In vivo Radiation Effects In Beagle Dogs

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Pacific Northwest NATIONAL LABORATORY
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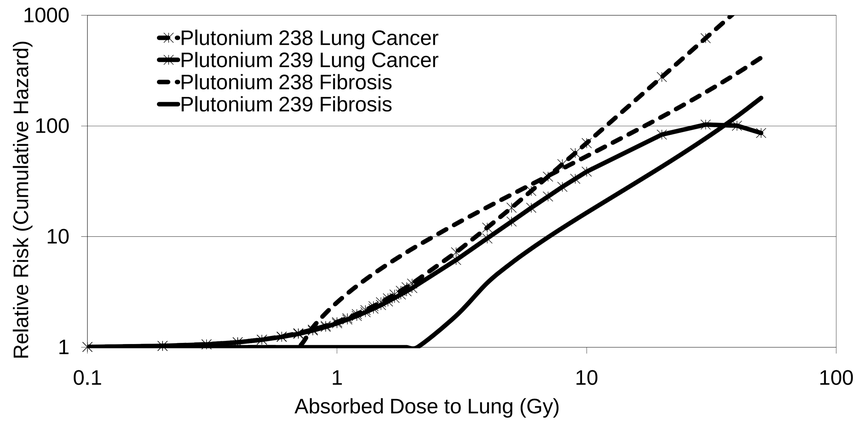
Quantification of the risk of health effects in humans from exposure to radiation is limited by the observational nature of most studies. Life-span animal studies were designed to supplement the human data and assist in risk assessment. Beginning in the 1950s, various national laboratories and universities conducted studies on incorporated radionuclides using beagle dogs.

The National Radiobiology Archives has been collecting, organizing, cataloging, and preserving these data and materials (including laboratory notebooks and archival tissue specimens), and making them available for future research or analyses.

The data available includes documentation of the type and amount of exposure, dose and dose-rate, pedigree, housing conditions, detailed clinical health information from annual physicals with detailed blood chemistry, and extensive postmortem information. Radionuclides studied include plutonium, cesium, and strontium.

Materials available include tissue preserved in paraffin blocks and pathology slides. Modern methods of molecular biology and biochemistry can use these materials to investigate potential biomarkers of risk and exposure as a function of time after exposure. Immunohistochemistry can be done on samples to compare with *in vitro* studies. These archived materials are useful for identifying primary and secondary targets and providing essential information on the optimal time course of potential mitigation and decorporation strategies.

Data on life-span studies have been used to estimate the risk of lung fibrosis and lung cancer in dogs after exposure to plutonium; currently, pedigree information is being used to evaluate a familial confounder of the risk of lung fibrosis or lung cancer. These data have also been used to explore lung, liver and bone cancer incidence with multistage modeling techniques.



Comparison of the dose-related hazard of lung cancer and lung fibrosis using data from dogs exposed to $^{238}PuO_2$ and $^{239}PuO_2$ at the Inhalation Toxicology Research Institute.

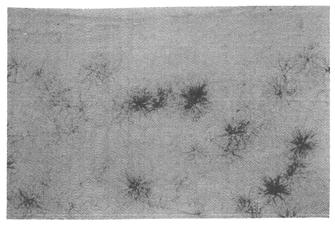


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FIGURE 3.9. Autoradiograph of Lung Sections from Dogs After Inhalation of $^{239}Pu(NO_3)_4$

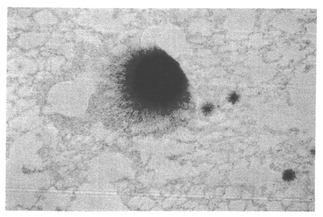

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FIGURE 4.6. Autoradiograph of Lung Section from Dog Given $^{238}PuO_2$ (Giant alpha star with tracks emanating from only part of the particle)

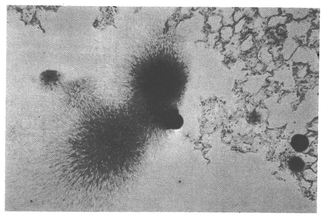

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FIGURE 4.5. Autoradiograph of Lung Section from Dog Given $^{238}PuO_2$ (Typical "alpha stars")

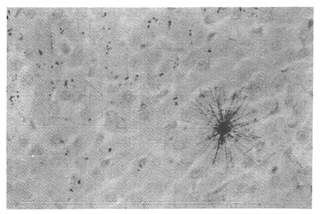

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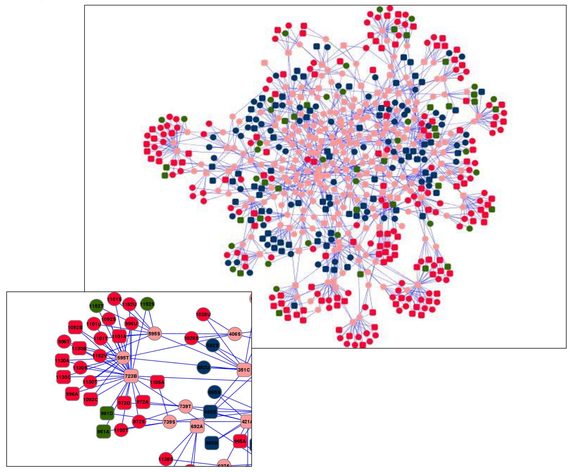
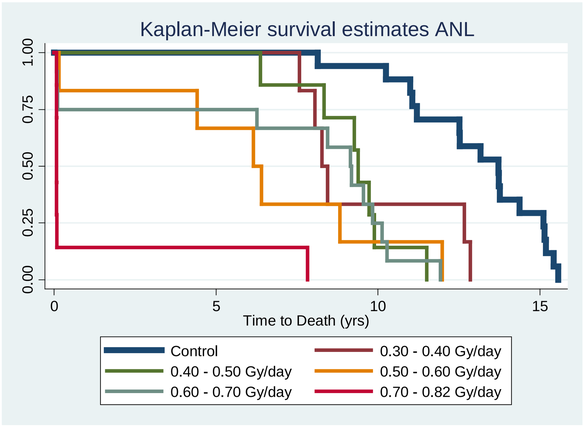
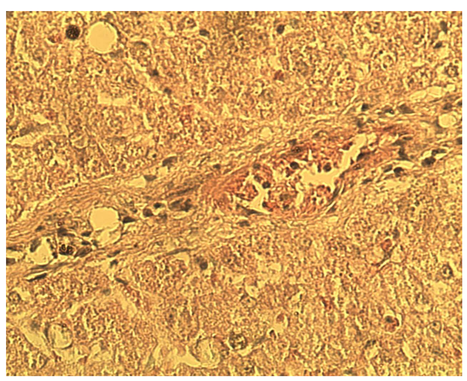
FIGURE 2.15. Autoradiograph of Liver Section from Dog After Inhalation of $^{238}Pu(NO_3)_4$

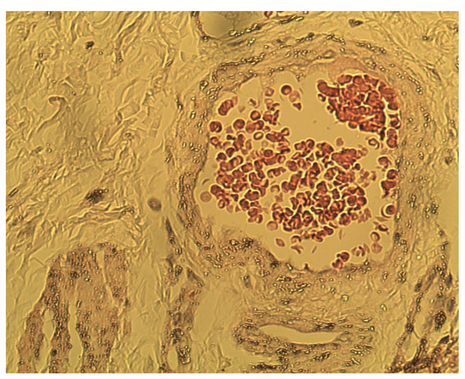
Network visualization methods were used to provide a quick display of associations between disease and familial or genetic susceptibilities. These networks were generated using data on dogs exposed to $^{238}PuO_2$ and $^{239}PuO_2$ at the Inhalation Toxicology Research Institute.



Survival curves using data from studies of beagle dogs exposed to $^{137}CsCl$ at the Argonne National Laboratory.







Liver and skin sections were successfully obtained from preserved tissue blocks from the beagle dog lifespan studies at Pacific Northwest National Laboratory.

Hazard and multistage models of cancer risk with risk estimates per unit of cumulative dose[a] from plutonium generated using data from the Inhalation Toxicology Research Institute and Pacific Northwest National Laboratory.

	Cox				Multistage				
Model	Deviance	Parameter[b]	Estimate	95% CI	Model	Stage *i* of 7	Deviance	Parameter[c]	Estimate	(95% CI)
239PuO2										
Lung Cancer										
Quadratic: $F(d)=[\beta_1 dose^2]$ $[\exp(\beta_2 dose)+\beta_3(month\_exposed*lab))]$					Linear-quadratic: $F(d)=[\beta_1(dose_i)+\beta_2(dose_i)^2][\exp(\beta_3 month\_exposed^{d}*lab^{f})]$					
	1654.11	β_1	0.89	(0.51- 1.64)		*i*=6	1265.44	β_1	4.98	(1.91- 10.7)
		$\exp(\beta_2)$	0.94	(0.93- 0.95)				β_2	0.82	(0.38- 1.73)
		$\exp(\beta_3)$	0.81	(0.67- 0.99)				$\exp(\beta_3)$	0.70	(0.58- 0.83)
238PuO2										
Lung Cancer										
Quadratic: $F(d)=\beta_1 dose^2$					Quadratic: $F(d)=\beta_1 dose_i^2$					
	752.36	β_1	0.45	(0.20- 1.00)		*i*=4	561.38	β_1	1546	(577- 3986)
Liver Cancer										
Linear: $F(d)=[\beta_1 dose]$ $[\exp(\beta_2 month\_exposed^{d})]$					Linear[b]: $F(d)=[\beta_1 dose_i]$ $[\exp(\beta_2 month\_exposed^{d})]$					
	247.10	β_1	39.5	(3.65- 100.1)		*i*=6	218.56	β_1	133	(61- 218)
		$\exp(\beta_2)$	0.8	(0.54- 0.95)				$\exp(\beta_2)$	0.8	(0.61- 0.97)
Bone Cancer										
Quadratic: $F(d)=[\beta_1 dose^2]$ $[\exp(\beta_2 dose^{e}+\beta_3 month\_exposed^{d})]$					Quadratic[b]: $F(d)=[\beta_1 dose_i^2]$ $[\exp(\beta_2 month\_exposed^{d})]$					
	1010.00	β_1	192.4	(101.1- 300.0)		*i*=6	766.91	β_1	894	(571- 1248)
		$\exp(\beta_2)$	0.80	(0.73- 0.87)				$\exp(\beta_2)$	0.90	(0.82- 0.98)
		$\exp(\beta_3)$	0.91	(0.84- 0.98)						

[a] Cumulative organ dose is expressed in Gy and lagged by one year.
[b] Based on the general model $h(t,d_i)=h(t_0)(1+F(d_i))$
[c] Based on the general model $h(t)=[Q_0(t)^{k-1}/(k-1)!][1+R_i(t;k,i)]$
[d] Month_exposed is defined with baseline is 12 months old at exposure
[e] Cell-killing term representing cells no longer at risk of cancer.
[f] Lab is defined as 1=ITRI; 0=PNNL

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