

# Determining the Relative Toxicity and RBE of Internal Emitters in Animals

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May 2009



# Comparative toxicity

- Alpha-emitters
  - Cancer, 1 to 30 x low-LET, animal studies
  - Non-cancer endpoints, 1 – 20 x low-LET, animal studies
  - EPA suggest RBE of 14 (90% CIs 5, 40)
  - ICRP radiation weighting factor of 20
- Beta-emitters
  - General consensus of RBE ~1 for higher energy emitters
  - Below 60keV higher
  - EPA suggest RBE of 2.4 (90% CIs 1.2, 5)
  - ICRP radiation weighting factor of 1

# Reasons for variability

- Possibility 1 – that this reflects true variability in the relative toxicity of radionuclide radiations
- Possibility 2 – variability that is seen is influenced by confounders and reflects poor control of confounders in some studies

# Possible confounders

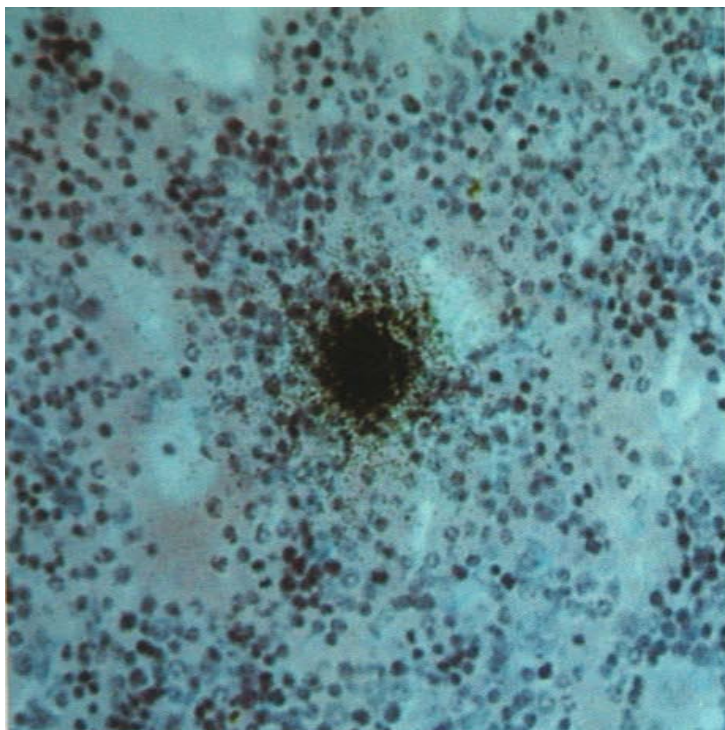
- Uncertain radionuclide dosimetry
  - e.g., comparing  $^{90}\text{Sr}$  and  $^{224}\text{Ra}$
- Problems resulting from bystander and abscopal effects
  - different organ distribution
  - different cellular distribution within organ
- Temporal differences in irradiation
  - e.g., comparing effects of short and long-lived radionuclides
- Power of studies – too few animals
- Studies not contemporaneous
  - e.g., comparing results of different studies

# New study

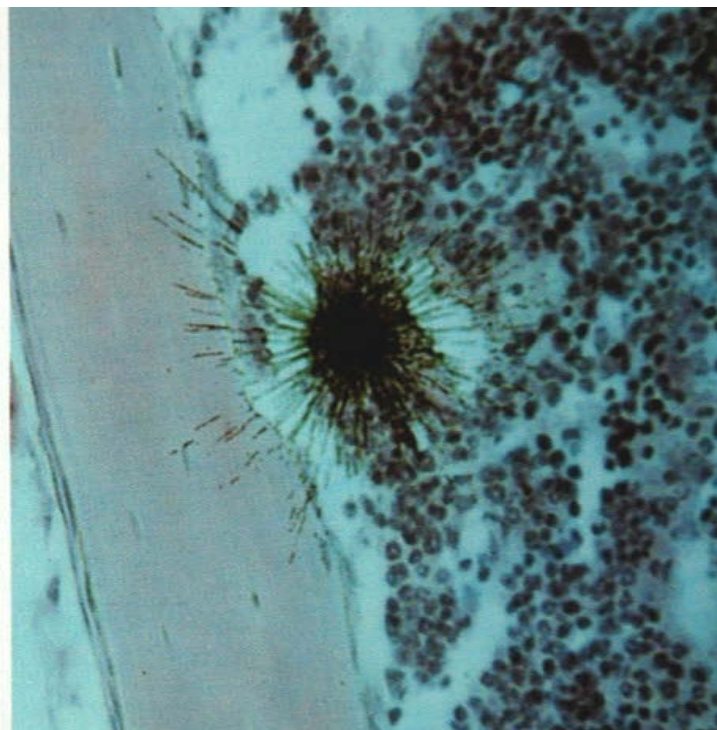
- Contemporaneous comparison of two radiations
- Radionuclides employed have no daughters – minimising dosimetry issues ( $^{45}\text{Ca}$  and  $^{242}\text{Cm}$ )
- Radionuclides incorporated into FAP to ensure the same distribution after inhalation / injection
- Radionuclides  $^{45}\text{Ca}$  ( $\beta$ ) and  $^{242}\text{Cm}$  ( $\alpha$ ) have the same half-life (163d) resulting in same temporal distribution of dose
- Track length of radionuclides similar

# Track lengths

$^{45}\text{Ca}$  - ~540 $\mu\text{m}$  (max)



$^{242}\text{Cm}$  - ~76 $\mu\text{m}$



# Power – injection study

- 3  $\beta$ -dose groups ( $\sim 0.5$ ,  $\sim 1.0$ ,  $\sim 1.5$ Gy) of 400 mice each
- 3  $\alpha$ -dose groups ( $\sim 0.5$ ,  $\sim 1.0$ ,  $\sim 1.5$ Gy) of 400 mice each
- 1 stable FAP control group of 600 mice
- 1 untreated control group of 71 mice
  
- Varied activity concentration of FAP so as to inject  $\sim$  the same number of particles ( $\sim 4.6 \times 10^6$ ) to each mouse
  
- All causes of death and lifespan

# Toxicity at lowest dose

<b>Endpoint</b>	<b>Median Excess RR (<math>\alpha / \beta</math>)</b>	<b>Calculated 95% CIs</b>	
		Lower	Upper
<b>Survival - All causes</b>	1.9	1.1	3.2
<b>Carcinoma - All</b>	2.3	1.7	3.0
<b>Sarcoma - All</b>	2.7	0.72	10
<b>Liver Carcinoma</b>	5.9	2.4	14
<b>Mammary Carcinoma</b>	1.1	0.49	2.3
<b>Lung Carcinoma</b>	2.9	0.27	31
<b>Uterus Carcinoma</b>	0.6	0.03	9.7
<b>Malignant Lymphoma</b>	0.9	0.04	19
<b>Liver Histiocytic Sarcoma</b>	2.1	0.05	85
<b>Lymph Node Histiocytic Sarcoma</b>	1.0	0.03	38

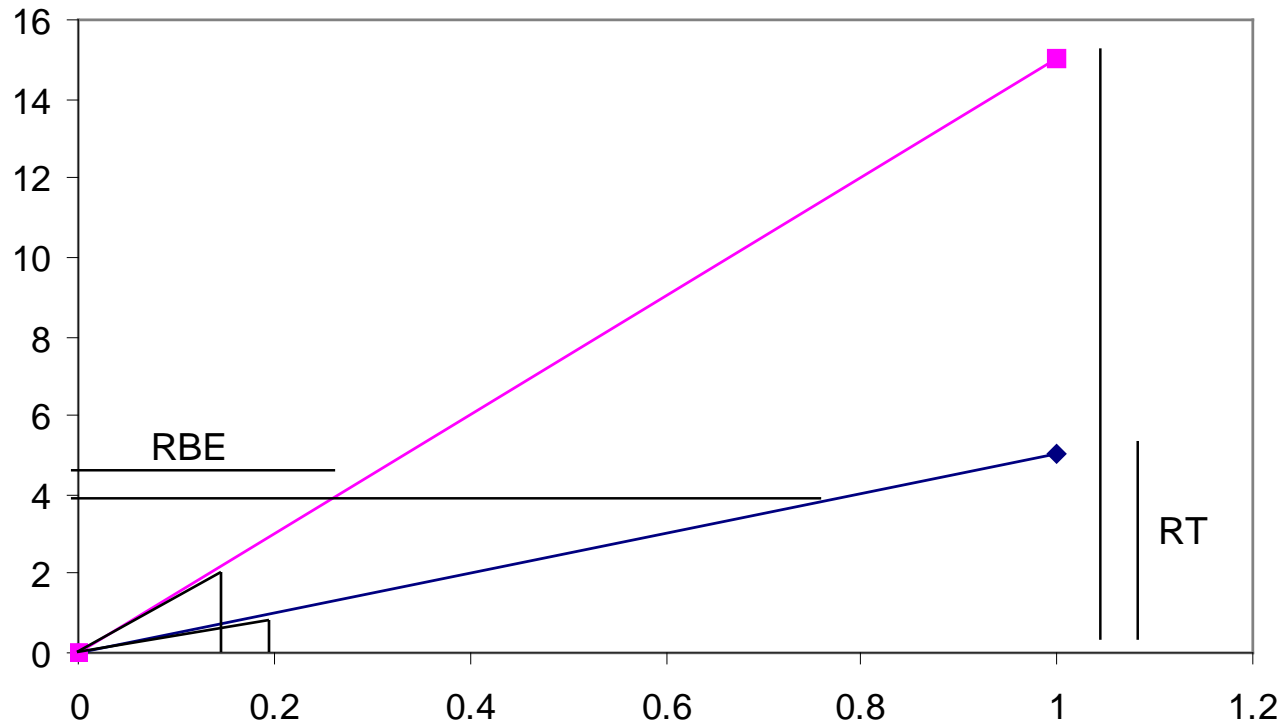
# Issue 1 - cherry picking

- Relative toxicity very variable
  - 2 for survival
  - 2 for all carcinoma
  - 3 for all sarcoma
  - 6 for liver carcinoma
  - 1 for mammary carcinoma
  - 0.6 uterine carcinoma
  - ~1 for myeloid leukaemia
- To get the big picture you need to look at all endpoints
- Results of studies using single endpoints unlikely to give a true picture

# Issue 2 – competing causes of death

<i>Endpoint</i>	<i>Risk Ratio</i>	
	<i>Absolute</i>	<i>Relative</i>
<i>Liver Carcinoma</i>	1.6	4.1
<i>Mammary Carcinoma</i>	0.9	1.6
<i>Lung Carcinoma</i>	1.1	2.8
<i>Uterus Carcinoma</i>	0.9	2.8
<i>Malignant Lymphoma</i>	2.5	5.2

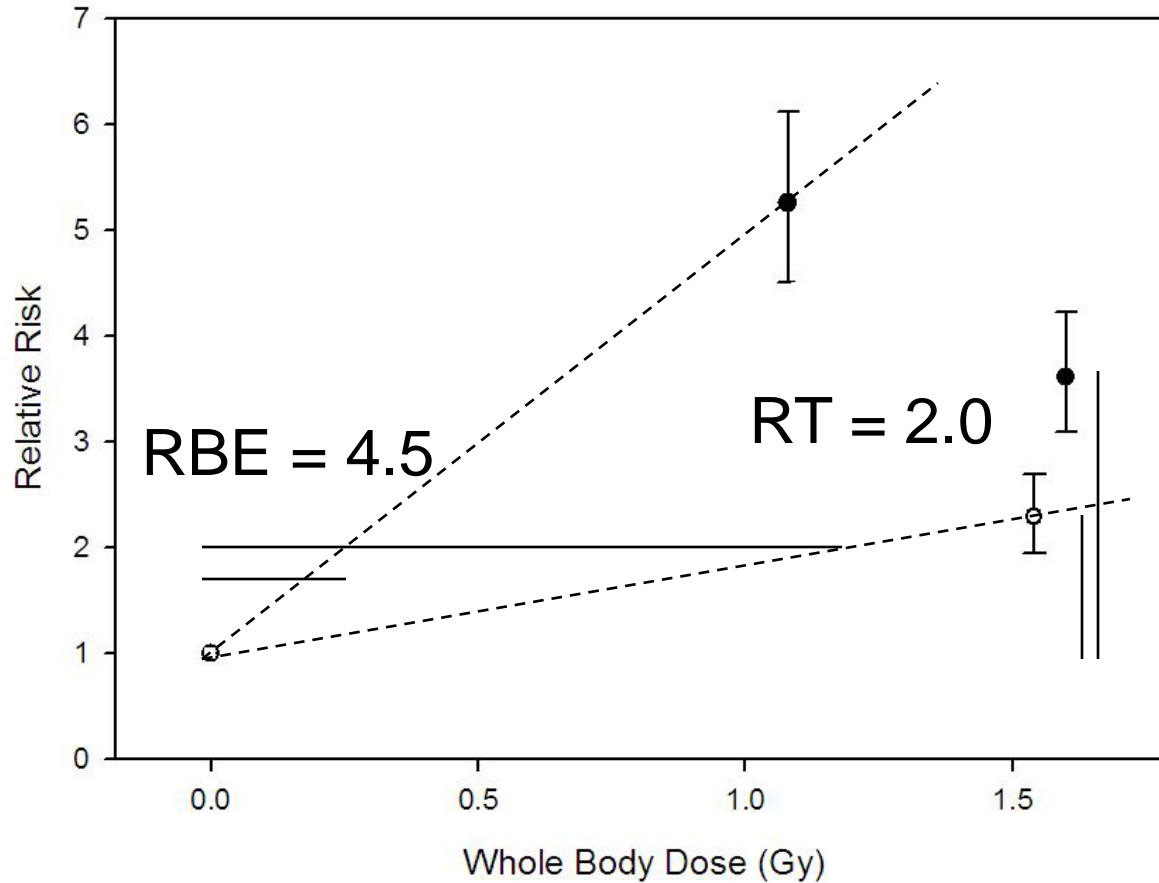
# RBE or relative toxicity



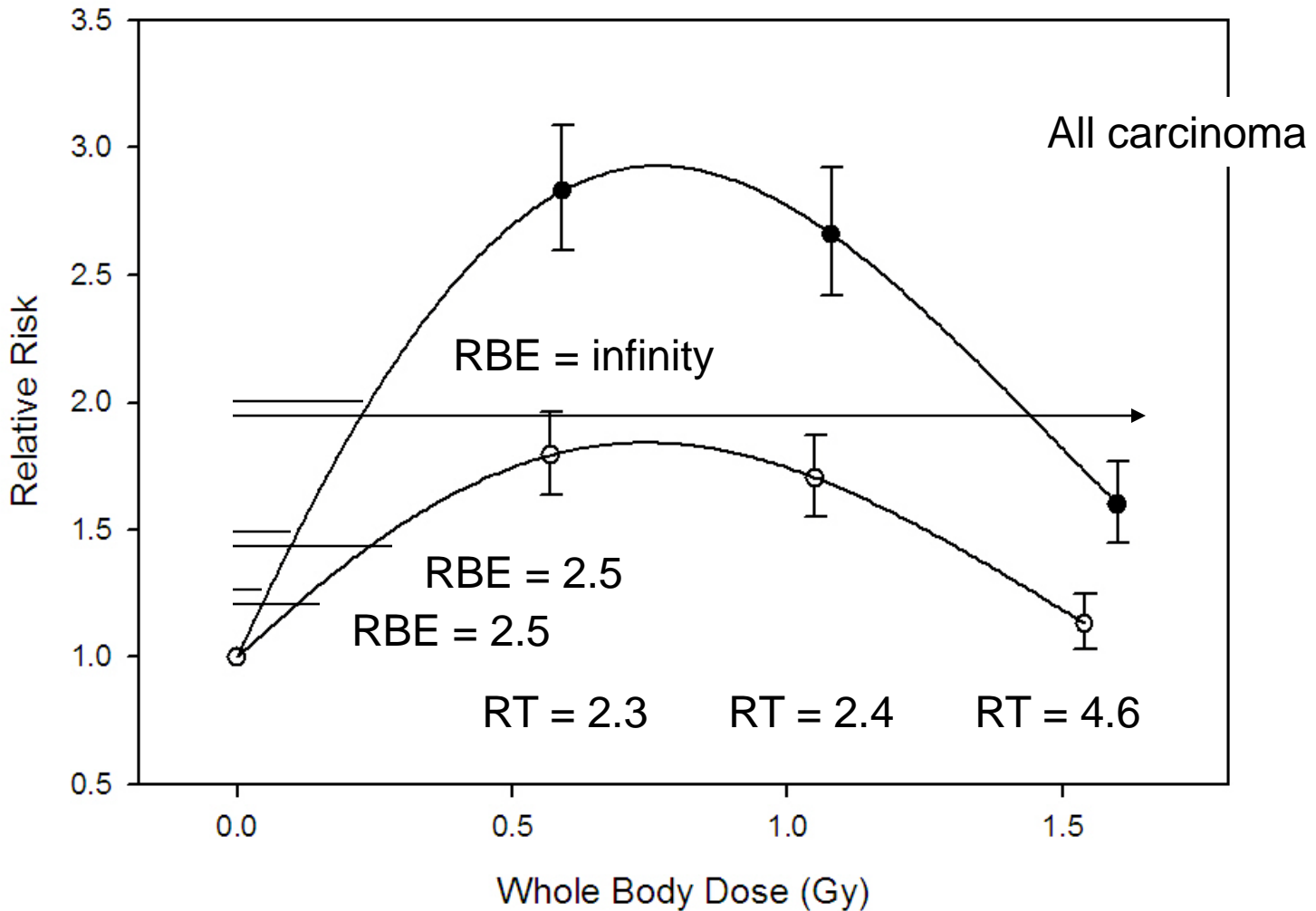
- Three measures: RBE,  $RBE_M$  and RT

# Issue 3 – isolated data

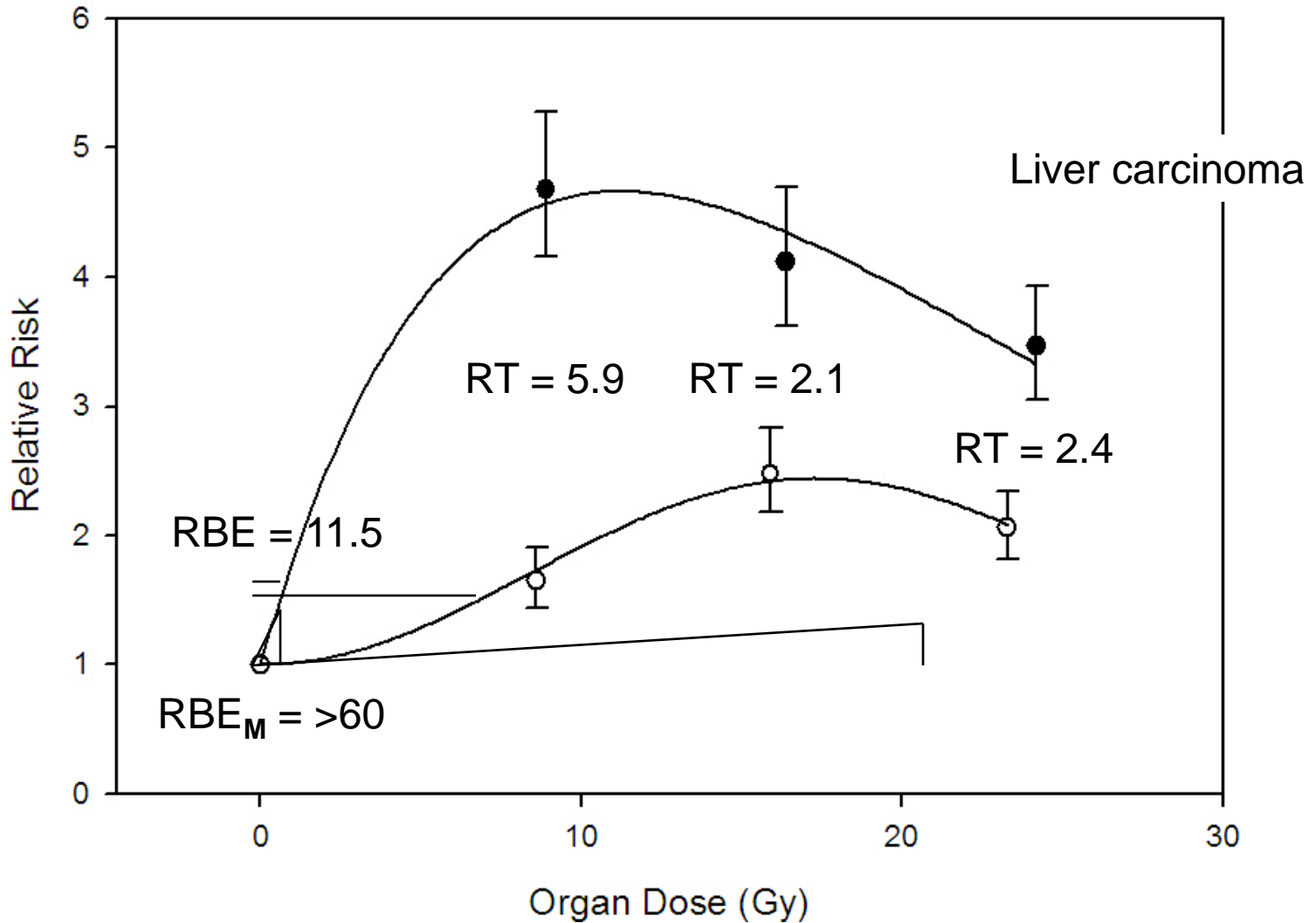
## Malignant Lymphoma



# Issue 4 - infinite RBE



# Issue 5 - non-linearity



# Additional constraints

In addition to identified confounders also need to:

- Look at all causes of death and survival
- Use a spread of relevant doses
- Take account of competing causes of death i.e., do not use raw incidence data
- Report data as relative risk
- Be cautious if using RBE – RT better

# Conclusion

- Almost impossible to control all factors
- A repeat study using different doses and/or different animal models is a possibility
- Could any pair of freely administered radionuclides be used?

# Possible radionuclide pair

## Promethium-147

$$T_{1/2} = 2.62 \text{ y}$$

$$\beta(\text{mean}) = 62 \text{ keV}$$

$$\text{Range (mean)} = 60 \mu\text{m}$$

## Curium-244

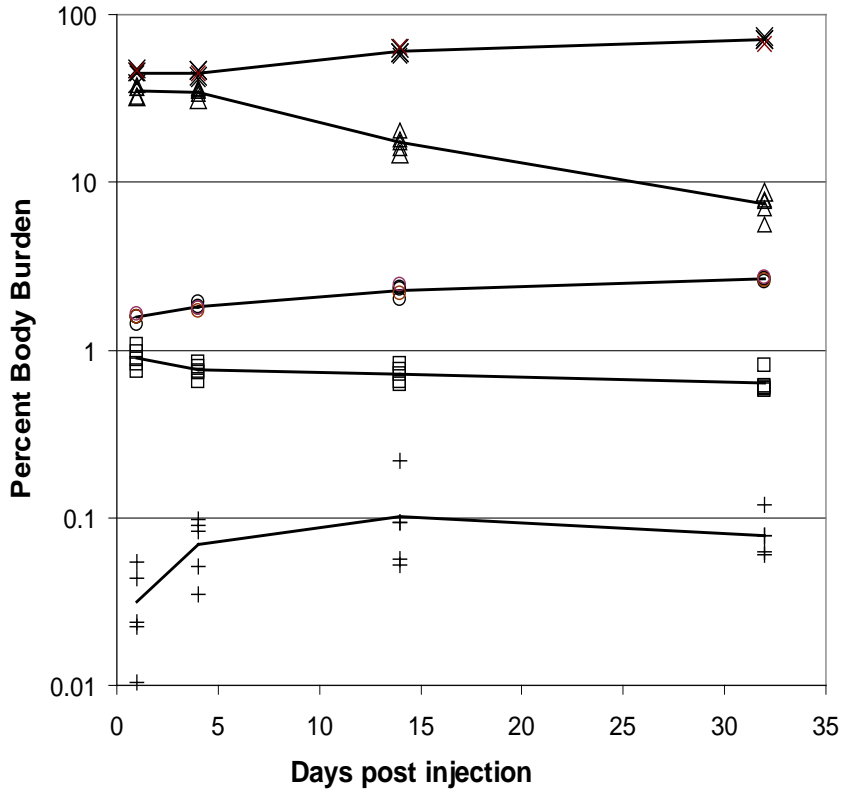
$$T_{1/2} = 18.1 \text{ y}$$

$$\alpha = 5.805 \text{ MeV}$$

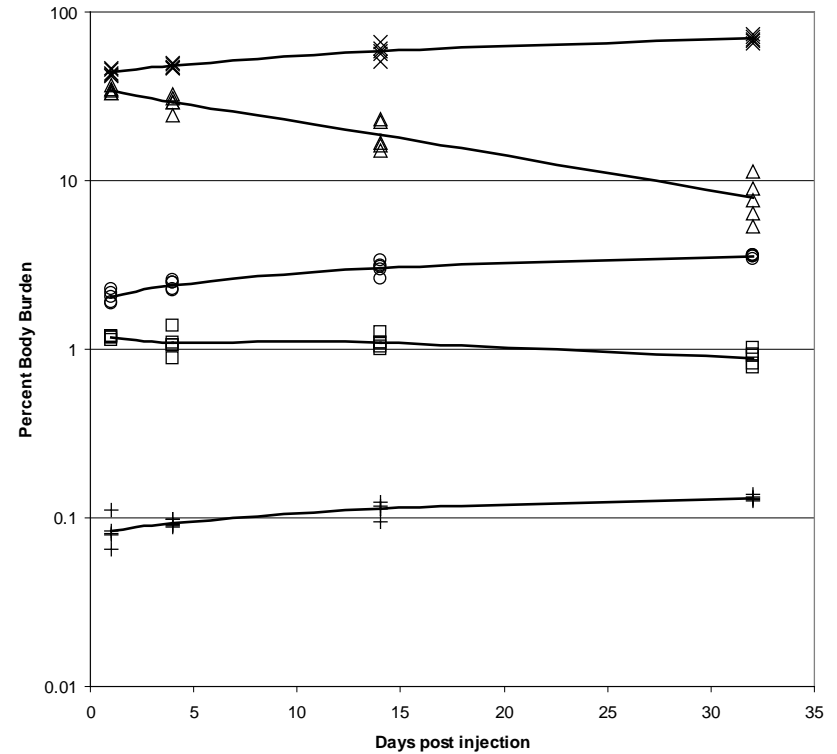
$$\text{Range} = 72 \mu\text{m}$$

# Possible radionuclide pair

## Promethium-147



## Curium-242



× = carcass, Δ = liver, □ = kidneys, O = femur, + = spleen