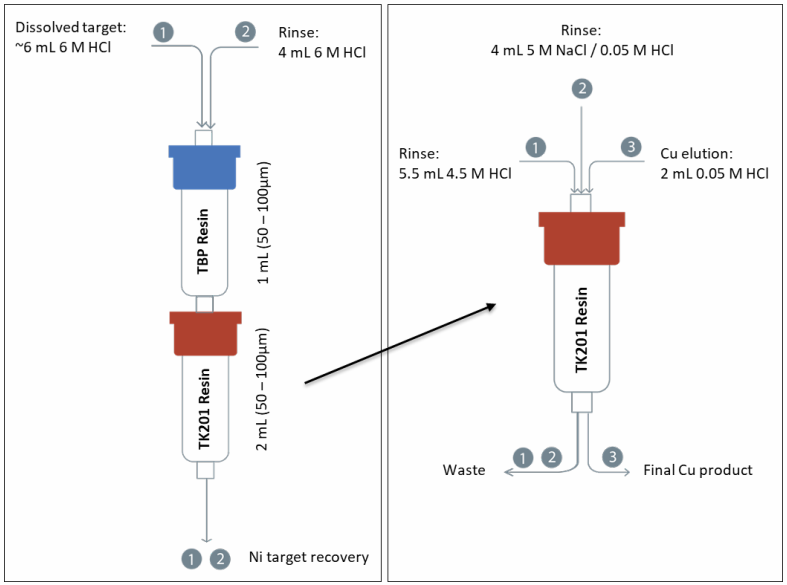
  => allows for Cu elution in 0.05M HCl

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

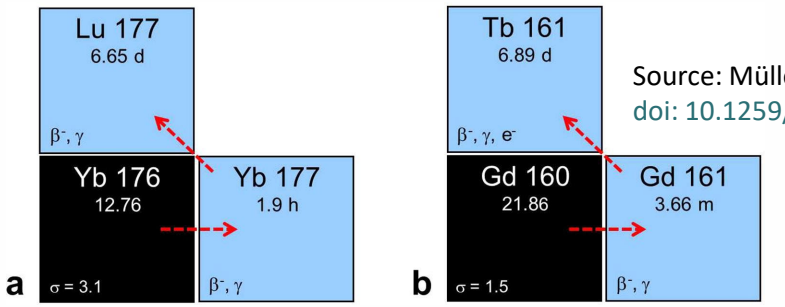
Johan Svedjehed[1], Christopher J. Kutyreff[2], Jonathan W. Engle[2,3] and Katherine Gagnon[1*]



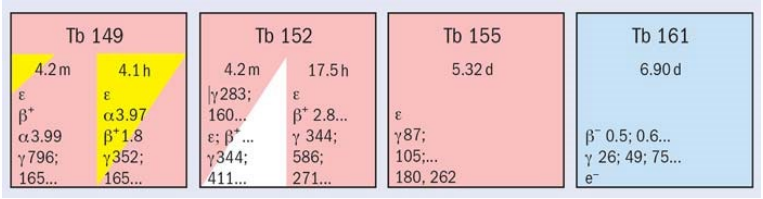
- Gagnon et al. use of NaCl/HCl for better pH control of eluate

Tb-161 separation from Gd targets

- 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



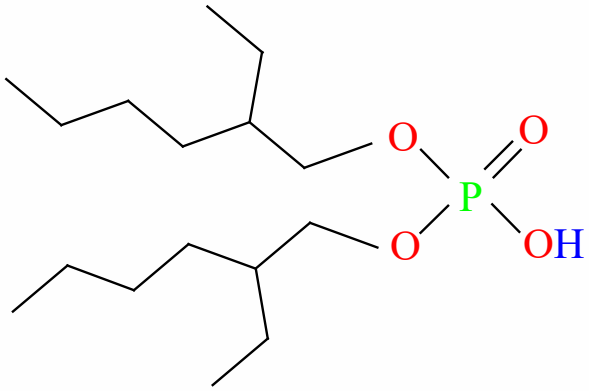
Source: Müller et al. 2018
doi: 10.1259/bjr.20180074



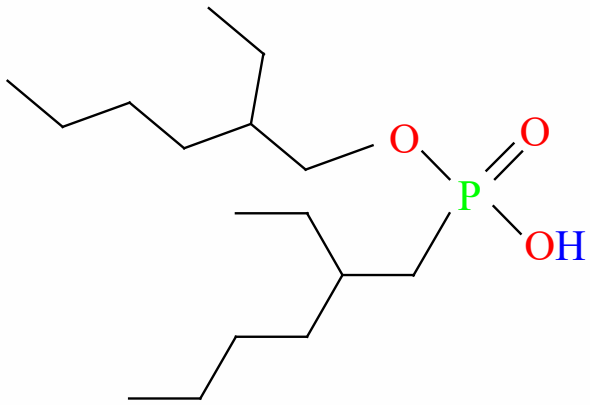
Terbium: a new 'Swiss army knife' for nuclear medicine
Source: https://cerncourier.com/a/terbium-a-new-swiss-army-knife-for-nuclear-medicine/

  - Irradiation of several hundreds of mg or more
  - Upscale on-going (incl. recycling) => typically 1g
- Use of 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
  - HPLC pump
  - QC/CoA per column (peak asymmetry) for TK211/2/3

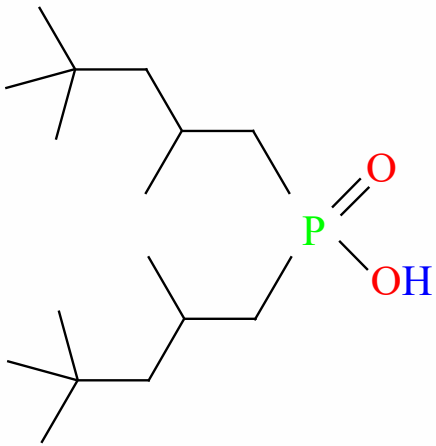
Lanthanide separation on TK211/2/3



HDEHP (LN)



HEH[EHP] (LN2)



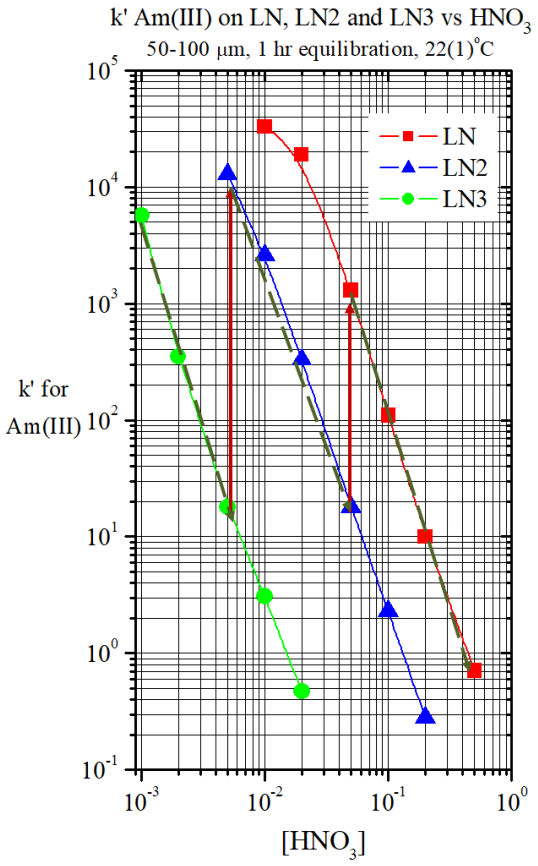
H[TMPeP] (LN3)

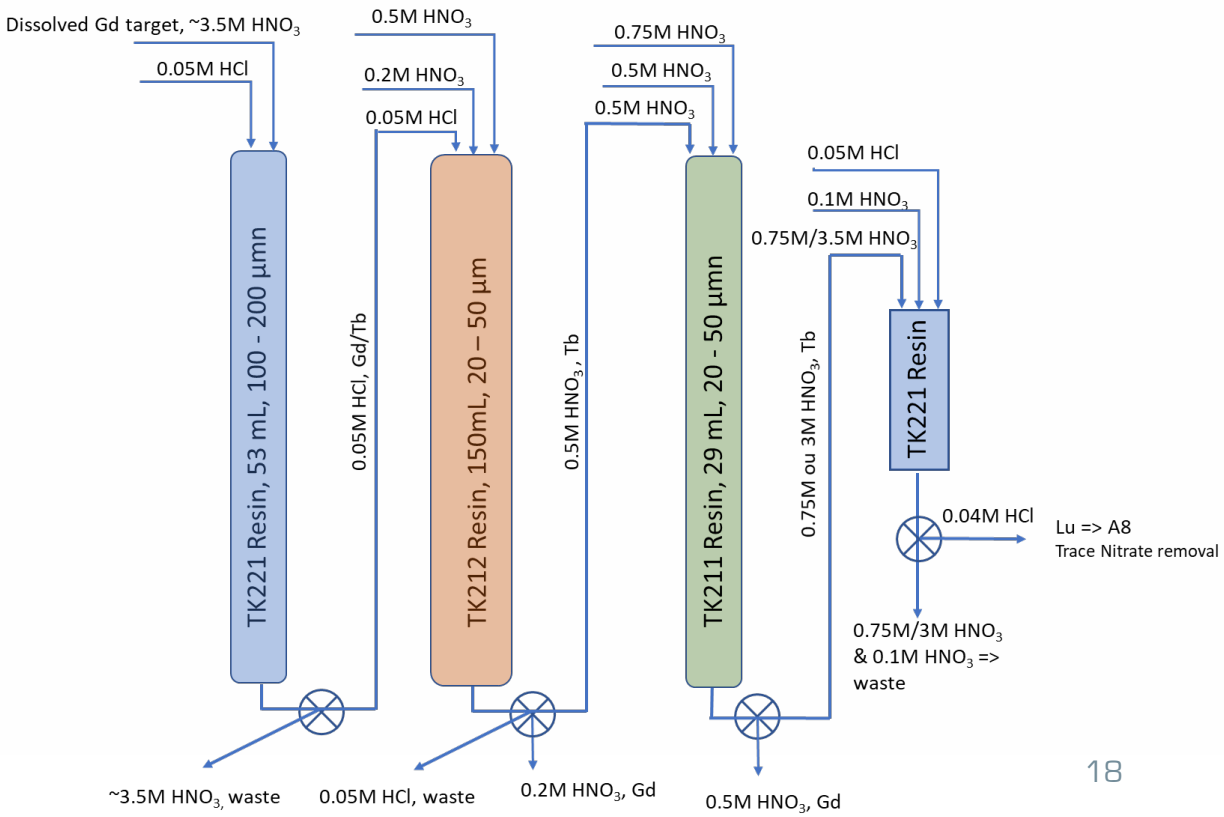
Extractants employed in **TK211/2/3**
- Extractant mixtures
- Optimized for high radiation stability

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

Tb separation from 500 mg Gd targets

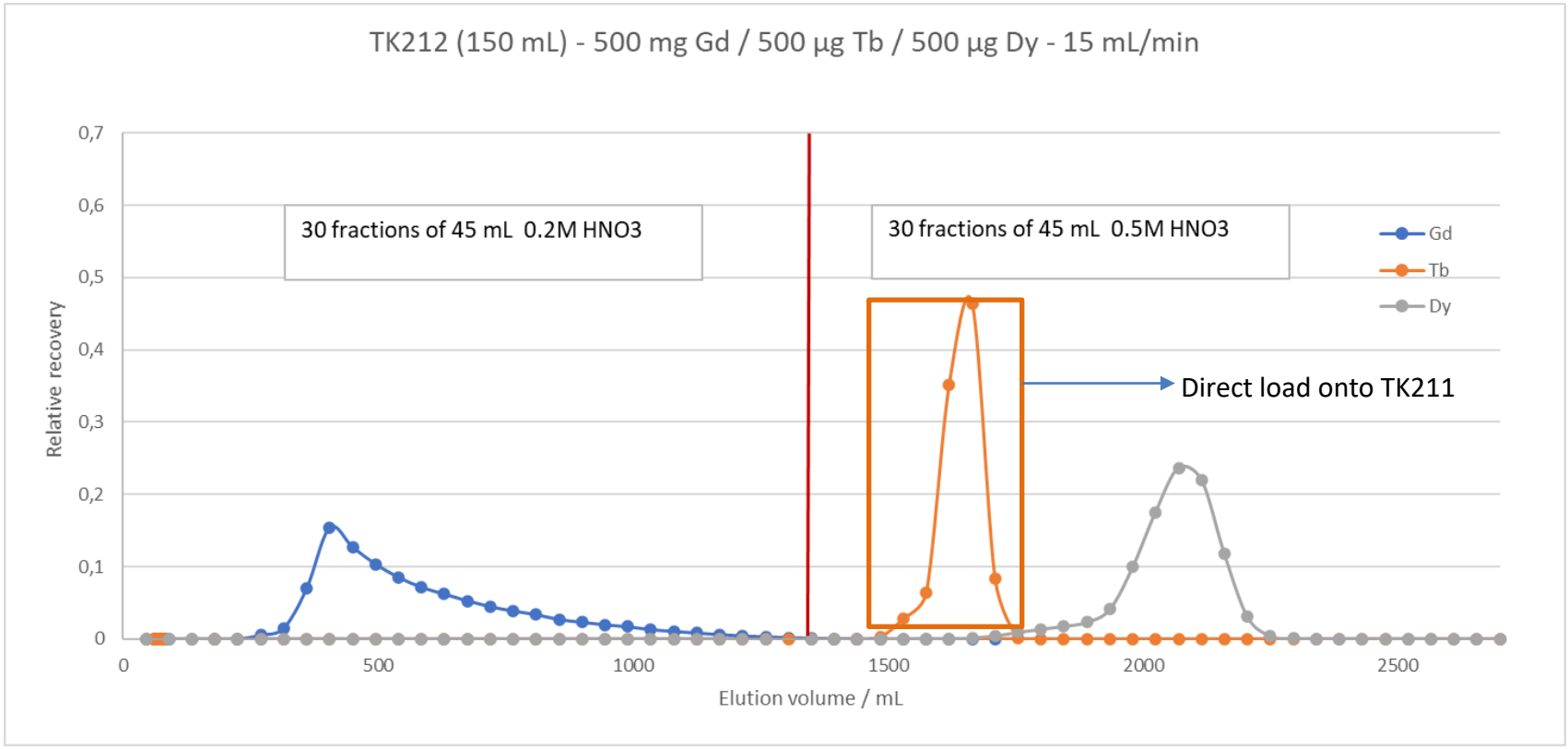
- Irradiated target typically oxide => dissolved in >3M HNO_3
- Conversion via TK221 Resin
- Sequential separation on TK212/TK211
- Final conversion to dilute HCl on TK221 + trace nitrate removal on AIX





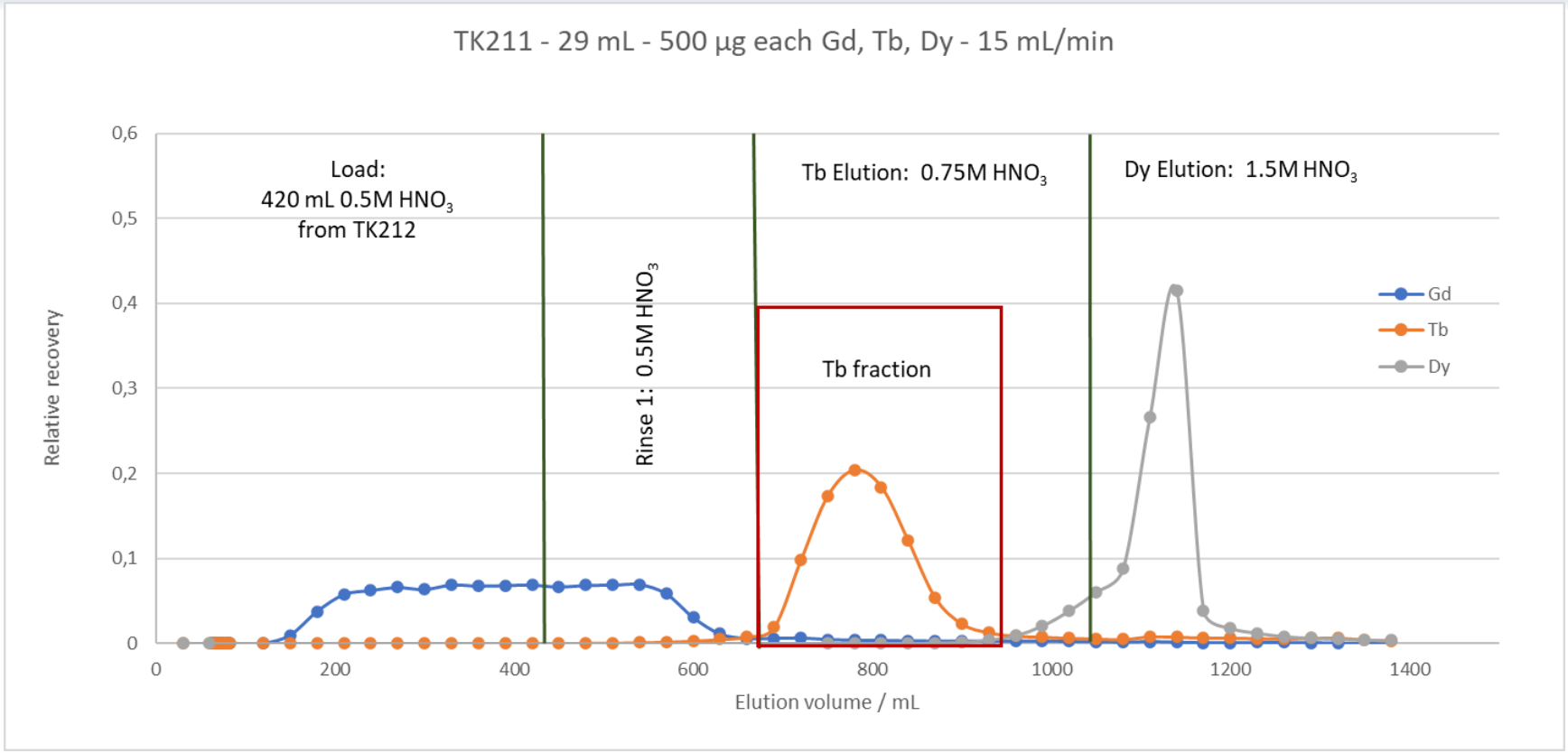
Tb separation from 500 mg Gd targets

- Initial separation on TK212 – 150 mL column (30cm x 2.5cm)
- Large amount of Gd present leads to significant tailing
- Tb separation from Gd and Dy – ideally using online detection
- Fine purification on TK211 (29 mL)



Tb separation from 1000 mg Gd on TK212 (150 mL column)

Tb purification 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: 2 options => 0.75M or 3.5M HNO_3 (3.5M HNO_3 preferable)
- Conversion to dilute HCl via TK221, A8 for nitrate removal
- Further improement via EtOH addition?

Some other on-going projects

- TK-TcScint
  - Direct Tc-99 measurement via impregnated PSm (=> Uni Barcelona)
- TK202 Resin
  - PEG based resin for Tc-99 separation from alkaline samples (e.g. after alkaline fustion)
- TK300 Resin
  - Cs and Rb selective resin based on a Calixarene
- TK102 Resin
  - Sr, Pb s& Ba/Ra separation
  - Higher k' and capacity than SR Resin

Impregnated membrane filters

- TK100, TK201, …
- In field preconcentration
- DGT (Diffusive Gradients in Thin Films) => 'bio-availability'

- Radium
  - TK101
  - New resins and macrocycles
- Rapid tests => Test sticks
- Separation of DTM
  - SE Resin
  - Zr-93, Fe, Mo, Nb,…
- New Sheets (DGA, CU,…)
- Microfluidics
- …

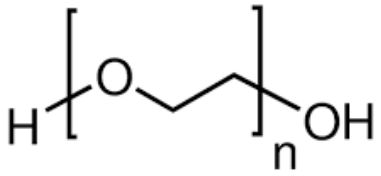
Thank you for your attention!

TRISKEM
Expertise in Separation Chemistry

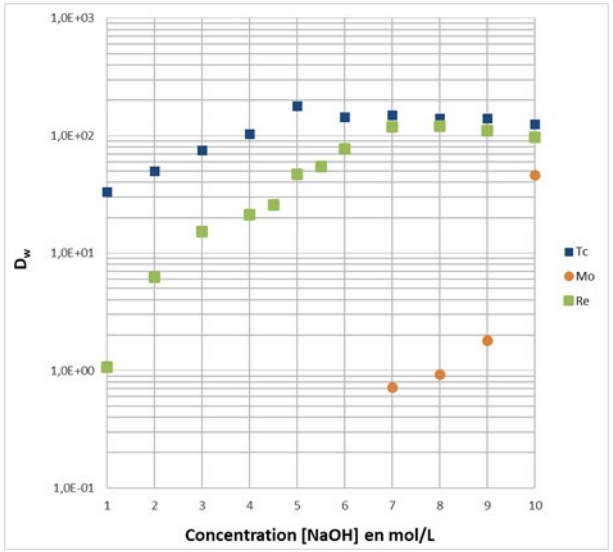
Tc-99 - new TK202 Resin

- Based on Polyethylene Glycol (PEG)

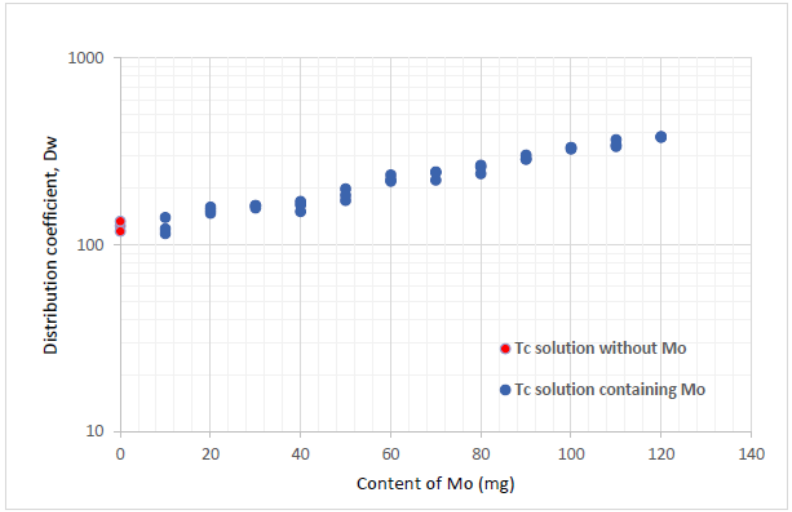
grafted on inert support



- 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-},…)
  - Originally: Separation of Tc-99m from high masses of Mo



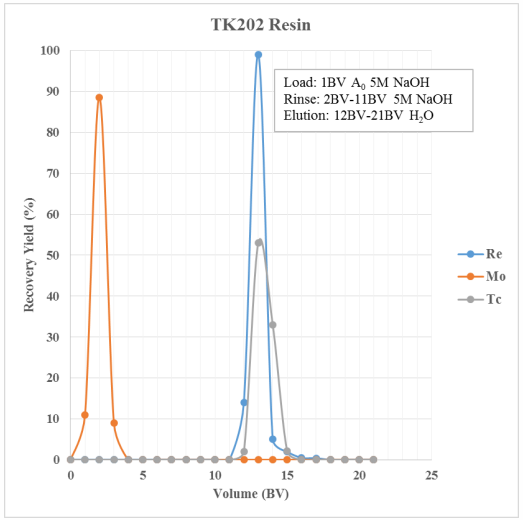
Dw values for Tc, Re and Mo on TK202 Resin, at varying NaOH concentrations. Tc data taken from Cieszykowska et al.(2).



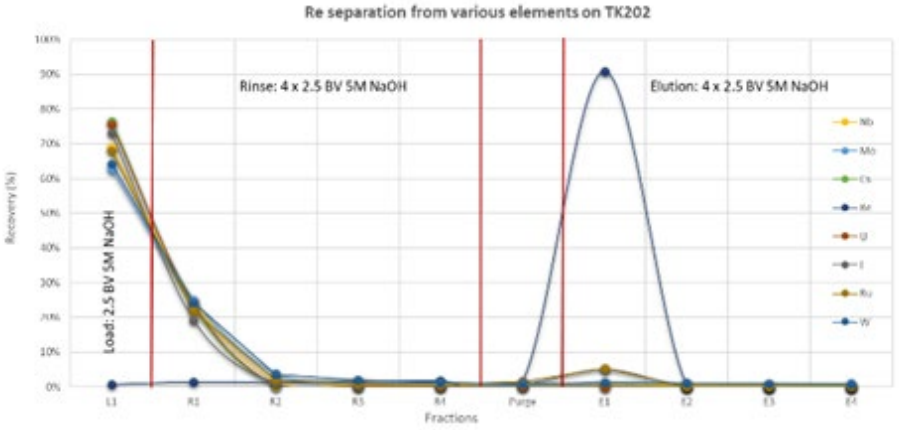
Dw values for Tc in 5M NaOH using 40 mg TK202 Resin, increasing amounts of Mo. Data taken from Cieszykowska et al.

Tc-99 - new TK202 Resin

- Tc retention from high NaOH (preferably 5 - 7M NaOH)
  - e.g. after alkaline fusion of decommissioning samples
- Re may serve as internal standard
- For high Mo samples:
  - Tc rec. > 90% for 6 – 8g Mo per g TK202
- Elution with water
  - Elution in small volume
    - Will still be alkaline
  - Pass through CEX for neutralisation and
  - through aluminium oxide for trace Mo removal and recovery as 0.9% NaCl solution



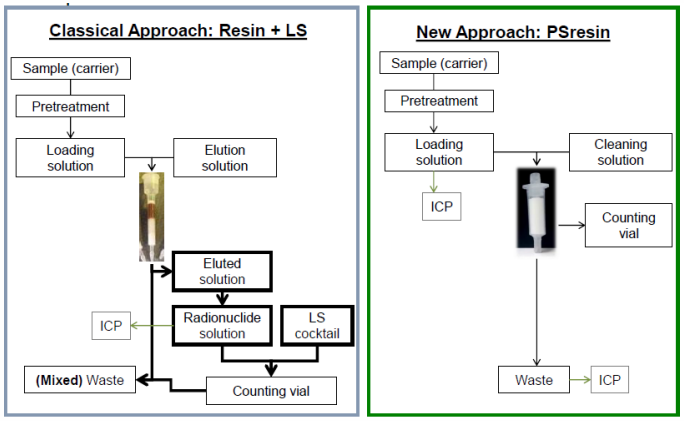
Re/Tc separation from Mo on TK202 Resin



Re separation from selected elements on 2 mL TK202 Resin cartridge, load and rinse at 1 BV/min, elution at 0.25 BV/min.

Tc-99 – New: TK TcScint

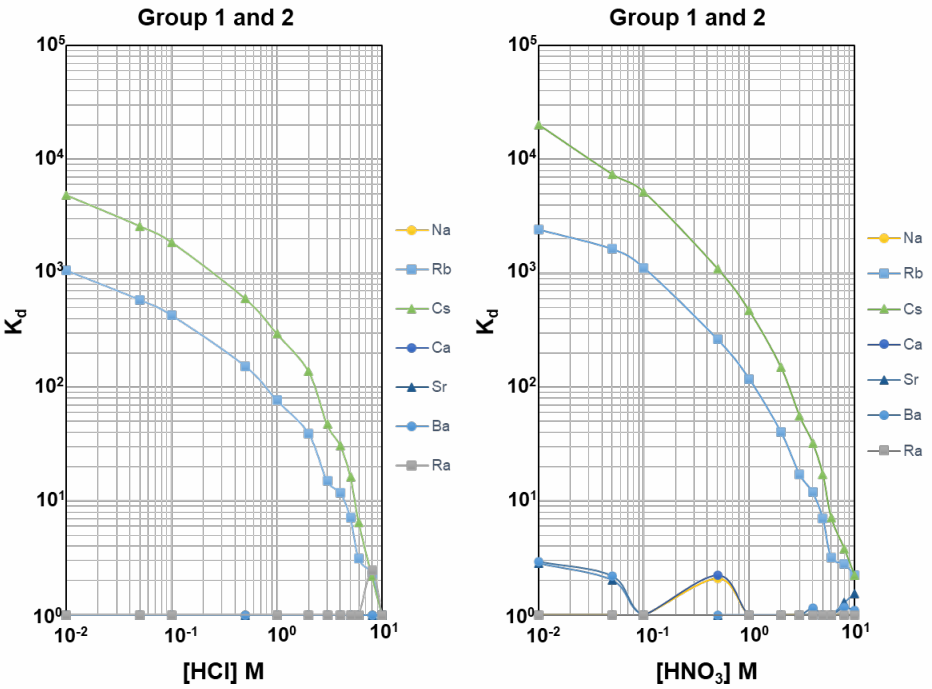
- Based on Plastic Scintillating microspheres (PSm)
- Scintillating beads impregnated with selective extractants
- Developped by García, Tarancón & Bagán
- Now available at TKI
- « TK ElScint » range of products
- First: « TK TcScint »
  - Aliquat based > selectivity similar to TEVA



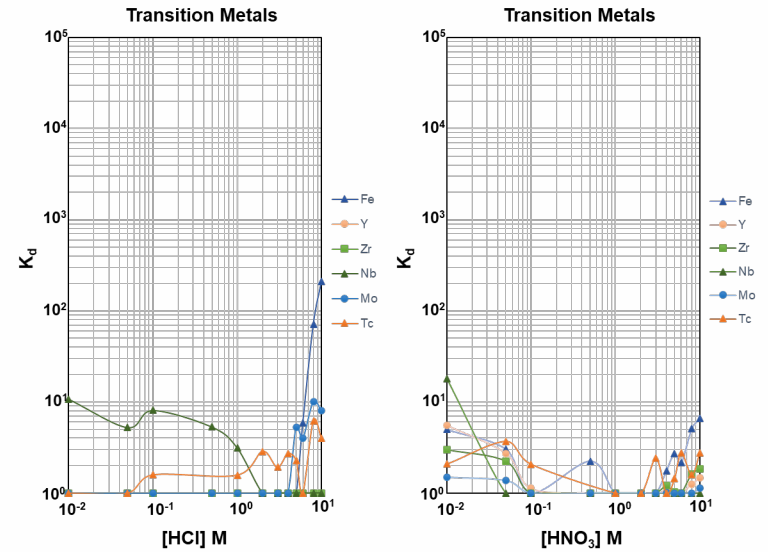
- Environmental/decommissioning monitoring => Tc-99 by LSC
- Direct measurement of cartridges after loading in LSC counter
  - Radioprotection, safety, hands-on-time, waste…
- Chemical yield via Re/ICP-MS in effluents

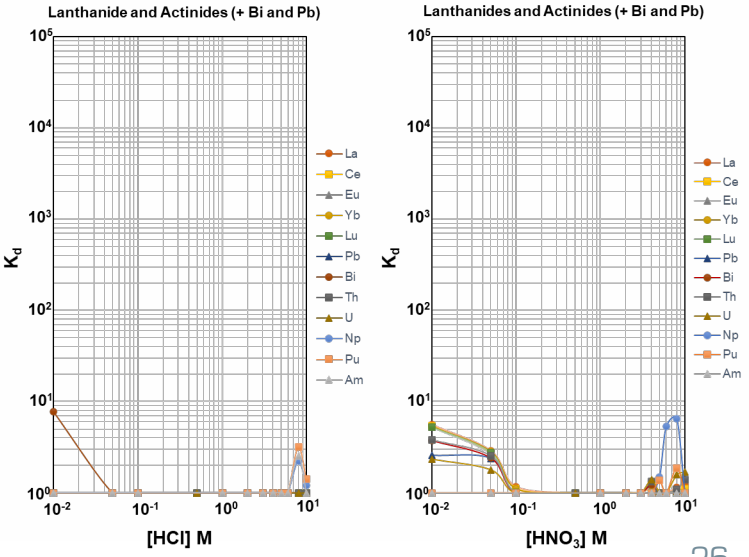
Upcoming - TK300 Resin

- Macrocycle based Resin
- Cs and/or Rb separation
- Selectivity for Cs and Rb over other éléments tested in HNO_3 and HCl

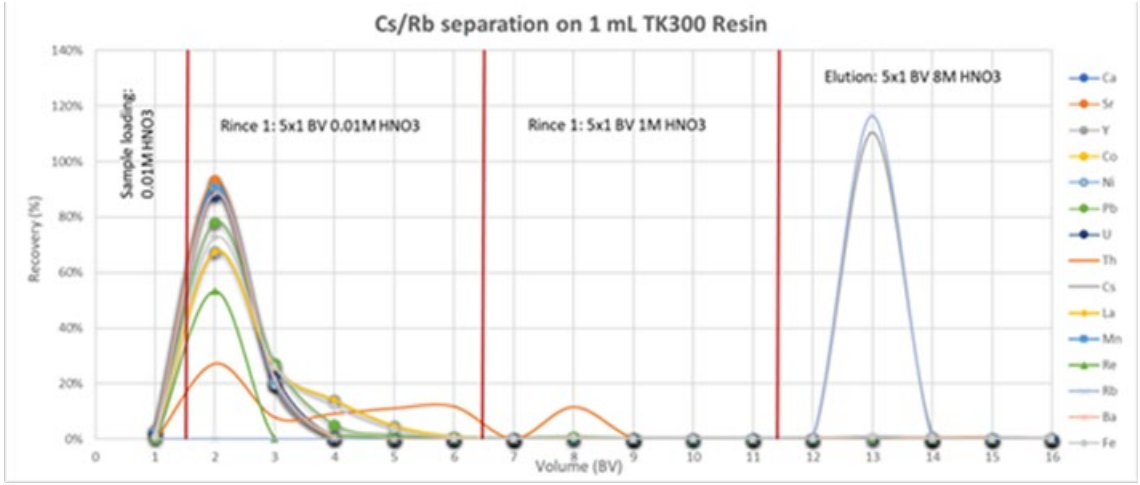


Data provided y B. Russel (NPL)

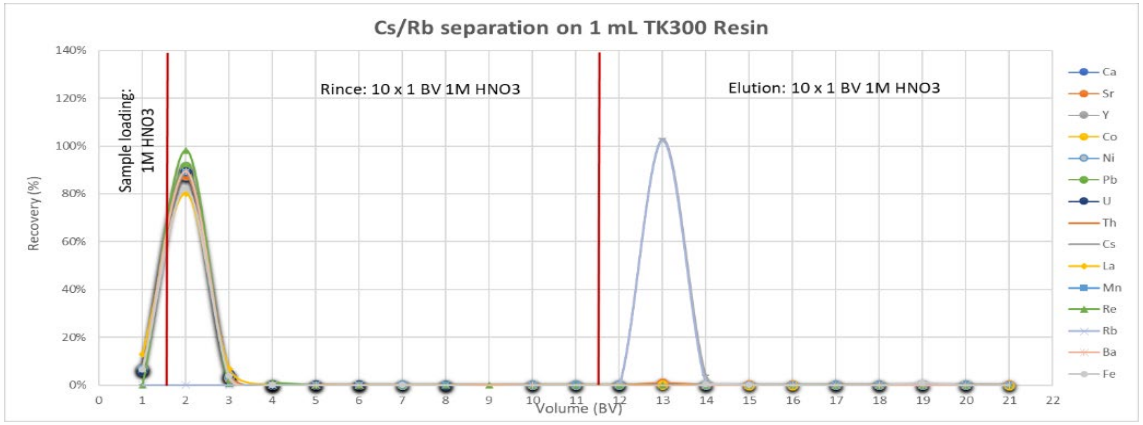




Upcoming - TK300 Resin



Elution study, Cs and Rb separation from selected elements on TK300 resin, loading from dilute acid.



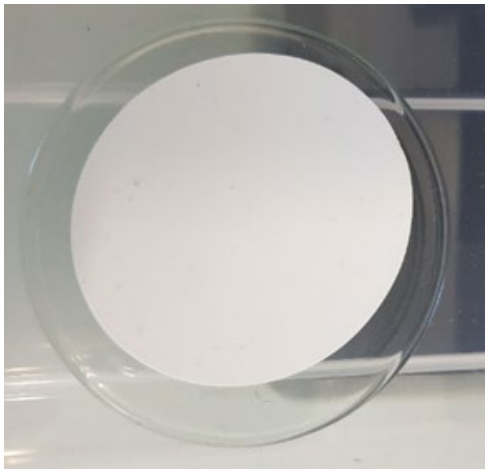
Elution study, Cs and Rb separation from selected elements on TK300 resin, loading from 1M HNO3

- Separation of Cs and Rb
- Retention over wide pH range (up to 1M HNO_3)
- Elution in >3M HNO_3
- Cs/Rb separation possible
- Alternative => push resin into LSC vial (=>TEVA)
  - Discs?
- Drawbacks:
  - Limited Cs capacity
  - Interference by K
  - Limits use for environmental samples

➢ Rather suitable for decommissioning samples

Under development

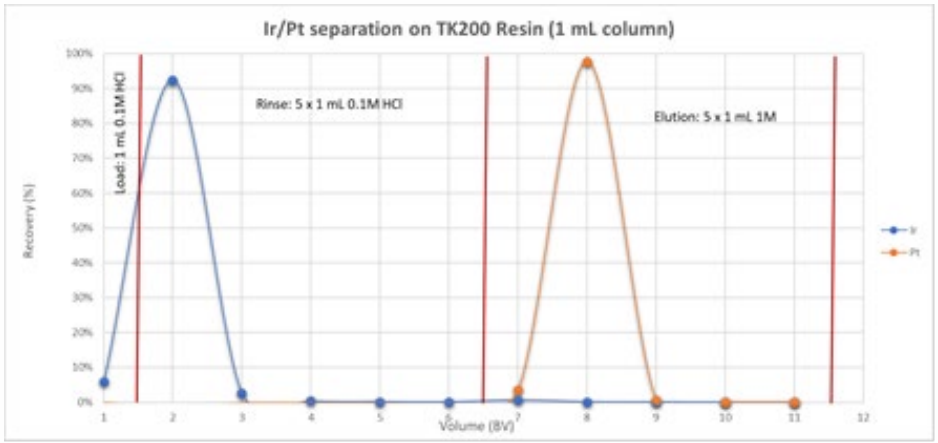
- Range of **extractive membrane filters (MF)**
  - Rapid separation (up to 50 mL / min)
  - Preferably for use with water samples (0.5 – 5L)
  - Sampling in the field
  - Passive Sampling (DGT)
  - Under development:
    - TK201 (Tc)
    - TK100 (Sr, Pb), TK101 (Pb, Ra)
    - CL Resin (iodine)
    - Calixarenes (Ra)
    - TK300 (Cs)
    - …
- Range of 'Test sticks'
  - Pieces of impregnated membrane on support
  - E.g. DGA for Ca,… (JCU, USouthampton)
  - Scintillating supports?



Other separations on TK200

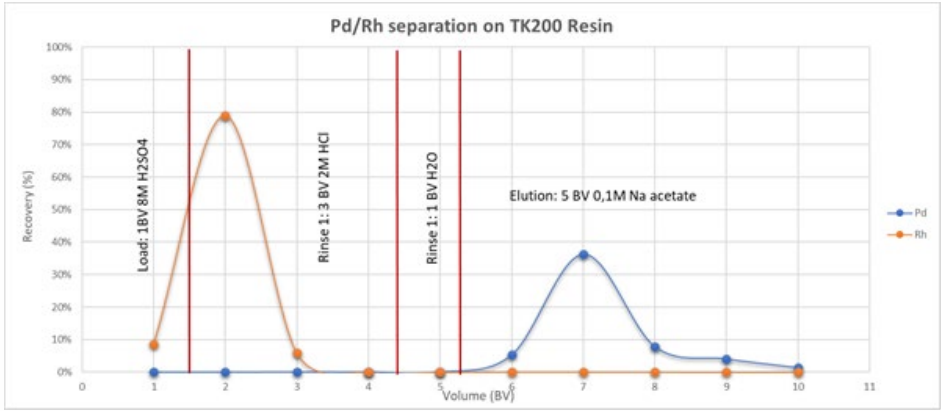
- Pd separation form Rh targets
- Main challenge: target dissolution & oxidation states
- Request: Pd separation from high H_2SO_4
- Removal of H_2SO_4 necessary
  - Rinse with 2M HCl
- Elution in acetate possible
  - To be optimized
- Separation on TK200 possible

• Pt separation from Ir



- Pt/Ir separation. Elution study, ICP-MS measurement

• Pd separation from Rh



- Pd/Rh separation. Elution study, ICP-MS measurement

- Pt separation from Ir targets
- Challenge oxidation state control
- Separation possible on TK200
- Alternative: use of TBP => Obata et al.
- [$^{188,\ 189,191}$Pt]cisplatin
- TBP and AIX based method
  - 3x 2 mL TBP cartridges followed by QMA cartridge

➢ **Also Zn from Cu targets**