LIFE-SPAN HEALTH EFFECTS OF RELATIVELY SOLUBLE FORMS OF INTERNALLY DEPOSITED BETA-EMITTING RADIONUCLIDES

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ABSTRACT: As part of a large research effort to study the lifetime health risks of inhaled radionuclides, Beagle dogs inhaled $^{90}SrCl_2$ or $^{144}CeCl_3$ or were injected intravenously with $^{137}CsCl$. Because these three compounds were soluble in body fluids, the resulting widely differing patterns of radionuclide distribution and dose reflected tissue affinities of the elements involved. Long-term health effects, predominantly cancers, were seen in the organs receiving the highest doses. Investigations are continuing on the extent to which other less irradiated organs may have also been affected.

INTRODUCTION: A major series of life-span studies on the effects of inhaled radionuclides is in progress at the Inhalation Toxicology Research Institute[1]. Both fission product and transuranic radionuclides are being studied. The primary goals of these studies are to determine the life-span health risks of inhaled radionuclides, the influence of various dose- and effect-modifying factors, and to extrapolate these results to possible human exposures, particularly those for which no direct human data currently exist. One of the important areas addressed in the fission-product studies is the influence of *in vivo* solubility of the inhaled material on the doses received by, and effects seen in, different organs and tissues. This report presents and compares results from three studies in which young-adult Beagle dogs inhaled $^{90}SrCl_2$ or $^{144}CeCl_3$ or were injected with $^{137}CsCl$. This comparison was chosen because of known differences in the pattern of metabolism and dosimetry among these three radionuclides, ranging from concentration mainly in one organ (^{90}Sr), several organs (^{144}Ce), and the whole body (^{137}Cs). Of particular interest are the relative distributions of radiation dose and long-term biological effects among organs exposed by these three regimens.

MATERIALS AND METHODS: Young adult Beagle dogs (12-14 mo, equal number of both sexes) inhaled, on a single occassion, different activity levels of either $^{90}SrCl_2$, or $^{144}CeCl_3$, or were injected once, intravenously, with $^{137}CsCl$. The 224 dogs used in these studies were divided as follows: ^{90}Sr, 66; ^{144}Ce, 55; ^{137}Cs, 54; and combined controls, 49. The exposure aerosols, consisting of the radionuclide plus a CsCl or $CeCl_3$ vector, had polydisperse size distributions with activity median aerodynamic diameters ranging from 1.5 to 2.4 μm (σ_g = 1.6 to 2.1). Exposures were completed in less than one hour. Each dog was whole-body counted immediately after radionuclide exposure and at selected intervals thereafter to determine the initial body burden and its retention as a function of time after exposure. Each dog's health status was evaluated periodically and illnesses considered not to be associated with the radiation exposure were treated using standard veterinary practices. All dogs were maintained in the ITRI kennel facility until they died or were euthanized when moribund. Complete necropsies and histopathological examinations were performed. When all dogs in a study were dead, all clinical and histopathological results and materials were reviewed to ensure accuracy and consistency of the diagnoses. All diseases were coded for

a FOCUS database using the SNOMED system modified for dogs. Absorbed beta doses were computed for individual organs or the whole body as appropriate for the radionuclides and forms used. These dose calculations were based on the whole-body retention data from each radionuclide-exposed dog in the longevity study and tissue distribution and retention data obtained from serially sacrificed dogs in separate, but similar, dosimetry studies. The small photon contribution was ignored except for the whole-body dose from ^{137}Cs where the photon portion contributed about one-third of the total dose.

RESULTS AND DISCUSSION: Table 1 presents the experimental design features for the three studies compared in this report. In each of these studies, a range of long-term retained burdens was studied, the highest of which led to early deaths within the first two years after exposure. Most of these early deaths were from hematologic dyscrasias resulting from irradiation of the bone marrow. Several others were due to radiation pneumonitis, pulmonary fibrosis, or hepatic degeneration. The focus of this report is on the remaining ~80% of the dogs that survived more than two years after exposure and, therefore, were at risk for the development of cancer and other later-occurring diseases.

Table 1
Experimental Design Features for Life-Span Studies of Dogs Exposed to Relatively Soluble Beta-Emitting Radionuclides

Study	LTRB[a] (MBq/kg)	Number of Dogs			
		Exposed		Controls	
		Total	>2 y[b]	Total	>2 y[b]
^{90}Sr	0.10 - 4.8	66	58	22	22
^{144}Ce	0.096 - 13	55	41	15	15
^{137}Cs	28 - 130	54	42	12	11

[a]LTRB = long-term retained burdens for exposed dogs
[b]Survived more than 2 y after exposure

Cumulative absorbed dose factors for organs in animals exposed to these three different patterns of radionuclide distribution are given in Table 2. The organs and tissues listed for ^{144}Ce are the four that received the highest total beta doses. Of these four, only two, bone and nasal mucosa, received significant doses from ^{90}Sr. In contrast, the relatively uniform whole-body distribution of ^{137}Cs produced about the same total dose (beta plus gamma) in all four organs.

Table 2
Cumulative Absorbed Beta Doses to 5000 Days after Exposure of Beagle Dogs to Radionuclides in a Relatively Soluble Form[2]

Organ/Tissue	Gy per MBq/kg LTRB[a]		
	$^{90}SrCl_2$	$^{144}CeCl_3$	$^{137}CsCl$[b]
Lung	---[c]	24	0.15
Liver	---	60	0.21
Bone	220	18	0.13
Nasal Mucosa	270	92	0.18
Whole Body	N/A[d]	N/A	0.21

[a]LTRB = long-term retained burden
[b]Doses for ^{137}Cs include gamma contribution
[c]--- = Dose <0.1% of skeletal dose
[d]Not applicable

Neoplasia was a prominent long-term finding in both the exposed and control dogs.[3,4,5] Table 3 gives the number of dogs in which primary malignant or benign tumors were found. All tumors, whether they were the primary cause of death, a major contributing disease or an incidental finding, are included. For this report, the controls for the three individual studies have been combined. One can roughly compare the number of tumors across the three exposed groups and the combined controls because the number of two-year survivors was about the same in each group.

Table 3
Occurrence of Primary Tumors in Certain Organs of Dogs that were Exposed to $^{90}SrCl_2$, $^{144}CeCl_3$ or $^{137}CsCl$ and Lived > 2 y after Exposure or in Control Dogs

Organ/Tissue	Number of Tumors[a]			
	^{90}Sr	^{144}Ce	^{137}Cs	Controls
Lung	2,1[b]	3,1	3,0	5,0
Liver	0,1	10,11	5,5	0,2
Bone	45,1	1,0	---[c]	---
Nasal Mucosa	3,0	5,0	4,0	---
Number of Dogs	58	41	42	48

[a] Some dogs had more than one tumor. In addition to the tumors listed, a number of tumors were found in other organs of dogs in each of these groups; many were incidental findings at necropsy.
[b] Number malignant, number benign
[c] --- = No tumors

The number of lung tumors was similar in all three exposed groups and the control group. These tumors were mainly bronchioloalveolar carcinomas and adenocarcinomas in dogs that died from 10 to 16.5 y after exposure. The exceptions were two ^{144}Ce-exposed dogs that died at 4.5 and 7.6 y after exposure in which a bronchioloalveolar adenoma and adenocarcinoma, respectively, were found. In the liver, bone and nasal mucosa, pronounced differences were found between the exposed dogs and the controls. No tumors were found in these organs in the control dogs except for two bile duct adenomas in the liver. A large number of liver tumors, both malignant (hemangiosarcoma, hepatocellular carcinoma, cholangiocarcinoma and neurofibrosarcoma) and benign (biliary cystadenoma and bile duct adenoma) were found in dogs exposed to ^{144}Ce or ^{137}Cs but not to ^{90}Sr. In contrast, the tumorigenic response in the ^{90}Sr-exposed dogs was primarily the occurrence of bone tumors (osteosarcoma, hemangiosarcoma and fibrosarcoma). No bone tumors were seen in the other groups except one osteosarcoma that occurred in a ^{144}Ce-exposed dog at 2.2 y after exposure. Tumors in the nasal mucosa, mostly carcinomas, occurred in all three studies, but not in the controls. The relative distribution of tumors between the $^{144}CeCl_3$ and $^{90}SrCl_2$ studies is consistent with the dosimetry information in Table 2. The occurrence of tumors in the livers and nasal mucosa of ^{137}CsCl-exposed dogs indicates that these tissues are relatively responsive to this radiation insult.

These initial analyses have been directed to organs and tissues that have been clearly identified as targets of radiation from these and other internally deposited radionuclides. Investigations are continuing on the question of whether additional organs or tissues may also be at risk from these different patterns of chronic beta irradiation. These results are providing valuable *in vivo* information on the appropriateness of current radiation-protection practices for internally deposited radionuclides.

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