• Inhaled Plutonium Nitrate in Dogs

The objective of this project is to determine the dose-effect relationships of inhaled plutonium nitrate in life-span studies in beagle dogs. The critical tissue after inhalation of "soluble" plutonium (such as plutonium nitrate) is generally considered to be the skeleton or liver, on the assumption that such plutonium will be rapidly translocated from the lung to skeleton and liver. In several rodent studies, however, inhalation of "soluble" plutoniuni has resulted in lung tumors as well as skeletal tumors.

INHALED PLUTONIUM NITRATE IN DOGS

Investigators:

G. E. Dagle, W. C. Cannon, H. A. Ragan, C. R. Watson, D. L. Stevens, F. T. Cross, P. J. Dionne, and T. P. Harrington

Technical Assistance:

J. F. McShane, S. L. Owzarski, G. L. Webb, S. L. English, and M. C. Perkins

Beagle dogs given a single inhalation exposure to $^{239}Pu(NO_3)_4$ are being observed for life-span dose-effect relationships. Lymphopenia occurred at the two highest dosage levels as early as 1 mo following exposure and was associated with neutropenia and reduction in numbers of circulatory monocytes by 4 mo postexposure. Radiation pneumonitis developed in one dog at the highest dosage level at 14 mo postexposure. More rapid translocation to skeleton and liver occurred following inhalation of $^{238}Pu(NO_3)_4$ than after $^{239}Pu(NO_3)_4$ inhalation.

Six dosage groups of 105 dogs have been exposed to aerosols of $^{239}Pu(NO_3)_4$ for life-span observations (Table 3.13). Sixty-one of these dogs were exposed in 1976 and 44 dogs in 1977. In addition, 20 dogs were exposed to nitric acid aerosols as vehicle controls, 20 dogs were selected as untreated controls for life-span observation, 25 dogs were exposed to aerosols of $^{239}Pu(NO_3)_4$ for periodic sacrifice to study plutonium metabolism and the pathogenesis of developing lesions, and 7 dogs were selected as controls for periodic sacrifice. Twelve dogs were exposed to aerosols of $^{238}Pu(NO_3)_4$ for periodic sacrifice to study deposition and translocation up to 1 yr. The dogs were exposed in aerosol chambers using techniques described in previous Annual Reports.

A digital computer system was used to model the early translocation of inhaled $^{239}Pu(NO_3)_4$ in dogs. Fractional uptake constants and biological half-lives for the relatively soluble transuranic nuclide in various

TABLE 3.13. Inhaled Plutonium Nitrate in Dogs: Exposures in 1976 for Life-Span Observations

Number of Dogs			Aerosol Parameters		
Planned	On Study	Initial Alveolar Deposition[a] nCi	AMAD[b] (μm)	GSD[c]	Concentration nCi/ℓ
10	5	5445 ± 1841	085	2 37	534 ± 118
20	10	2293 ± 509	0.93	2.23	322 ± 66
20	13	312 ± 68	0.81	1.98	99 ± 20
20	20	56 ± 17	0.65	1.97	18 ± 4
20	20	8.2 ± 4.4	0.51	1.87	2.6 ± 0.5
20	20	2.2 ± 2.4	0.33	2.07	0.6 ± 0.3
20	17	Vehicle	—	—	—
20	20	Control	—	—	—

[a] Initial alveolar deposition estimated from thoracic count 2 wk post exposure
[b] Activity Mean Aerodynamic Diameter
[c] Geometric Standard Deviation

organs or compartments were estimated using activity levels measured in urine and fecal samples, in tissues obtained at necropsy, and external 17-keV X-ray body counts. The model prediction for each of the compartments is compared with the corresponding data and the model parameters are adjusted until a "best fit" is obtained for all compartments. The model fitting process is, by necessity, an interactive procedure since adjustments to one of the compartments will affect others. Preliminary data suggests that 0.046 of the initial alveolar deposition is excreted in feces from day 4 to day 28; this correlation is useful for comparison to dogs inhaling insoluble transuranics. Body counts for estimating initial alveolar deposition improve using the cube root of the weight of the dog. The modeling data is presently used for estimating dose (rad) to organs in dogs on life-span studies.

Preliminary data comparing the tissue distribution of $^{238}Pu(NO_3)_4$ and $^{239}Pu(NO_3)_4$ indicate that $^{238}Pu(NO_3)_4$ is more rapidly translocated to bone and liver than $^{239}Pu(NO_3)_4$ (Table 3.14). Additional tissue distribution analyses will be made on dogs killed 3 mo and 1 yr postexposure to further study the comparative distribution of $^{238}Pu(NO_3)_4$ and $^{239}Pu(NO_3)_4$. It is interesting to note the low accumulation of both isotopes in the tracheobronchial lymph nodes.

Lymphopenia was present at the two highest dosage levels at 4 wk postexposure; by 4 mo postexposure there was lymphopenia, neutropenia, and reduced numbers of circulating monocytes at the two highest dosage levels (Figure 3.12). No effects were observed on erythroid parameters.

TABLE 3.14. **Inhaled Plutonium Nitrate in Dogs**

Nuclide	Time Post Exposure	Animal Number	Total Body, nCi	Distribution, Percent			
				Lung	Skeleton	Liver	Tracheal Lymph Nodes
$^{239}Pu(NO_3)_4$	3 days	1359	78	92	3	2	0.1
		1375	72	92	5	1	0.0
		1407	84	52	19	11	0.2
	4 weeks	1336	32	71	20	6	0.2
		1341	22	65	19	13	0.1
		1344	52	59	16	22	0.1
		1329	484	70	19	8	0.1
		1346	901	77	10	10	0.2
		1347	694	72	14	9	0.3
	3 months	1522	58	55	28	12	0.4
		1529	49	52	24	18	0.3
		1539	71	53	25	19	0.2
$^{238}Pu(NO_3)_4$	3 days	1544	126	41	22	12	0.1
		1549	54	50	15	12	0.2
		1554	86	58	16	9	0.1
	4 weeks	1545	90	17	44	31	0.2
		1552	93	18	34	41	0.1
		1553	58	26	43	23	0.2

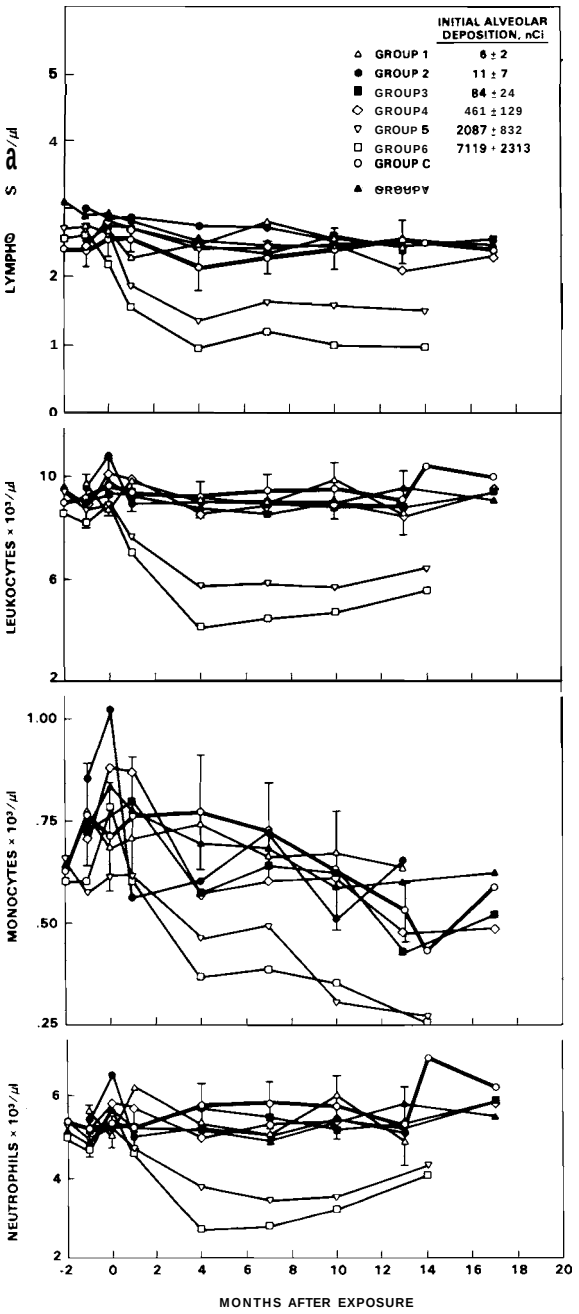

FIGURE 3.12. Mean Lymphocyte, Leukocyte, Monocyte and Neutrophil Values from Dogs after Inhalation of $^{239}Pu(NO_3)_4$

Radiation pneumonitis developed in one high-dosage dog at 14 mo postexposure. This dog had dyspnea, hypoxia, hypercapnea, and weight loss before euthanasia was performed.