Lovelace Respiratory Research Institute

Medical Countermeasures for Treating Internal Deposits of Radionuclides

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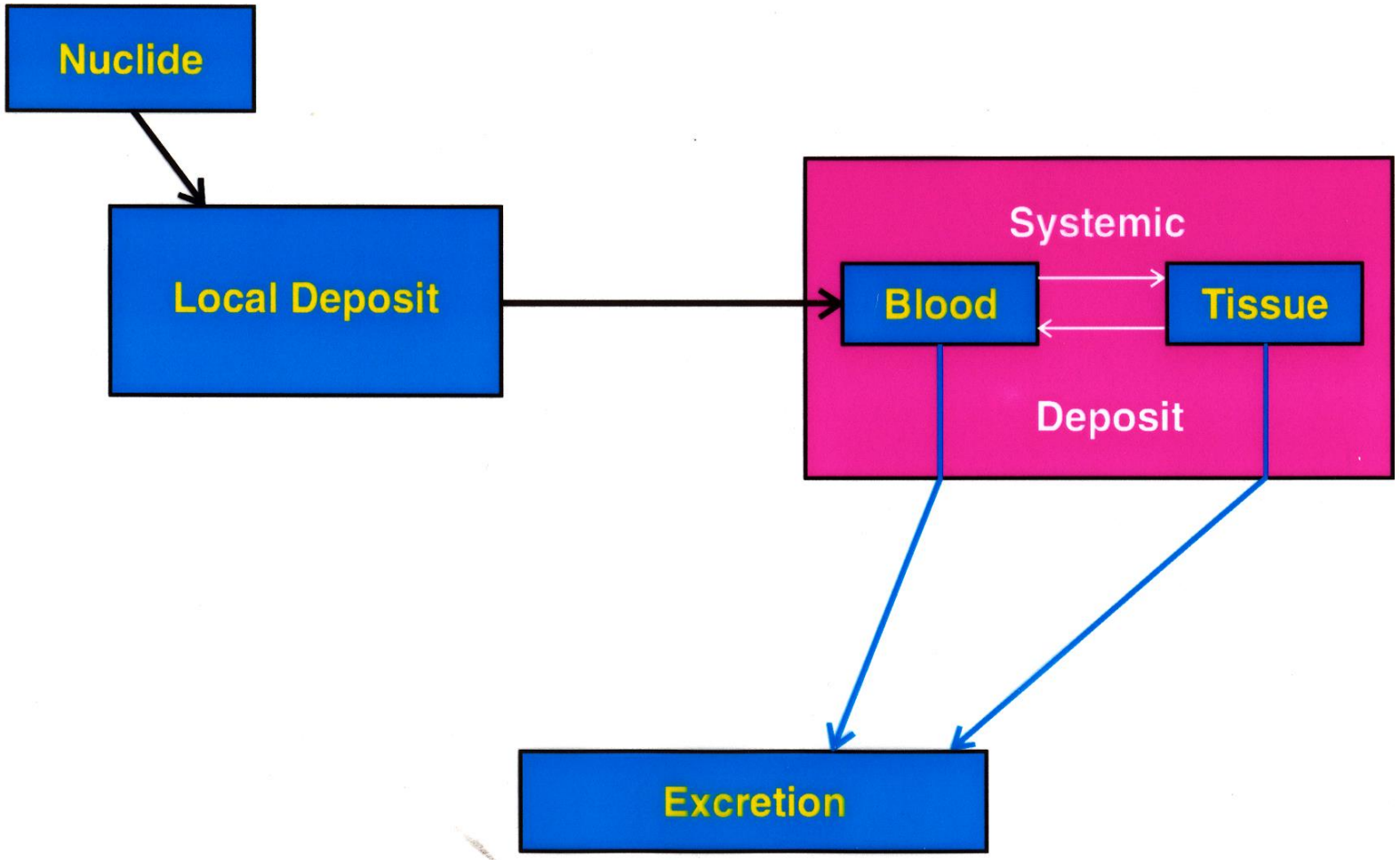
Goal of Decorporation

DECORPORATION

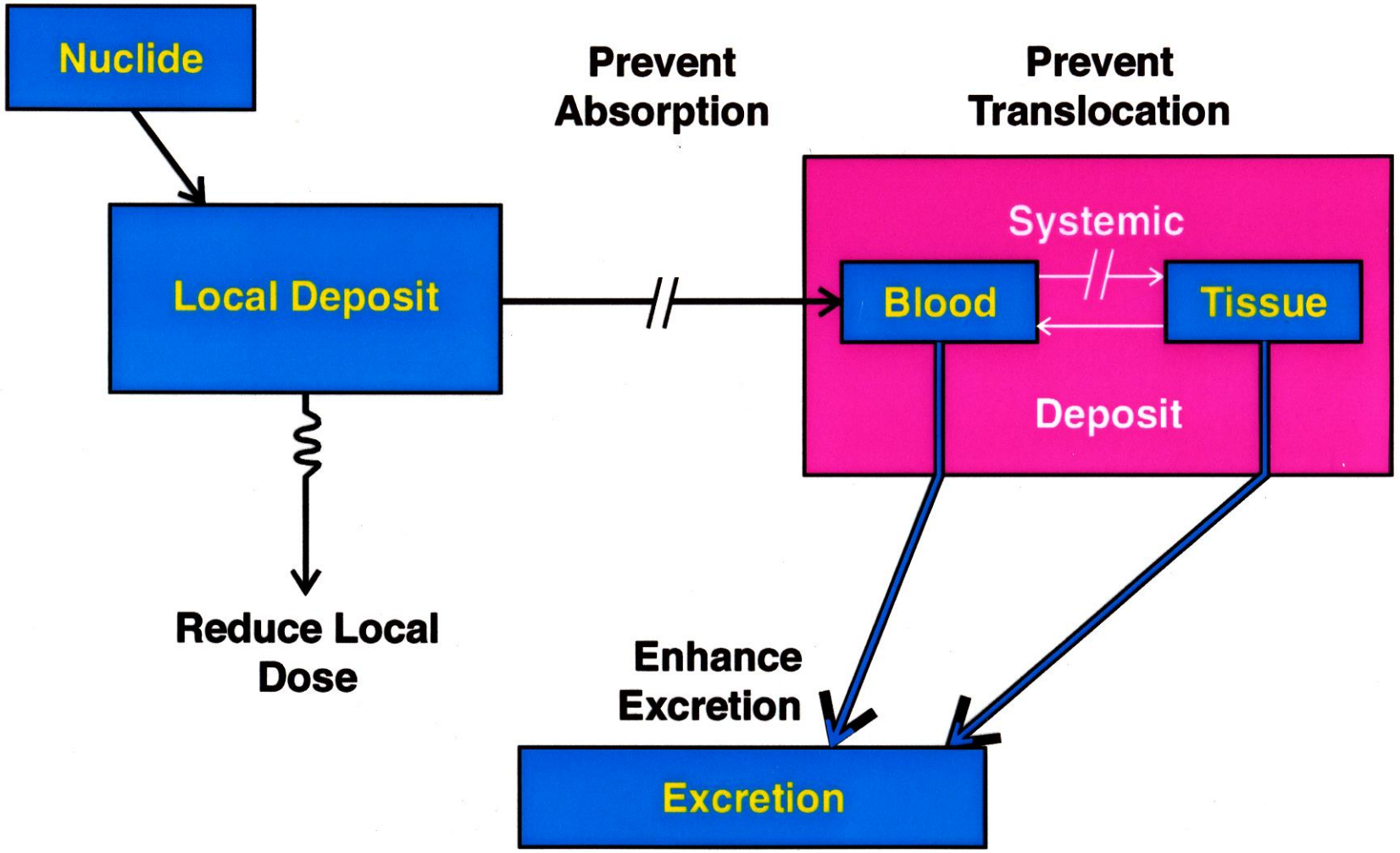
DOSE REDUCTION

RISK REDUCTION

Decorporation Strategy



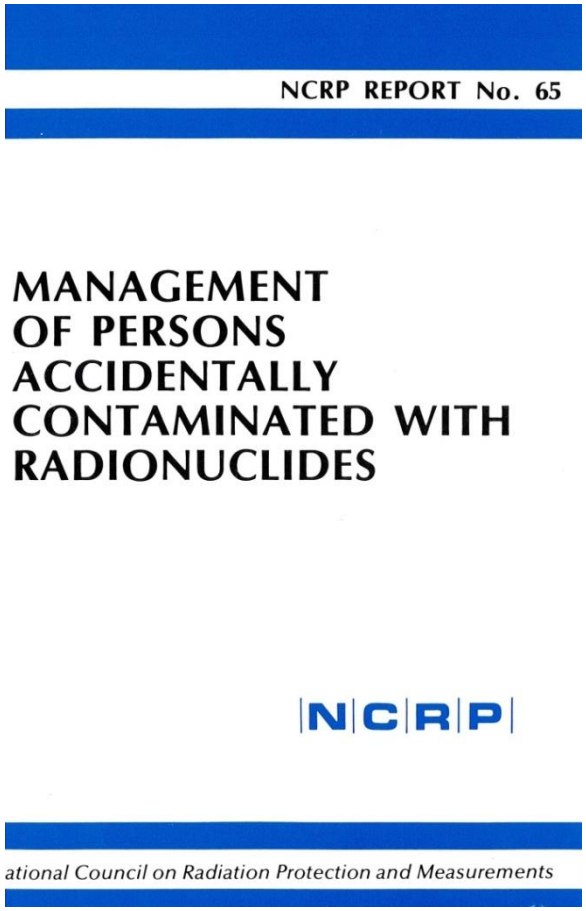
Decorporation Strategy

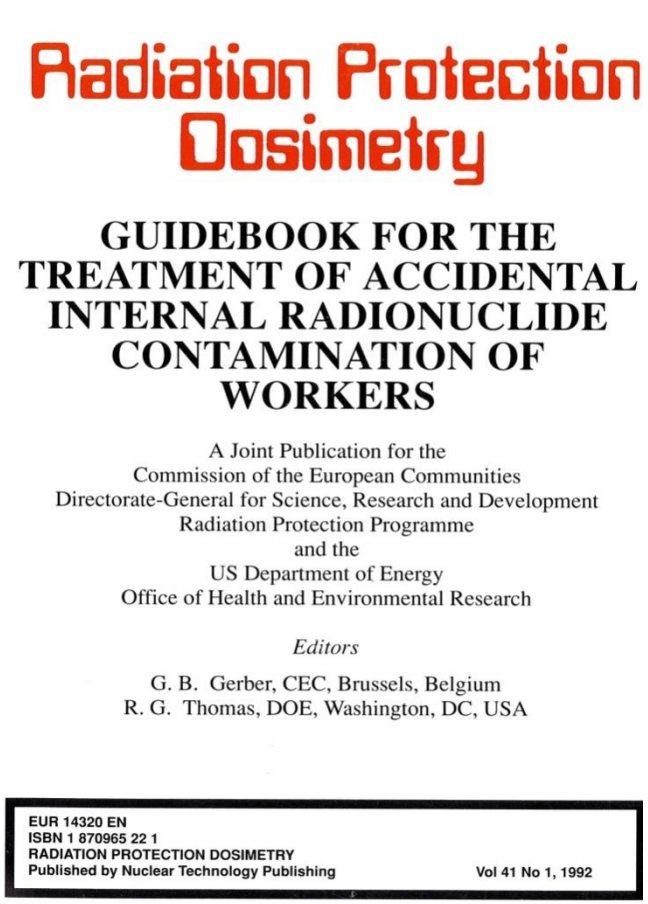


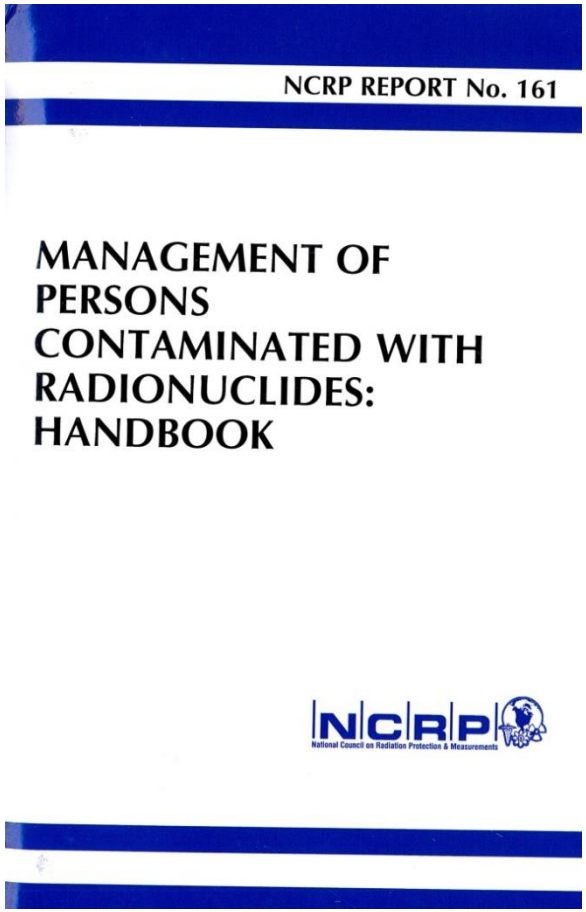
Treatment Strategies for Highly Contaminated People

- Chemical Methods for Soluble Materials
  - Blocking agents (KI)
  - Isotopic dilution (Ca, Zn, K)
  - Ion exchange (Prussian Blue, alginates)
  - Chelating agents
    - EDTA (Pb, Zn, Cu, Cd, Cr, Mn, Ni)
    - DTPA (Pu, Am, Cm, Lanthanides)
    - DMSA, DMPS, BAL (Hg, Pb, Cd, As, Au, Po)
- BARDA stockpile (USA)

Some Consensus Guidance







Features of DTPA (diethylenetriaminepentaacetic acid)

- Ca and Zn chelates (Ca better on day 1)
- Administered dose: 30 μmole kg^{-1} (1 g per 70 kg)
- Accepted routes of administration
  - Intravenous injection or infusion
  - Nebulized DTPA solution
- GI absorption: about 3%
- Effective for Th, Pu, Am , Cm, Cf
  - Not U, Np
- Matching drug and actinide biokinetics is key to successful decorporation

Example of DTPA Efficacy in Humans

- 1976 Hanford ^{241}Am accident in which one worker received an intake of about 200 MBq
- DTPA treatment begun within 2 h of exposure; multiple treatments daily over first weeks, daily for about 1 y, then more separated.
  - 583 g administered 1976-1980
- Surgery plus daily surface decon during first week
  - 185 MBq → 14 MBq in 10 d
- Total excretion:
  - 41 MBq (half in first 3 d)
  - 80% in urine
  - 98% in 1 y
- About 99% dose sparing to systemic organs

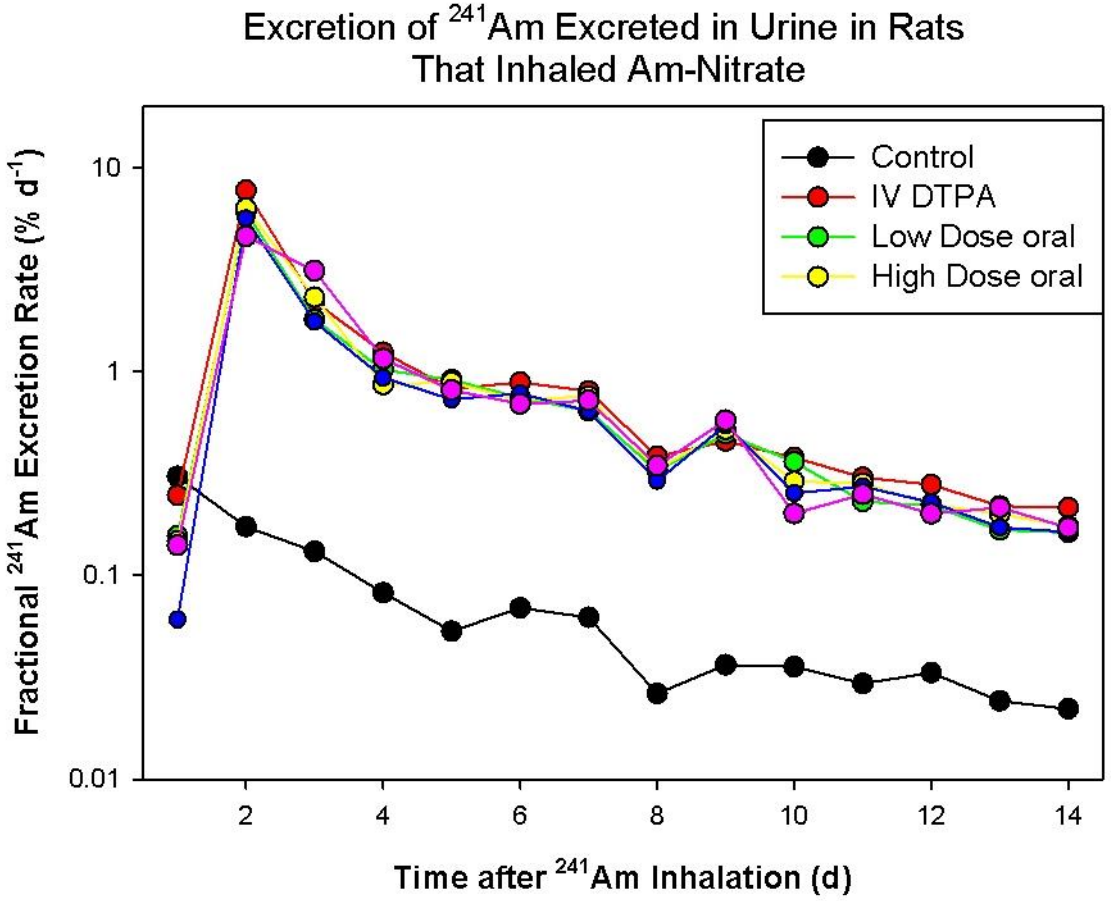
Issues and Research with Actinide Decorporation

- Oral forms:
  - Need for stockpiling
- Targeting intracellular deposits:
  - Liposomes
- Targeting inhaled deposited radionuclides:
  - Aerosols
- Need for better chelating agents?

Efficacy of an Oral Formulation of DTPA

- Rats given single inhaled dose of $^{241}Am(NO_3)_3$
- CaDTPA at 1 d
- Either IV or oral (high and low dose) ZnDTPA daily through 7d
- Sacrifice at 14 d
- Material balance design (>90% recovery)

Efficacy of Oral Formulation of DTPA for Decorporating Am-241 In Rats



(proprietary data)

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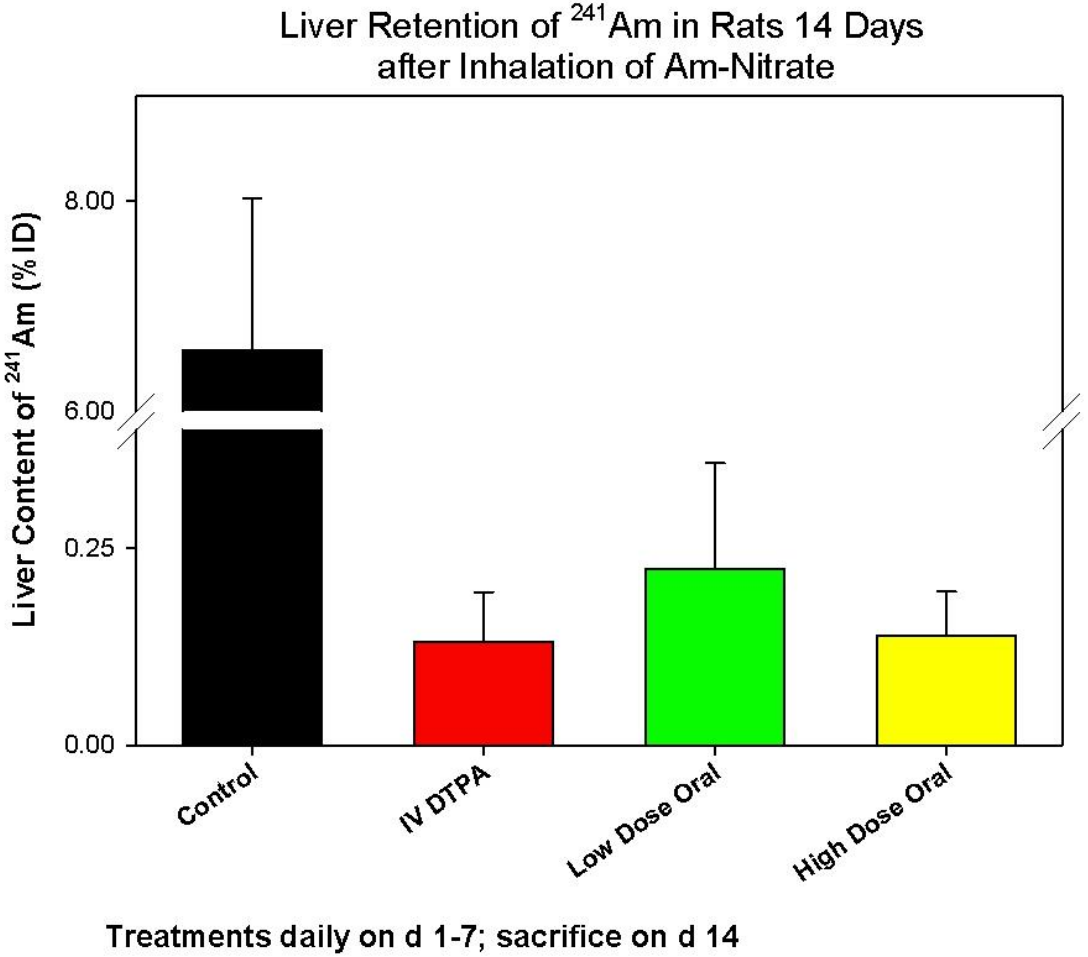


(proprietary data)

Enhancing Intracellular Uptake of DTPA for Decorporation

- ^{238}Pu-citrate injected IV in rats
- DTPA (free, or conventional or “stealth” liposome) @ 2 h
- At 16 d:

Sample	Ctrl	Free	Lip(conv)	Lip(stlth)
Liver	4.8	3.6	1.5	2.6
Bone	63	50	45	42
Urine	7	16	25	22

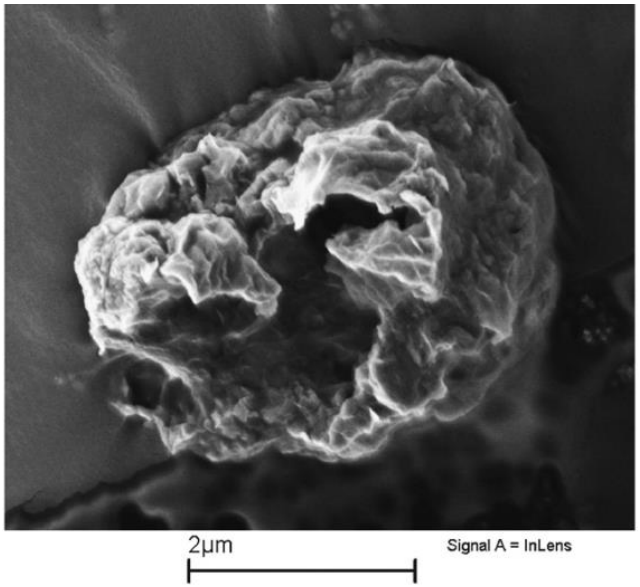
- Prolonged retention of stealth liposomes; increased intracellular uptake

Phan et al. 2004

Targeting Inhaled Actinide in Lung

- Dry powder DTPA powder
- Insufflated into rats exposed to ^{238}Pu-nitrate 2 h or 7 d previous

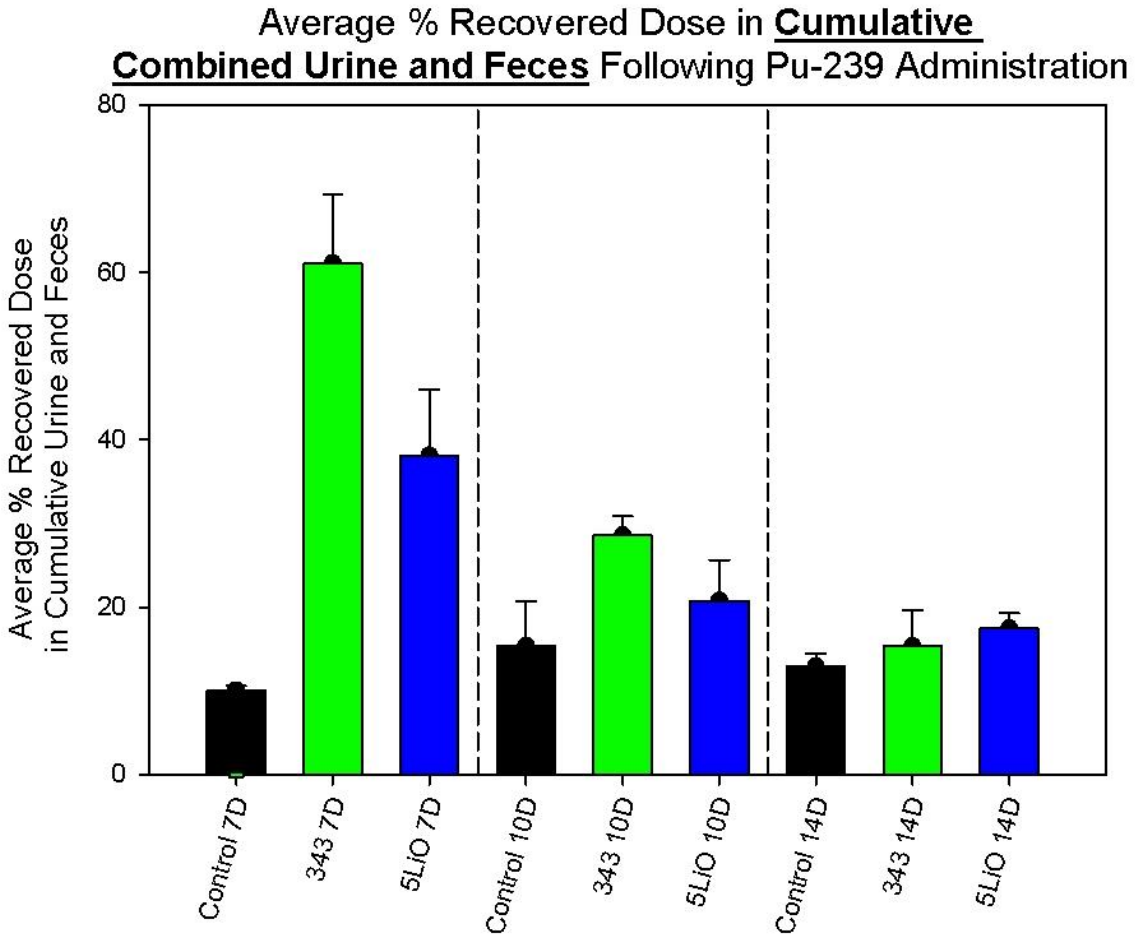
	% Initial Lung Dose		
	Lung	Bone	Liver
Control	32	30	2.3
DTPA-iv (1h)	25	24	1.2
DTPA-aer (1h)	8	16	1.0
DTPA-iv (7d)	27	26	1.1
DTPA-aer (7d)	19	30	1.2



Efficacy of LBNL HOPO Compounds for Decorporating Pu-239 in Dogs

- Groups of 3 female dogs
- Single IV injection of ^{239}Pu-citrate
- 3,4,3 Li[1,2 HOPO] (octadentate) or 5-LiO[Me 3,2 HOPO] (tetradentate) ligands
  - Single oral administration given at 0.5, 3, 7 days after Pu
  - 3,4,3 Li[1,2 HOPO] @100 µmole/kg; 5-LiO[Me 3,2 HOPO] @300 µmole/kg
- Sacrifice 7 days after therapy
- Material balance design (about 87% average recovery)

Efficacy of LBNL HOPO Compounds for Decorporating Pu-239 in Dogs



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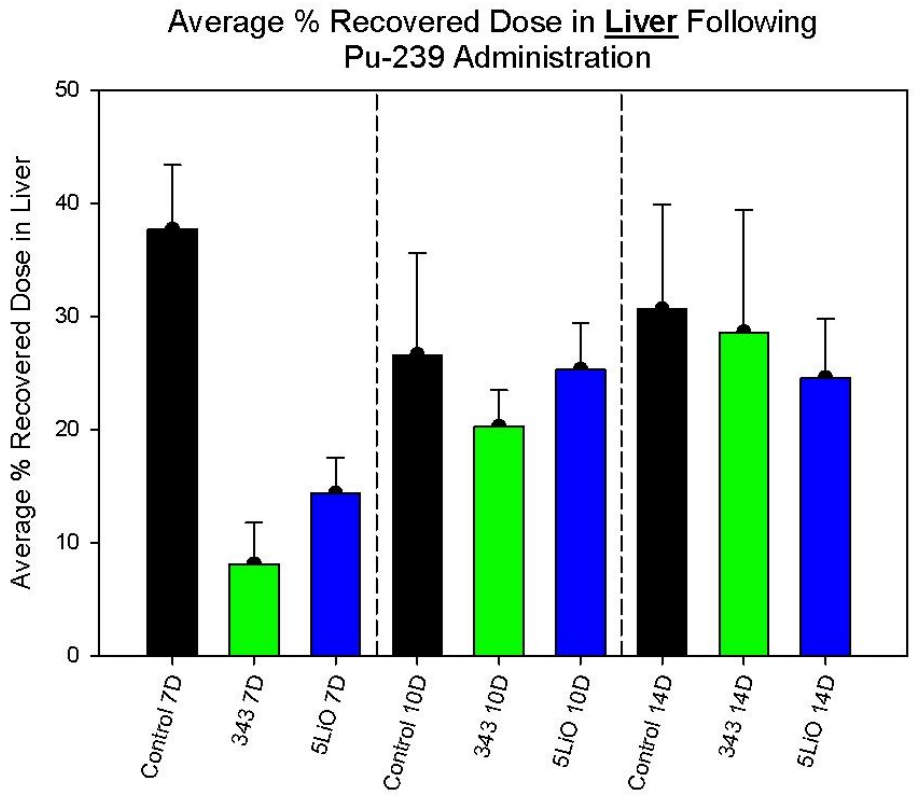

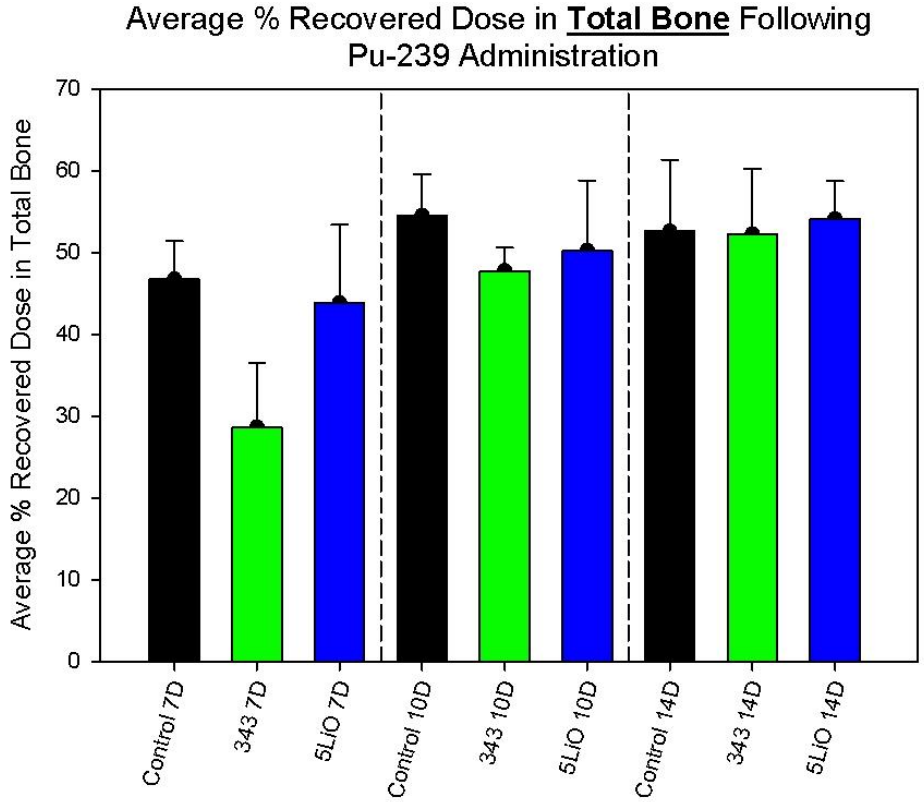

Summary

- For trivalent and tetravalent actinides, good treatments exist using DTPA
- Recent research seeks to improve efficacy and ease of administration by:
  - Oral formulation
  - Dry powder aerosols for inhaled radionuclide
  - Enhancing intracellular uptake
  - Demonstrating new compounds
- Chelators for other radionuclides needed:
  - For example, Co, Sr, Ir, Po, Ra
  - Pediatric formulations needed

Sustained Action of DTPA for Decorporating Pu in Humans

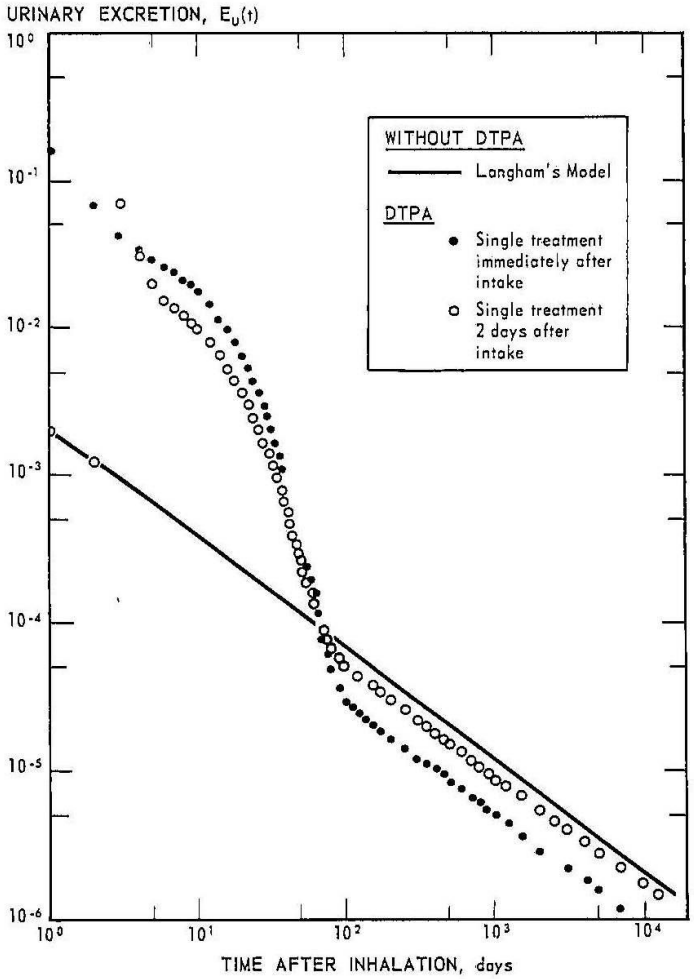

FIG. 3. Comparison of predicted urinary excretion rates after acute intake of transportable plutonium with DTPA administered immediately and 2 days after contamination.

Hall et al. *Health Phys. 1978*

TREATMENT STRATEGIES FOR HIGHLY CONTAMINATED PEOPLE

Reduce the dose to be received by accelerating radionuclide removal

- **Physical Methods for Insoluble Materials**
  - **Skin decontamination**
  - **Nasal irrigation**
  - **Emetics, gastric lavage, purgatives**
  - **Surgical excision**
  - **Bronchopulmonary lavage**