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COMPARISON OF BONE LESIONS INDUCED BY INHALED $^{90}SrCl_2$ or $^{238}PuO_2$

Fletcher F. Hahn, Nancy A. Gillett, Bruce B. Boecker,
Ray A. Guilmette and Bruce A. Muggenburg

Inhalation Toxicology Research Institute
Albuquerque, New Mexico 87185

Radionuclides inhaled in a soluble form translocate from the lung to other organs of the body. A frequent site of deposition and retention is the skeleton. If the dose delivered to the skeleton is high enough, bone tumors may result. Both $^{90}SrCl_2$ and $^{238}PuO_2$ are radionuclides that have induced bone neoplasms in Beagle dogs after inhalation exposure. In this paper, we compare and contrast the bone tumors induced by these two radionuclides that have emissions with widely different energy and linear energy transfer characteristics.

Results were compared from two large dose-response studies involving Beagle dogs that inhaled radionuclides. Details of experimental design, exposure methods, husbandry and results of the specific experiments have been reported. (Gillett, N.A., *et al.* JNCI (1987) 79: 357-376; Hahn F.F., *et al.* JNCI (1981) 67: 917-927.)

Because of the differences in the solubility of the two radionuclides, different patterns of dose rate to the skeleton occurred in the two life-span studies. The $^{90}SrCl_2$ translocated rapidly to the skeleton, and little was retained in other organs. In the skeleton, the ^{90}Sr was retained with a half-time of over 5 years. Inhaled $^{238}PuO_2$ was retained in the lung for a prolonged time with a half-time of greater than 100 days. The retention pattern was complex because of an increased rate of clearance from the lung beginning at about 100 days after exposure due to breakup and increased solubility of the particles. The increased solubility led, in turn, to increased translocation to the liver and skeleton. The ^{239}Pu was retained in the skeleton with a half-time of over 5 years.

The total numbers of primary bone cancers observed in the two life-span studies are shown in Table 1. These tabulations include multiple, primary bone tumors that occurred in a single dog.

TABLE 1

PRIMARY BONE TUMORS IN BEAGLE DOGS
EXPOSED BY INHALATION TO $^{90}SrCl_2$ OR $^{238}PuO_2$

Radionuclide Aerosol	Number of Dogs Exposed	Number of Dogs with Primary Bone Tumors	Number of Primary Bone Tumors	TOTAL SKELETAL DOSE(Gy)		Survival of Dogs with Bone Tumors, Days to Death After Exposure - Median (range)
				All Exposed Dogs Median (range)	Dogs with Tumors Median (range)	
$^{90}SrCl_2$	66	30	42	60 (4-220)	120 (28-220)	1744 (759-3472)
$^{238}PuO_2$	168	92	122	2.0 (0.1 - 13)	2.6 (0.3 - 9.8)	1938 (1125-4815)

The tumor phenotypes are shown in Table 2. The classification scheme follows that of Pool (Pool, R. R. - Tumors of Bone and Cartilage in Tumors of Domestic Animals, J. E. Moulton (ed.) U. of Cal. Press (1990)). Of the ^{90}Sr-induced tumors, only 62% were osteosarcomas. Of these osteosarcomas, 37% were osteoblastic, but relatively nonproductive, indicating greater anaplasia.

TABLE 2

PHENOTYPES OF BONE CANCERS IN BEAGLE DOGS
THAT INHALED $^{90}SrCl_2$ OR $^{238}PuO_2$ (% OF TOTAL)

TUMOR PHENOTYPES	$^{90}SrCl_2$	$^{238}PuO_2$
Osteosarcomas		
Osteoblastic	23	63
Fibroblastic	2.4	8.2
Chondroblastic	4.8	11
Combined	17	4.9
Telengiectatic	12	4.1
Giant Cell	2.4	0.8
Poorly Differentiated	0	5.7
(TOTAL)	(62)	(98)
Fibrosarcoma	7.1	1.6
Chondrosarcoma	0	0.8
Hemangiosarcoma	29	0
Myxosarcoma	2.4	0
(TOTAL)	(38)	(2)

In contrast, 98% of the ^{238}Pu-induced tumors were osteosarcomas. Two-thirds of these osteosarcomas were osteoblastic, and most were productive, indicating greater differentiation. Another point of contrast was the relatively high percentage of hemangiosarcomas (29%) and telangiectatic osteosarcomas (12%) induced by ^{90}Sr.

The distribution of skeletal location of the primary bone tumors is shown in Table 3. In dogs that inhaled $^{90}SrCl_2$, a majority of the tumors occurred in the rib, scapula and the bones of the skull and pelvis. With inhaled $^{238}PuO_2$, a majority of the tumors occurred in the lumbar vertebra, pelvis, and head of the humerus. This distribution of tumors is similar to that shown in studies of these radionuclides administered by other routes, such as injection, that give similar radiation dose patterns to the bone. (Gillett, N. A., *et al.* submitted to Int. J. Radiat. Biol. (1991)). (Miller, S.C., *et al.* Life-span Radiation Effects Studies in Animals, p. 286-298, Thompson, R.C. and Mahaffey, J. A. (eds.) OSTI, US DOE, 1986).

TABLE 3

DISTRIBUTION OF SKELETAL LOCATION OF PRIMARY BONE TUMORS IN BEAGLE DOGS EXPOSED TO $^{90}SrCl_2$ OR $^{238}PuO_2$ (% OF TOTAL)

SKELETAL LOCATION	$^{90}SrCl_2$	$^{238}PuO_2$
Axial		
Skull	26	3.3
Vertebra, Cervical	4.8	6.4
Vertebra, Thoracic	2.4	18
Vertebra, Lumbar	2.4	15
Pelvis (Incluidng sacral vertebrae)	14	13
Rib	19	3.3
Sternum	0	3.3
(TOTAL)	(69)	(62)
Appendicular		
Scapula	12	5.6
Humerus	7.1	25
Femur	4.8	5.6
Tibia	7.1	1.6
(TOTAL)	(31)	(38)

Radiation osteodystrophy was frequently present in the dogs exposed to ^{238}Pu, but seldom in those exposed to with ^{90}Sr. In the ^{238}Pu-exposed dogs, radiation osteodystrophy was characterized by osteitis fibrosa, osteosclerosis and, rarely, osteoporosis. Of the 92 dogs with bone tumors, radiation osteodystrophy was

detected in 67 (73%). The vertebra and humerus were the bones most frequently involved, but the rib and femur were involved in some cases.

Radiation osteodystrophy in the ^{90}Sr-exposed dogs was characterized by bone infarction, microinfarction cavities, peritrabecular fibrosis, and new bone formation. These lesions were minimal and were observed primarly in rib sections of dogs dying prior to 1300 days after exposure. Of the dogs dying from primary bone tumors, seven (23%) had minimal lesions of radiation osteodystrophy in non-neoplastic bone adjacent to the tumors. Thus, radiation osteodystrophy is probably not a necessary antecedent of bone neoplasia induced by either ^{238}Pu or ^{90}Sr, but may frequently accompany the process.

The results of these two studies show that the alpha-emitting radionuclide, ^{238}Pu, induced primary bone cancers that were 98% osteosarcomas, primarily of the vertebra, pelvis and humerus. The beta-emitting radionuclide, ^{90}Sr, induced bone cancers that were osteosarcomas, but included significant numbers of hemangiosarcomas (29%). The tumors were primarly of the skull, rib, pelvis, and scapula. Radiation osteodystrophy was a frequent finding with ^{238}Pu exposure, but rare with ^{90}Sr exposure. In neither case, however, did radiation osteodystrophy appear necessary for the neoplastic process.

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