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Remotely-prepared $^{224}Ra/^{212}Pb$ generator columns:

Process overview & recent performance evaluations

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U.S. DEPARTMENT OF ENERGY BATTELLE

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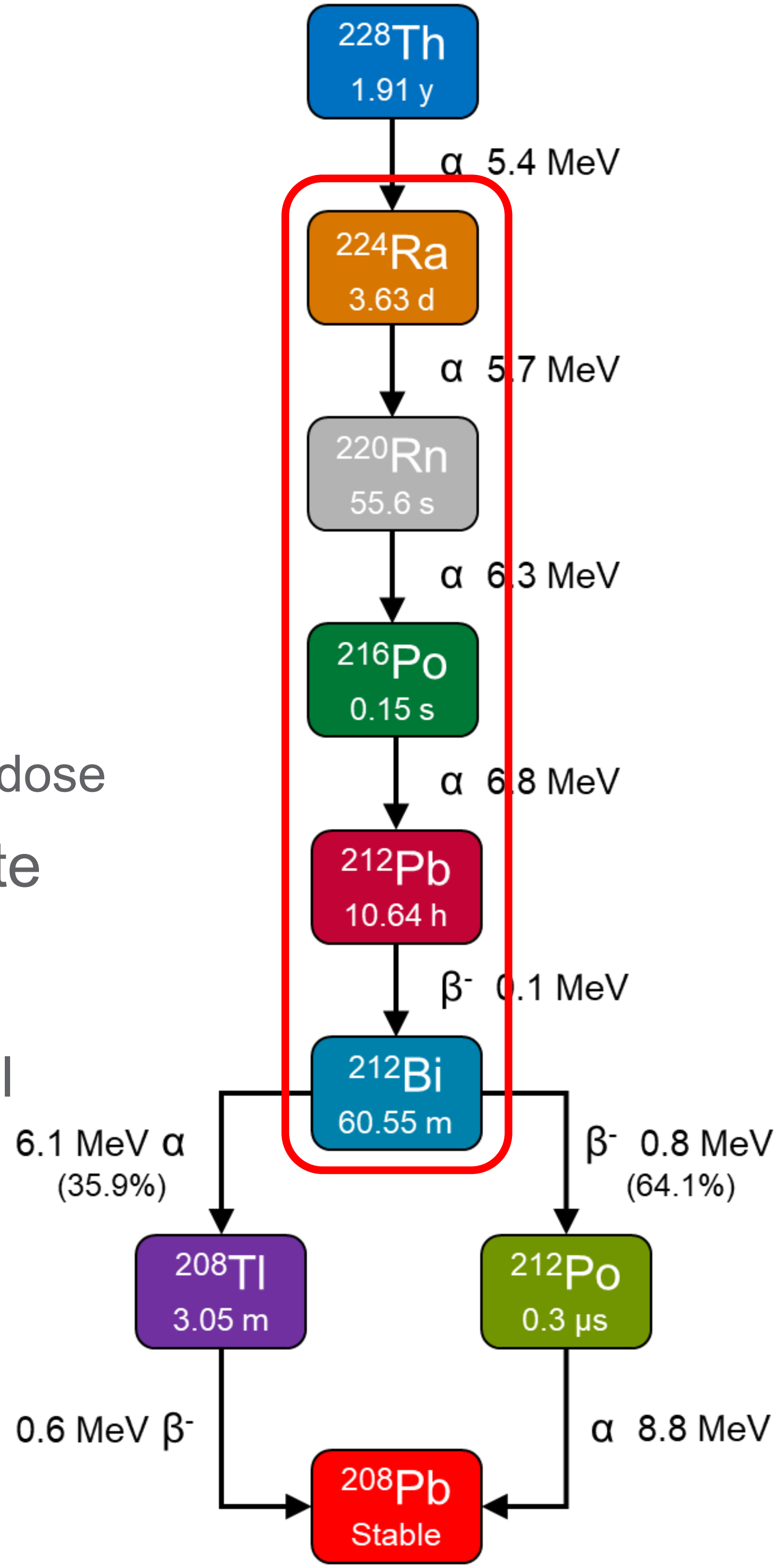
Purpose of Work

- Limited generator availability in the U.S.
  - NIDC presently supplies generators
  - Historically a manual assembly process
    - ✓ Time & dose intensive
- Generator demand is increasing
  - Requires improved assembly efficiencies w/ decreased production team dose
- PNNL set out to develop a fully automated fluidic system to isolate ^{224}Ra from ^{228}Th feedstock and prepare ^{224}Ra-loaded generator columns
  - In FY21, we set up & demonstrated the process up to ~3 mCi level
  - In FY22, we scaled up to clinically relevant levels (11-19 mCi)



Part I.
Automated preparation of ^{212}Pb generator

Research Objectives

- Developed the process chemistry for in-line isolation of ^{224}Ra from ^{228}Th, and the remote assembly of ^{224}Ra-loaded generator columns

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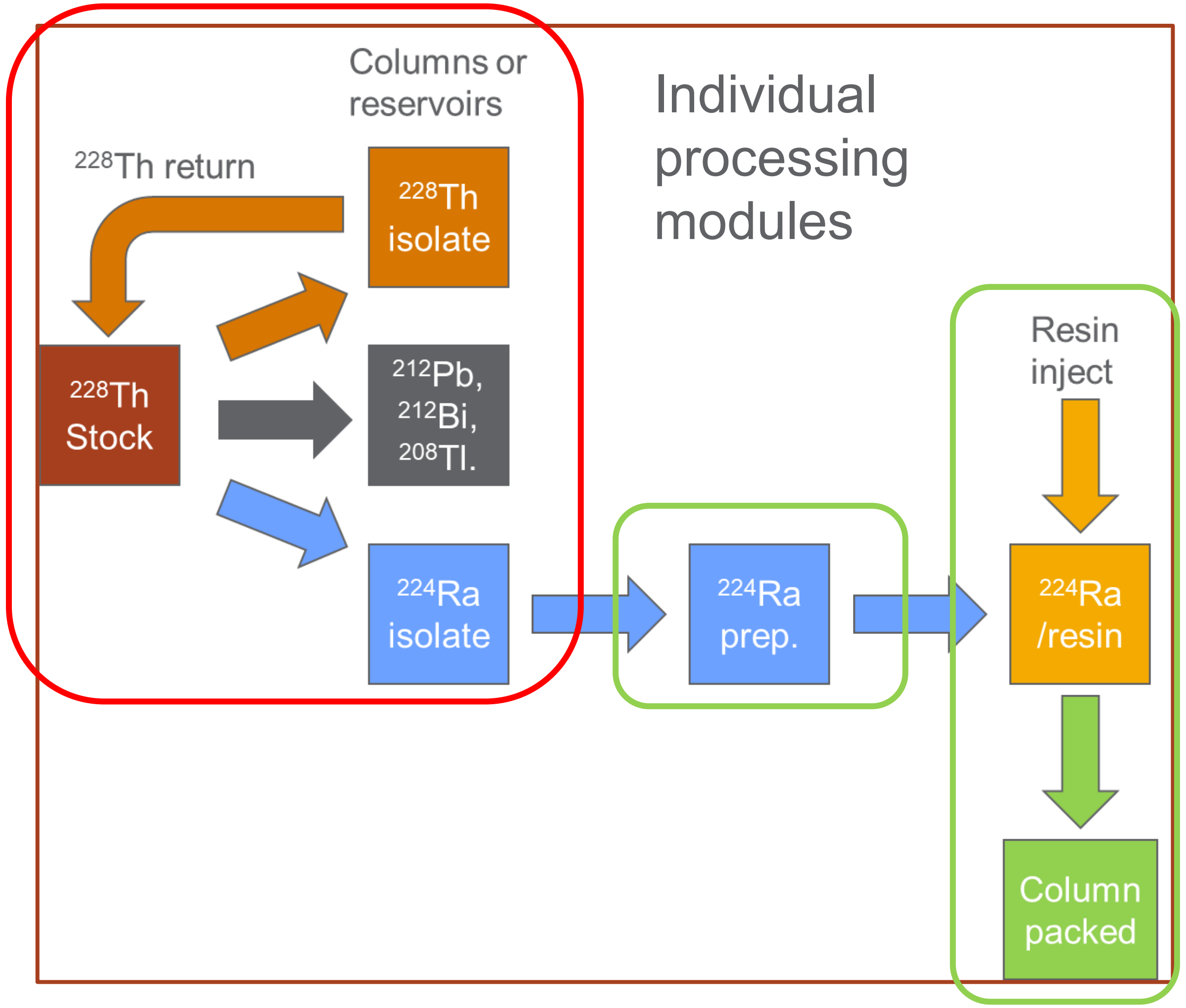
- Developed three fluidic modules
  - Module 1: ^{224}Ra purification from ^{228}Th
    - ✓ In-line removal of dose contributors
    - ✓ Radionuclidically pure ^{224}Ra
    - ✓ Recovery and reuse of ^{228}Th



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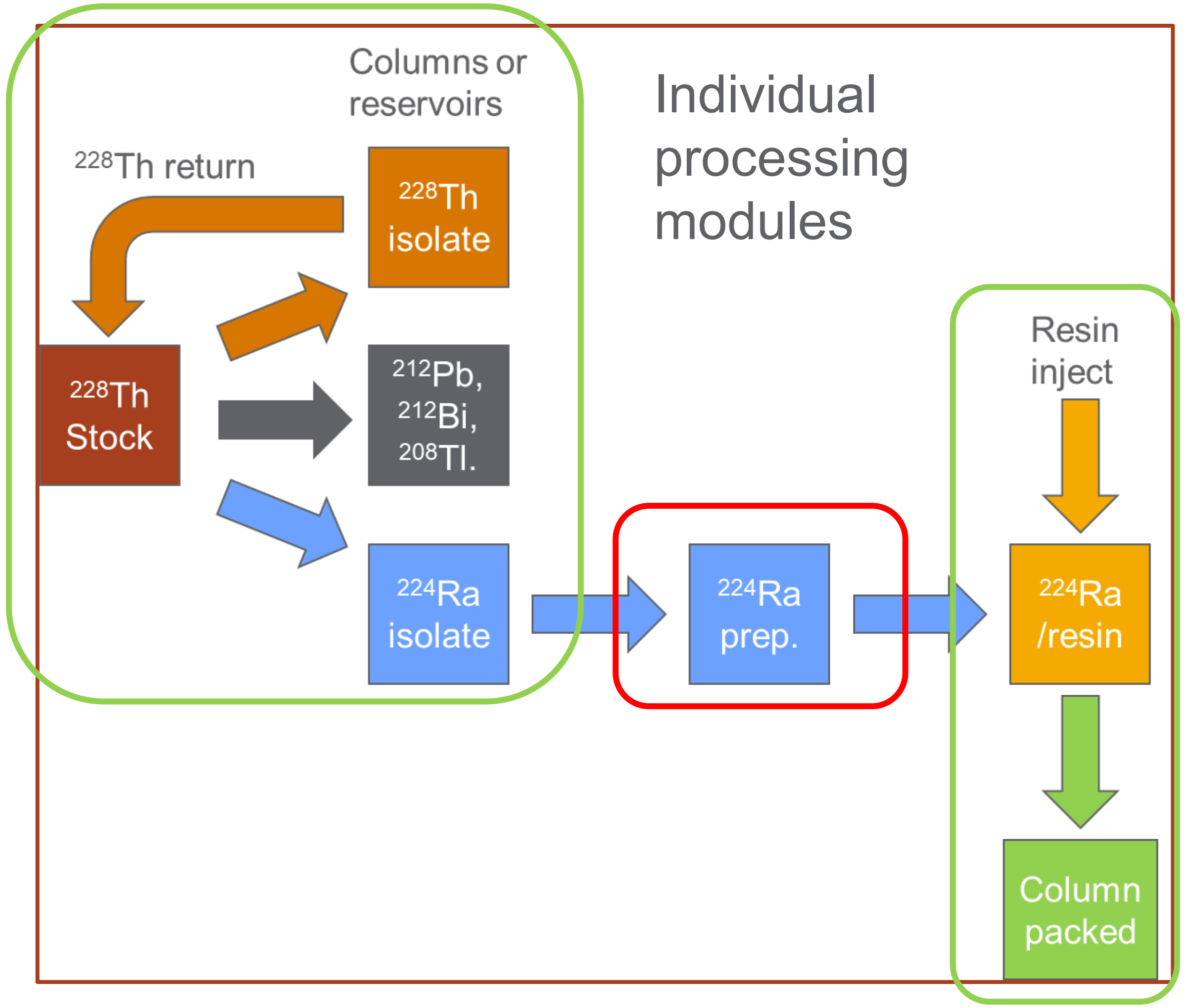
  - Module 2: ^{224}Ra preparation step
    - ✓ Convert ^{224}Ra form for optimal CatIX sorption
    - ✓ Progeny-free, low-dose



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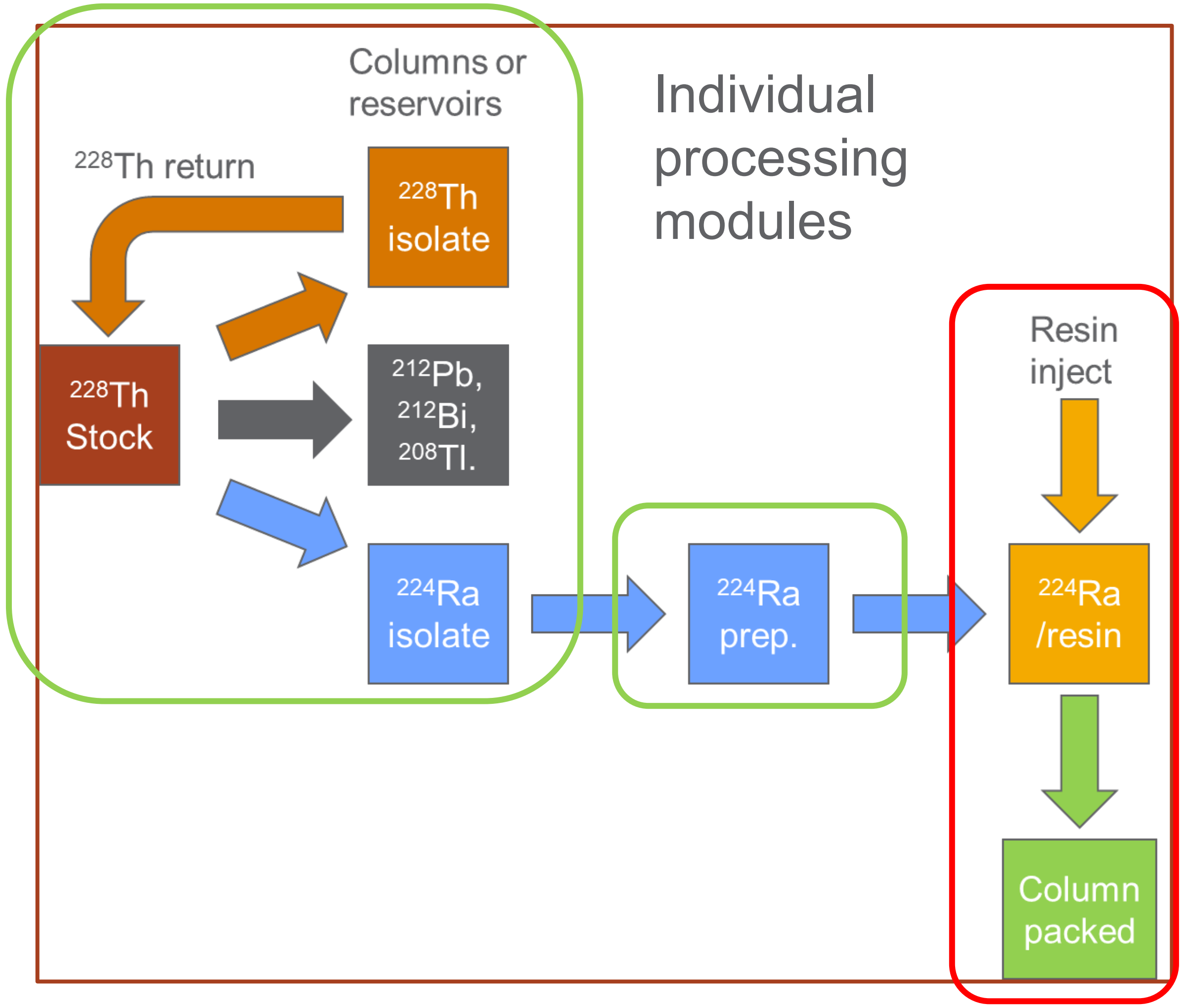
  - Module 2: ^{224}Ra preparation step
    - ✓ Convert ^{224}Ra form for optimal CatIX sorption
    - ✓ Progeny-free, low-dose
  - Module 3: ^{224}Ra / resin binding and column packing
    - ✓ Homogenously loaded column beds
      - ✓ 224Ra adsorbed across all resin beads
    - ✓ High ^{224}Ra binding yield



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- ☑ Integrated the modules into an end-to-end system
- Current: Process optimization & generator testing
  - ~1 h end-to-end, from ^{228}Th feedstock injection to packed ^{212}Pb generator column ready for load-out
  - Human intervention limited to:
    - ✓ ^{228}Th stock insertion (front end, accomplished inside hot cell)
    - ✓ Generator column disconnect (back end)

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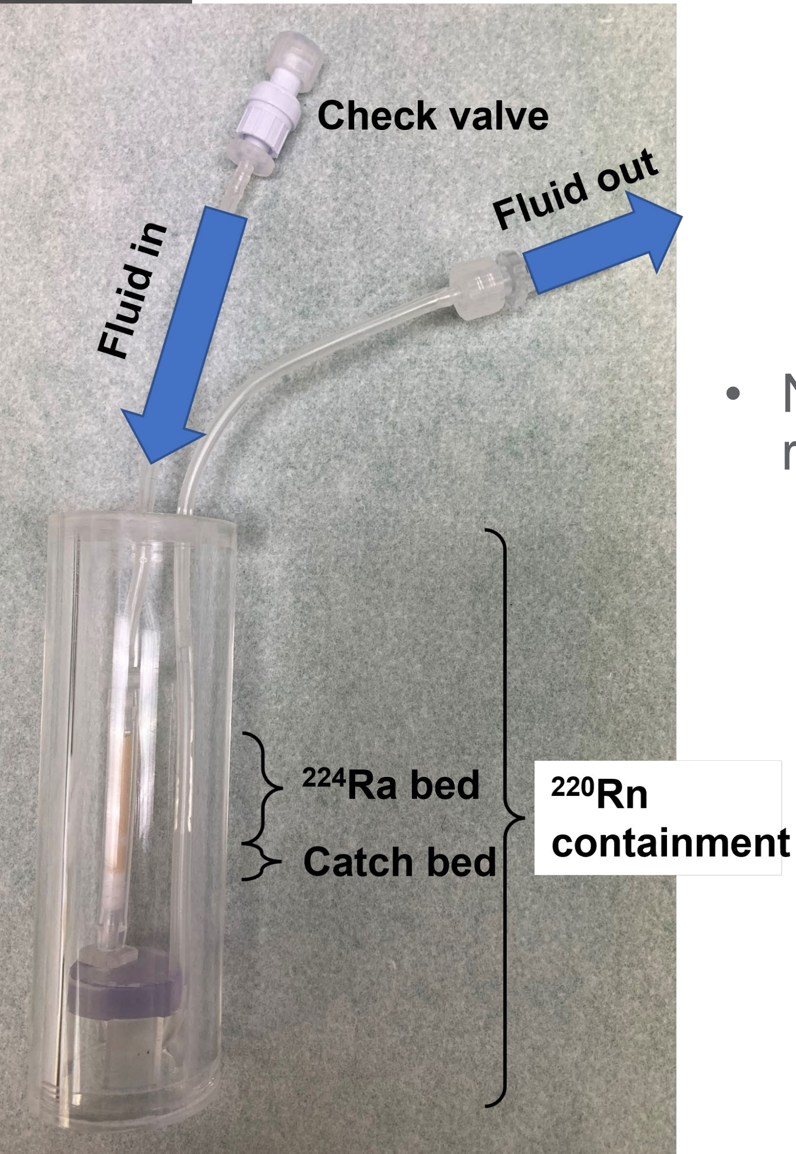
  - Human intervention limited to:
    - ✓ ^{228}Th stock insertion (front end, accomplished inside hot cell)
    - ✓ Generator column disconnect (back end)
- Near future: Transition from "R&D" to routine production
  - Build system into a hard-walled radiological containment structure

Final generator packing step

- ^{224}Ra-loaded resin is slurried & delivered in-line to generator column housing assembly



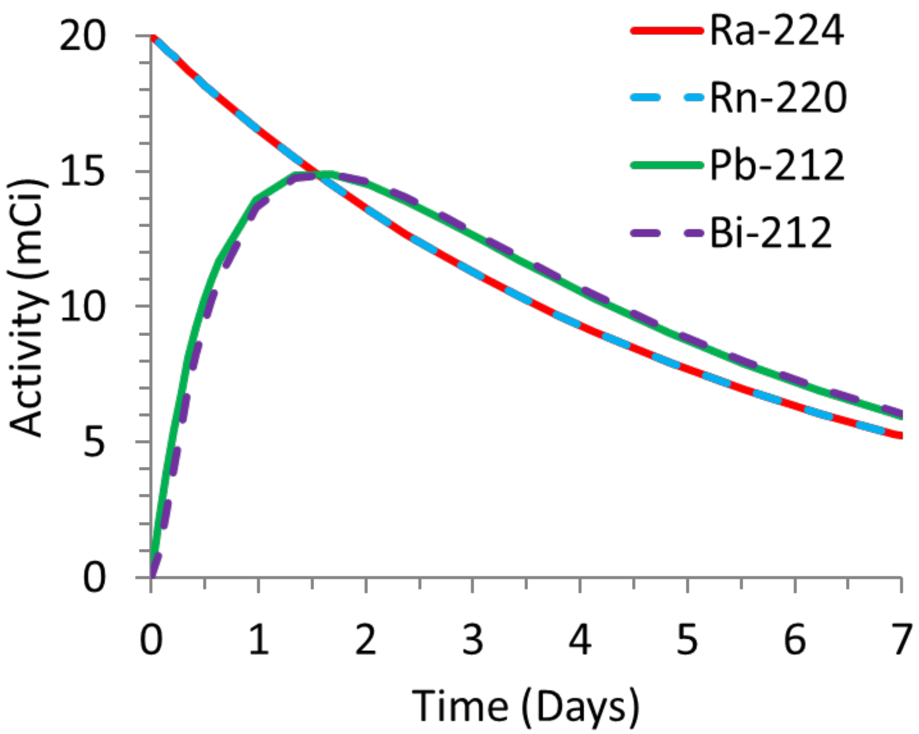
- New acrylic shell assures reduction of:
  - Bremsstrahlung radiation (primarily from ^{208}Tl beta (β_{max}=1.8MeV); and
  - Containment of virtually all ^{220}Rn

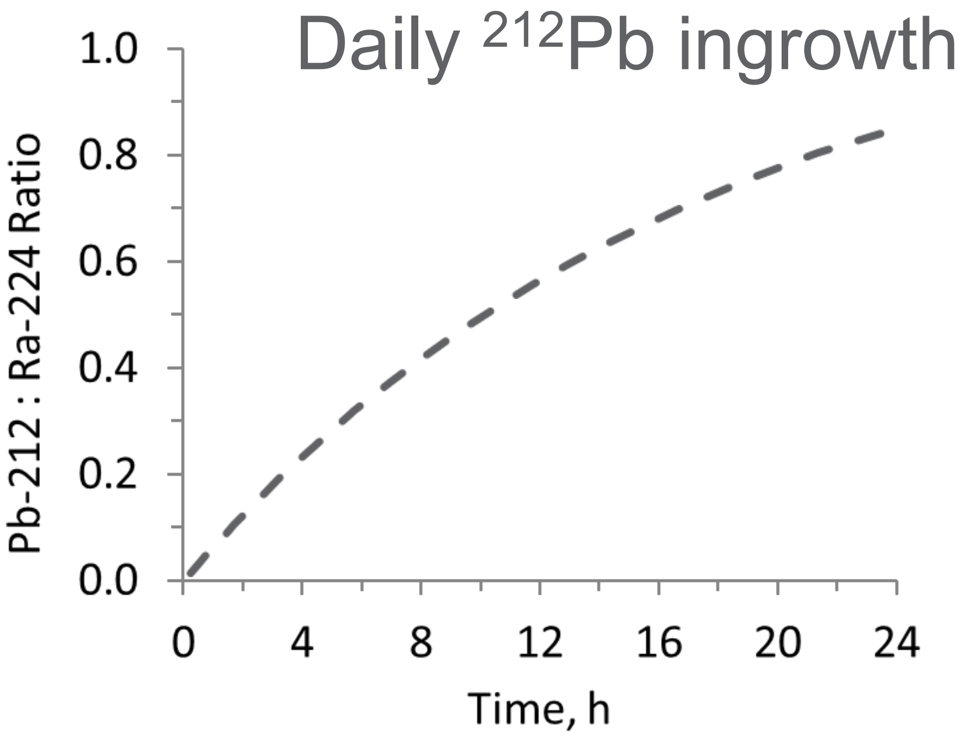
Part II.
^{212}Pb generator performance evaluations

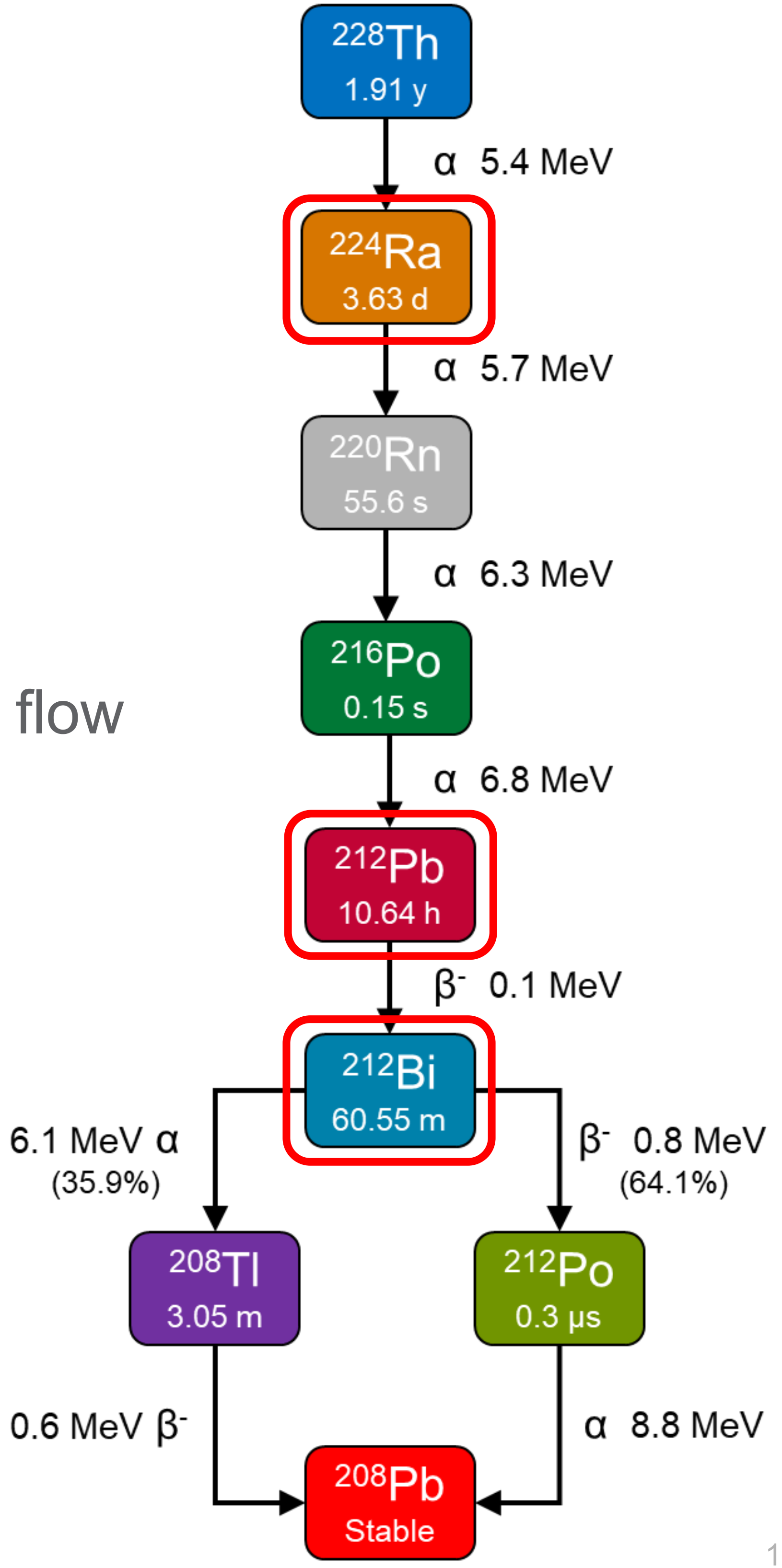
- Recent testing performed up to ~19 mCi

^{212}Pb / ^{212}Bi generator column performance testing

- Conduct daily milking tests for 10-12 days
  - Evaluate ^{212}Pb + ^{212}Bi co-elution in 2 M HCl
    - ✓ (w/ & w/o a disposable “catch column”)
  - Evaluate in-line ^{212}Pb conversion to acetate buffer
- All milkings performed using digital pumps for absolute volume & flow rate control







^{212}Pb milking yield: Traditional milking

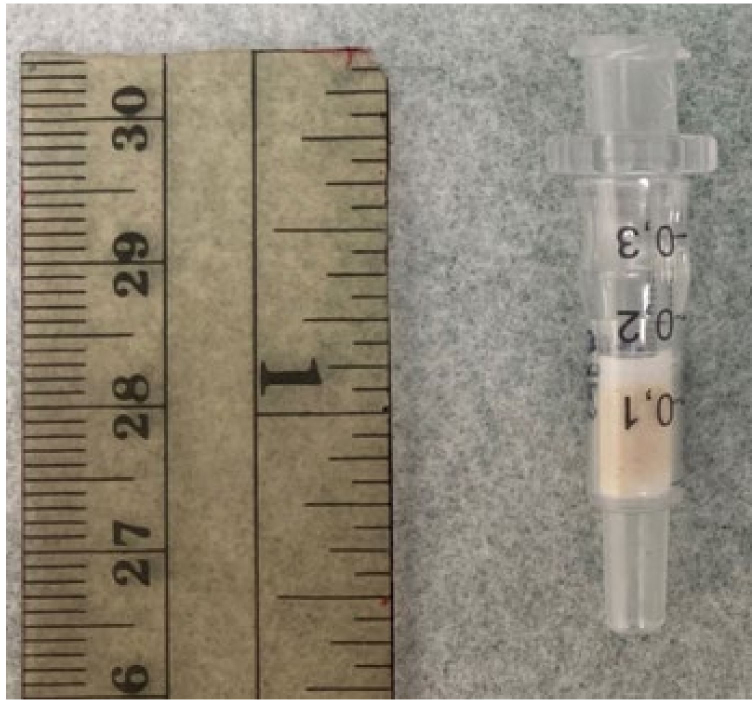
- Simple generator column milking process:
  - Flow rate = 1.0 mL/min
  - 1.0 mL 2 M HCl, followed by 1.0 mL H_2O flush & air for storage
    - ✓ Elutes ^{212}Pb & ^{212}Bi together

Traditional milking

Activity level	Generator	Mean yield, (%)	Uncertainty, ±1s (%)	n
Sub-clinical	3	93.64	1.52	3
	4	93.77	1.33	3
	6	92.02	3.57	3
	Mean	**93.14**	**2.22**	**9**
Clinical	7	92.48	2.88	7
	8	94.81	0.84	3
	9	94.98	0.75	4
	Mean	**93.69**	**2.38**	**14**
	Grand mean	**93.48**	**2.28**	**23**

^{212}Pb milking yield: w/ "catch column"

- Simple generator column milking process:
  - Flow rate = 1.0 mL/min
  - 1.0 mL 2 M HCl, followed by 1.0 mL H_2O flush & air for storage
    - ✓ Elutes ^{212}Pb & ^{212}Bi together
  - Generator milked with "catch column"
    - ✓ "catch column" placed between generator outlet & ^{212}Pb collection vessel



Disposable ~100µL MP-50 resin bed

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w/ "catch column"

Activity level	Generator	Mean yield, (%)	Uncertainty, ±1s (%)	n
Sub-clinical	3	92.20	3.87	5
	4	88.00	8.49	3
	6	86.84	1.42	3
	Mean	**88.22**	**6.88**	**12**
Clinical	7	84.00	5.13	6
	8	92.48	0.63	5
	9	90.06	6.24	4
	Mean	**88.44**	**5.73**	**15**
Grand mean		**88.34**	**6.14**	**27**

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^{212}Pb milking yield: Tandem column

- Tandem column milking process (method adapted from [1]):
  - Flow rate = 1.0 mL/min
  - 1.0 mL 2 M HCl generator milking volume, followed by 2 M HCl wash of tandem col.
  - DI water rinse of tandem col.
  - ^{212}Pb elution w/ 1.0 mL NaOAc (pH ~6)
    - ✓ Elutes ^{212}Pb *sans* ^{212}Bi

Traditional milking

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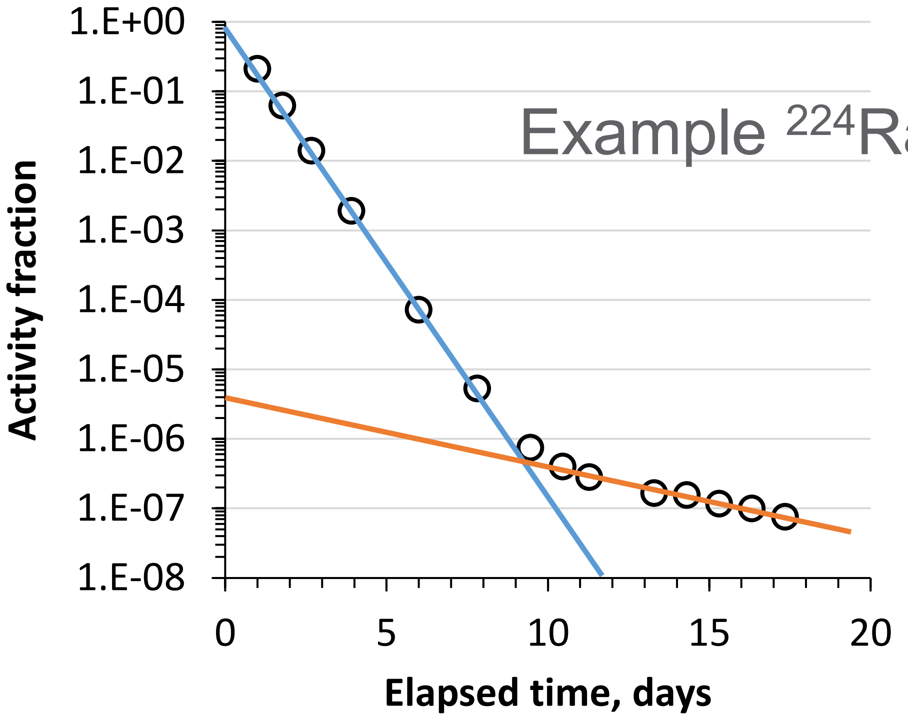
Tandem column

Activity level	Generator	Mean yield, (%)	Uncertainty, ±1s (%)	n
Sub-clinical	6	92.93	0.29	2
Clinical	7	94.55	1.35	3
	8	92.45	0.93	2
	9	91.74	2.34	4
	Grand mean	**92.85**	**1.87**	**11**

[1] M. Li, et al., "Automated cassette-based production of high specific activity [$^{203/212}$Pb]peptide-based theranostic radiopharmaceuticals for image-guided radionuclide therapy for cancer", *Appl Rad & Isotop*, 127 (2017), 52-60.

Evaluation of ^{224}Ra breakthrough

- Each milked ^{212}Pb product fraction evaluated for presence of ^{224}Ra
- We age the milked products to determine ^{224}Ra content @ t = 0
  - Count data modeled by two-component exponential decay best fit (*SigmaPlot 14.0*)
  - Generator 9 (~19 mCi) milkings are illustrated here



Example ^{224}Ra determination @ t=0 approach

Evaluation of ^{224}Ra breakthrough

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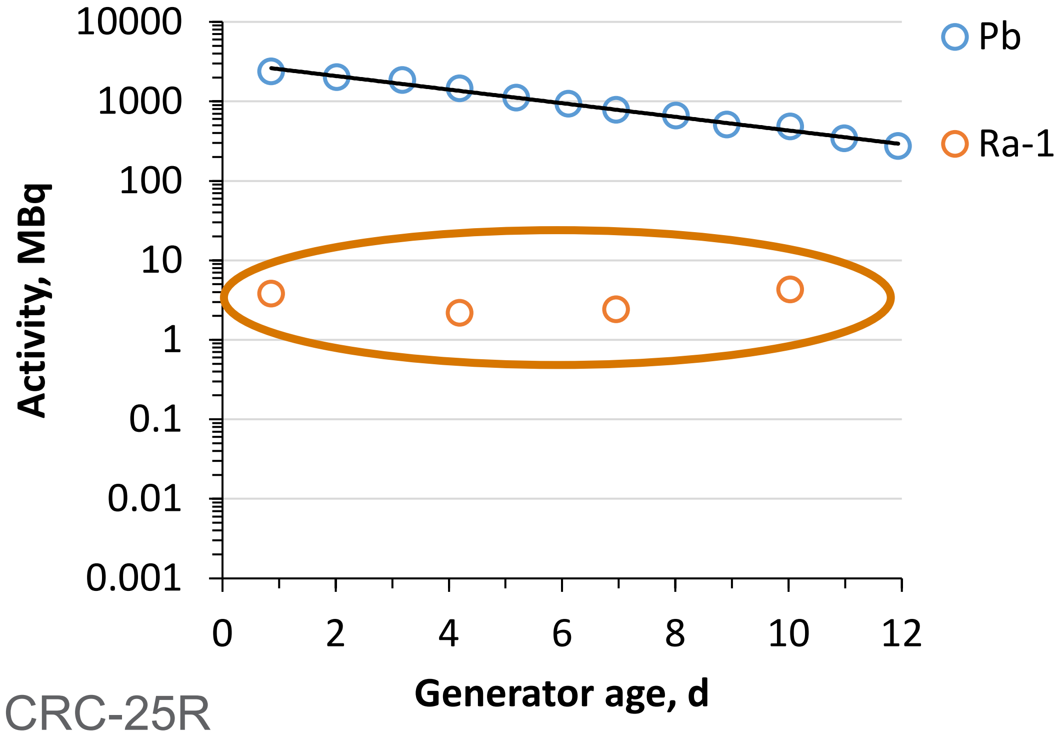
Traditional milking (Ra-1)*



* y-axis is ^{212}Pb+^{212}Bi activity, as ‘030’ setting on Capintec CRC-25R

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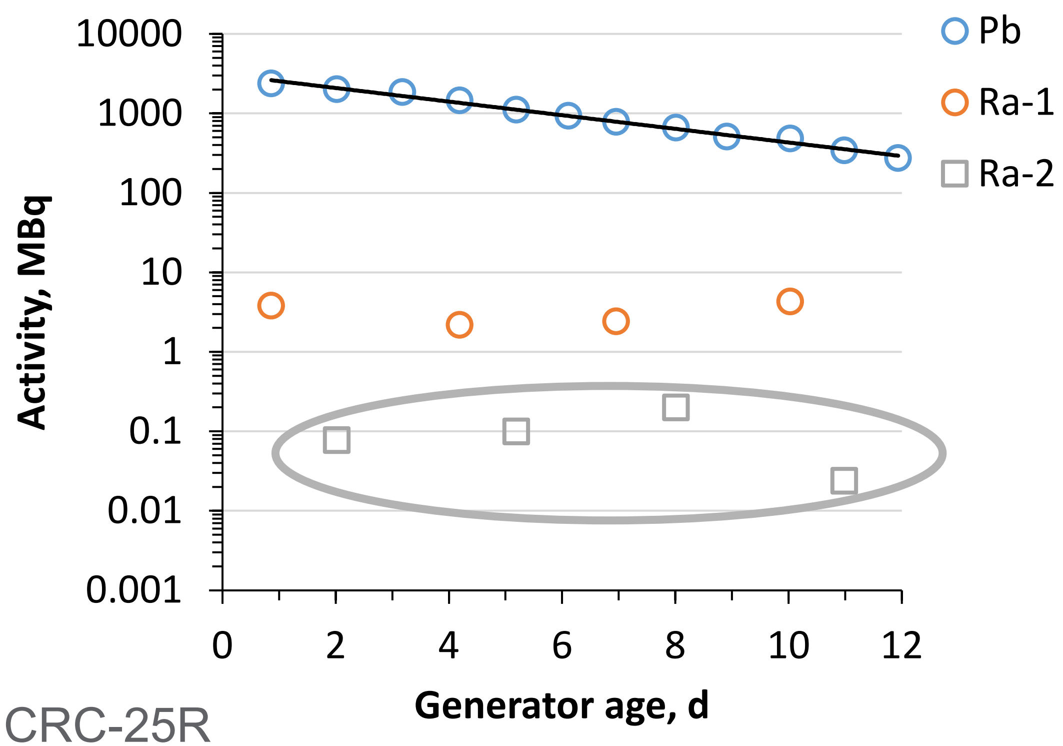
w/ “catch column” (Ra-2)*



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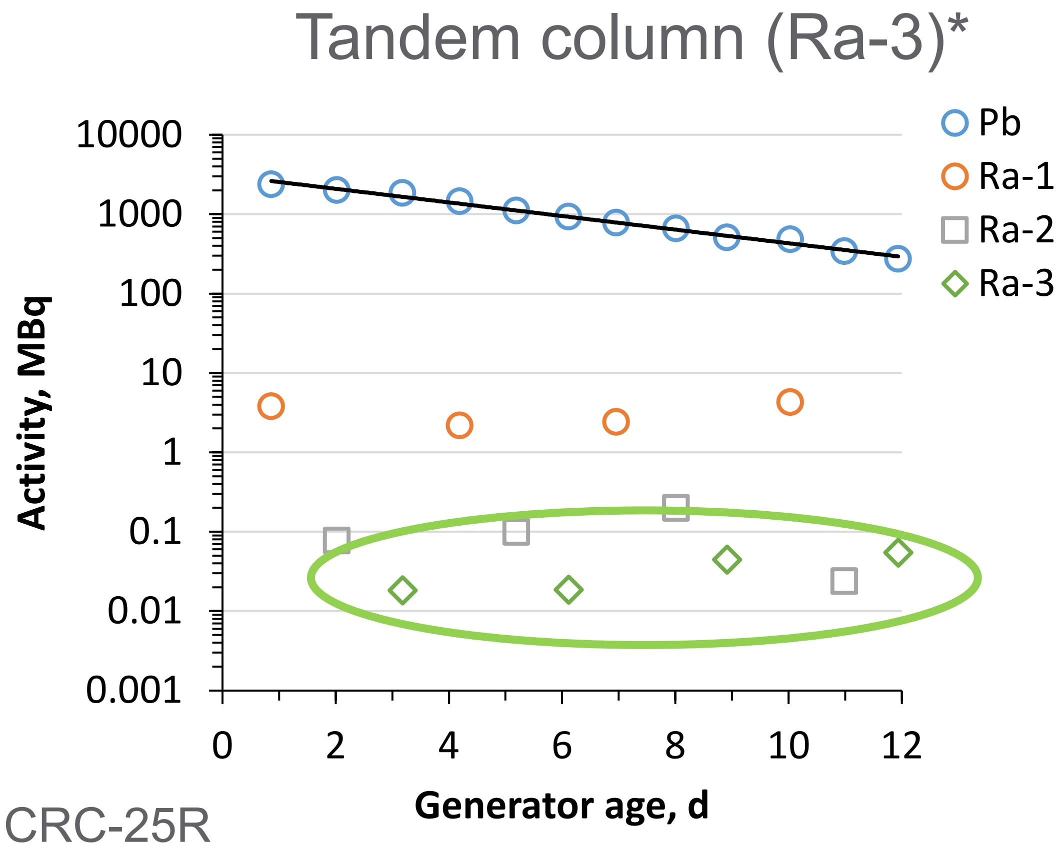

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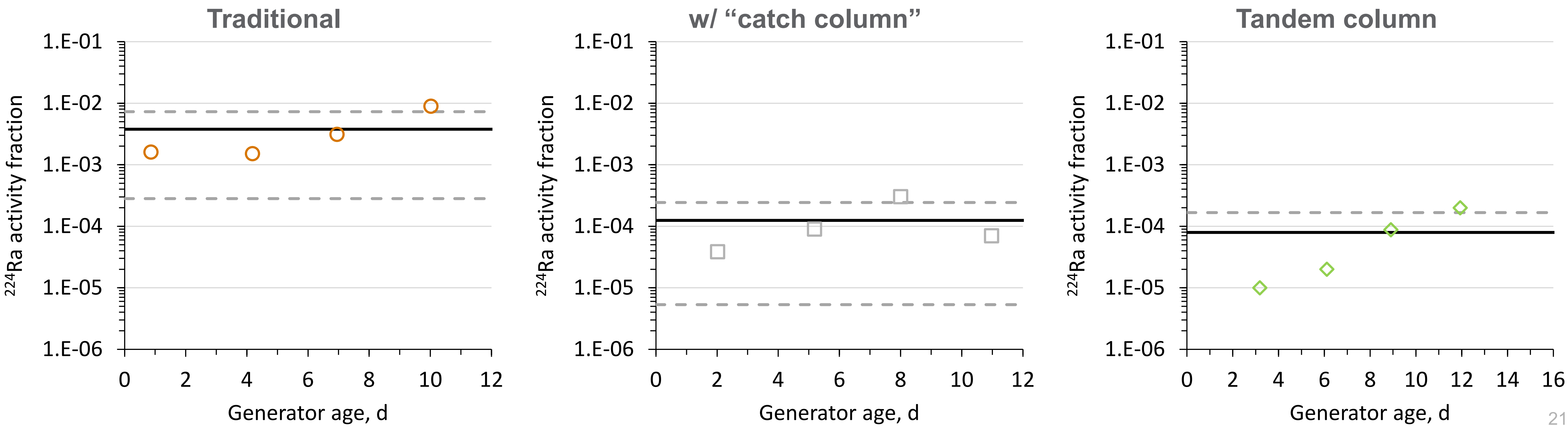
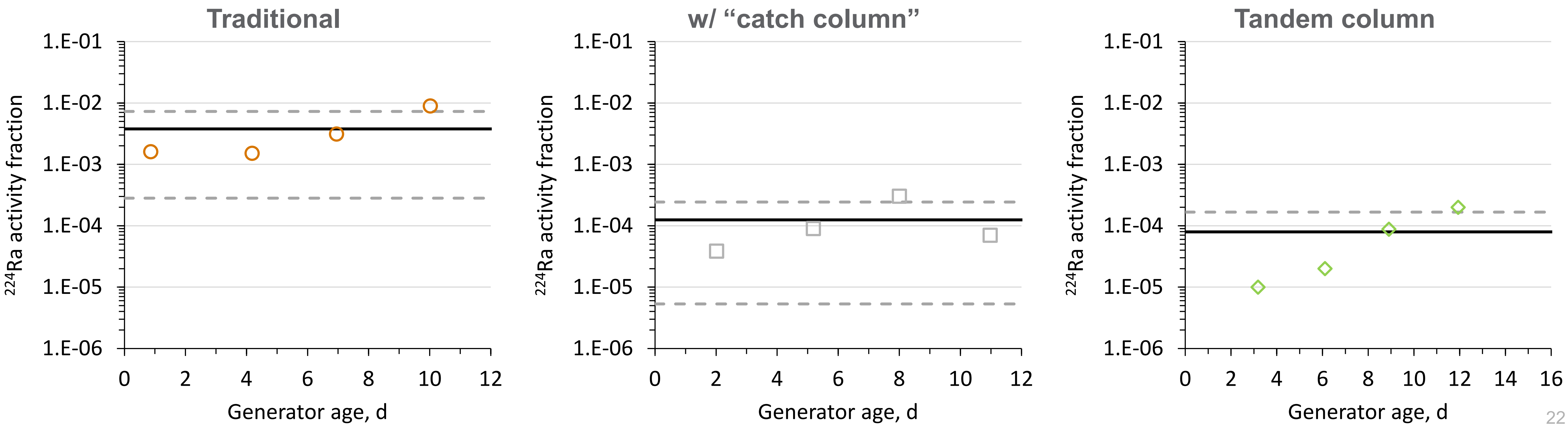
Evaluation of ^{224}Ra breakthrough, cont'd

- ^{224}Ra breakthrough fractions for Generator 9 are illustrated below



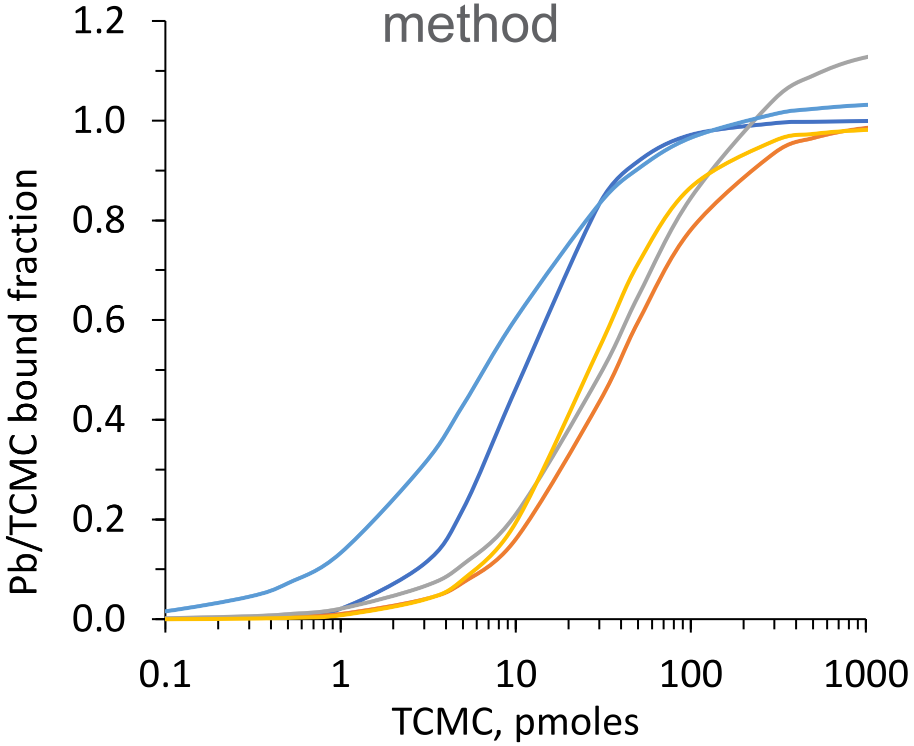
Evaluation of ^{224}Ra breakthrough, cont'd

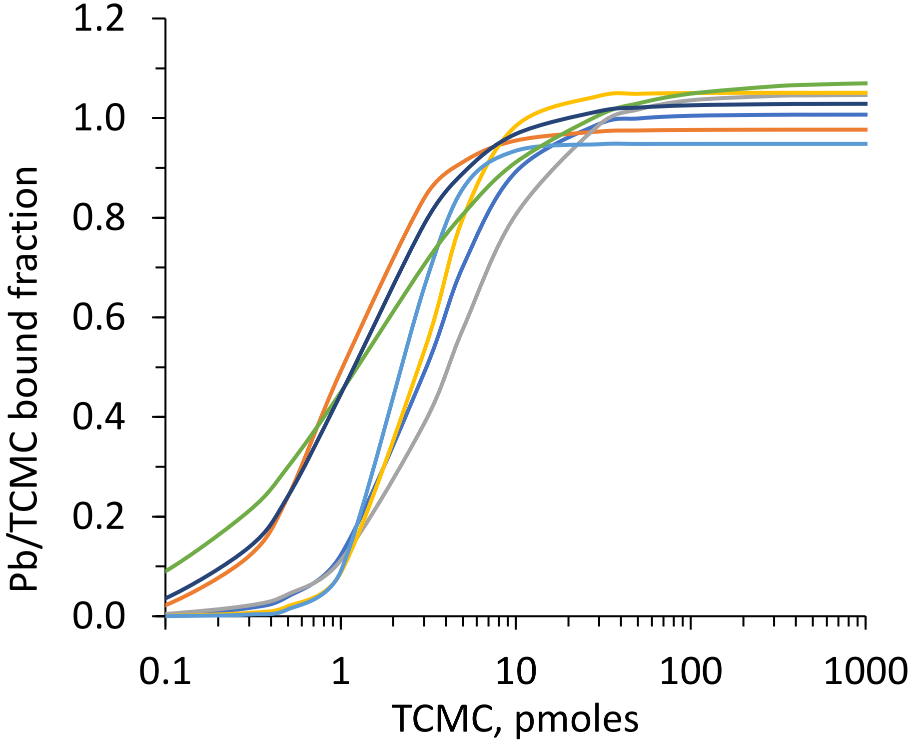
- ^{224}Ra breakthrough fractions for Generator 9 are illustrated below
- Overall mean values across all generators prepared to date (± 1s):
  - **Traditional:** **(3.0 ± 2.1) x 10^{-3} (n=20)**
  - **w/ catch col.:** **(1.9 ± 1.7) x 10^{-4} (n=25)**
  - **Tandem col.:** **(1.8 ± 1.8) x 10^{-4} (n=17)**

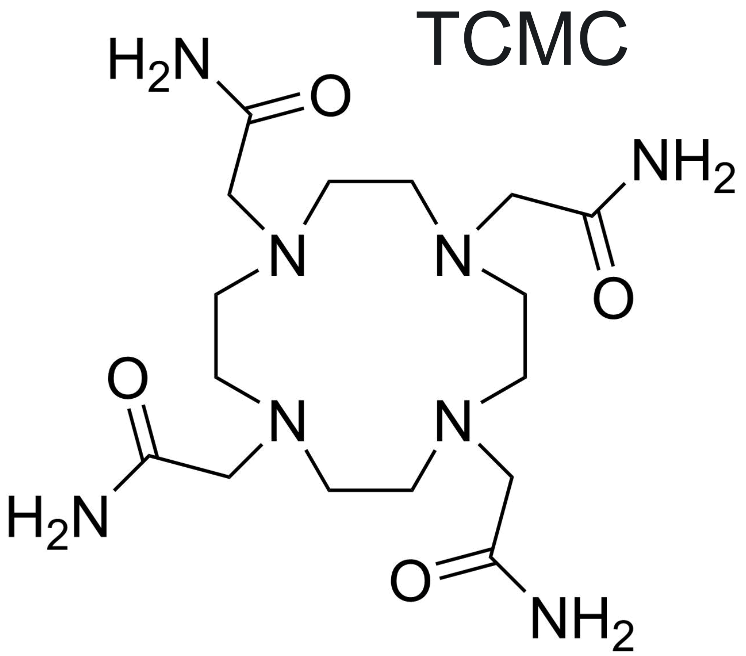


Radiolabeling studies on ^{212}Pb product fractions

- Conducting ^{212}Pb product titrations with TCMC chelate [2] to assess $^{208+212}$Pb binding affinities in NaOAc sol'ns
  - 1/10th of product added to increasing quantities of TCMC, in pH 6 NaOAc buffer
  - [*Preliminary*] evaluation of differences in $^{208+212}$Pb binding to TCMC between the various milking methods described herein
    - ✓ To date, we see a ~10x Pb:TCMC binding improvement when employing the tandem column method







[2] 1,4,7,10-Tetrakis(aminocarbonylmethyl)-1,4,7,10-tetraazacyclododecane

Next steps for FY23:

- PNNL working towards becoming a NIDC supplier (≤ 15 mCi)
  - Would begin with monthly production schedule, with capacity to increase production frequency as demand dictates
- Concurrently, we will evaluate our ability to produce higher-activity generators (≤ 50 mCi)
  - And will assess whether higher activities result in diminishing generator performance / radiolytic effects
- [Contact NIDC if interested in conducting an independent performance evaluation on these generators]

Summary

- Developed a remote fluidic system for auto-preparation of generators
  - Dramatic reduction in production staff dose
  - End-to-end processing time of ~1 h
  - Reproducible ^{224}Ra loading (±2%)
  - Near-quantitative ^{228}Th feedstock recycling (99.6±1.2%)
  - Acrylic shell inhibits Bremsstrahlung & ^{220}Rn leakage
- FY22 was first generator testing at clinical (11-19 mCi) levels
  - Pb milking yields (~90% in 1mL of 2M HCl)
  - Radionuclidic purity (^{224}Ra breakthrough) is dependent on three milking options evaluated
  - $^{208+212}$Pb product binding evaluations w/ TCMC chelate are ongoing
    - ✓ Pb:TCMC binding is dependent on milking option; with tandem column method demonstrating highest TCMC binding efficacy
- In FY23:
  - Anticipate transition to production on behalf of NIDC
  - And, anticipate evaluating generators w/ scaled-up ^{224}Ra levels

Acknowledgements

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- PNNL's Shielded Facilities Organization (SFO):
  - ✓ Johnny Trevino
  - ✓ April Wickersham
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  - ✓ Marilyn Wirth
- System & software support:
  - ✓ Jared Johnson

Thank you!