INHALATION TOXICOLOGY OF $^{144}CeCl_3$ IN THE BEAGLE DOG

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INTRODUCTION

To ensure that radiation protection guidelines provide adequate protection against long-term health effects from internally deposited radionuclides, it is necessary to know what organs and tissues incur the highest risks and how different physical, chemical, and biological factors may alter the dose-response relationships. Data from exposed groups of people provide a critically important foundation for our understanding of radiation risks but they do not provide all of the necessary information required to address the above concerns. To provide this information for inhaled fission product and actinide aerosols, life-span studies are being conducted using Beagle dogs and other species at the Lovelace Inhalation Toxicology Research Institute (ITRI).

The fission product ^{144}Ce was chosen for study because of its prevalence in irradiated fuel of operating nuclear reactors, the energetic beta emissions from its short-lived daughter, ^{144}Pr, and its relatively long physical half-life, 284 days. Life-span studies were conducted using dogs that inhaled ^{144}Ce in a relatively soluble form, $^{144}CeCl_3$, and a group of control dogs. All of the $^{144}CeCl_3$-exposed dogs are dead; this report gives a brief summary of the results obtained to date.

MATERIALS AND METHODS

Two groups of dogs were used in these studies; 70 dogs were assigned to the life-span dose-response study and 27 dogs were assigned to a parallel, serial sacrifice study of the radiation dose distributions. All dogs assigned to the dose-response study were purebred Beagles 12 to 14 months of age and weighing between 6.7 and 13 kg at time of exposure. Of the 70 dogs, 55 were exposed to ^{144}Ce and 15 served as controls. The exposure aerosol was produced by nebulizing a solution containing ^{144}Ce in a 0.7 to 1% CeCl solution in a 0.1 or 1.0 N HCl solution. The resulting aerosol had an activity median aerodynamic diameter of 1.5 to 2.4 μm and σ_g = 1.6 to 2.1. After a brief, nose-only inhalation exposure (4 to 28 min), each dog was whole-body counted to determine the initial body burden. Whole-body counting was used at periodic intervals in these studies to determine the patterns of long-term retention. After 20 to 60 days, the dogs were transferred from individual metabolism cages to a kennel facility where they were housed two per run by sex. The health status of each dog was evaluated periodically throughout the dog's life and illnesses not associated with the radiation exposure were treated using standard veterinary practices. All dogs were maintained until they died or were euthanized. Complete necropsies were performed. Tissue specimens collected for histopathologic examination were embedded in paraffin, sectioned at 5 μm, and stained with hematoxylin and eosin routinely as well as special stains where appropriate. The clinical and pathologic findings were used to establish the cause of death and occurrence of major diseases.

Dosimetry calculations were estimated on the organ-average absorbed beta dose from ^{144}Ce-^{144}Pr. The small gamma contribution was ignored. Dosimetry informa-

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tion obtained from dogs that were serially sacrificed over the first 512 days after exposure in the dose distribution study (1) were used along with the whole-body counting data from each exposed dog in the life span study to determine organ doses individually (2).

The lifetime risk of cancer was calculated from the exposed dogs that lived more than 2 years after inhalation exposure. The risk for a given type of cancer was first computed on an annual basis by dividing the number of cancers of that type seen in a given year by the sum of all absorbed doses to that organ for all dogs living at the beginning of the year being calculated. This result was corrected for the observed incidence of that cancer in unexposed control dogs and for survival of exposed dogs to that time after exposure. These annual risks were summed to obtain the lifetime risk. The variance of the annual risk for exposed and control dogs was estimated for each year using the bionomial distribution. The square root of the sum of the variances of the annual risks was used to construct the 95% confidence interval for lifetime risk.

RESULTS

The whole-body retention pattern for ^{144}Ce inhaled as $^{144}CeCl_3$ was similar to that seen for other inhaled materials, with a rapid drop in body burden occurring during the first 2 days as the ciliated portions of the respiratory tract were cleared by mucociliary activity by way of the oropharynx to the gastrointestinal tract. Because of the low solubility of ^{144}Ce in the gastrointestinal tract, most of this material passed through unabsorbed and was excreted in feces. The long-term retained burden (LTRB) ^{144}Ce remaining after early clearance was complete, represented, on the average, 43% of the initial body burden. The LTRB had a whole-body retention half-life that increased with time after exposure and approached the physical half-life of ^{144}Ce. Although the dogs were originally entered into the study in defined exposure groups, there was sufficient variability among the achieved long-term retained burdens that they formed a continuum ranging from 0.096 to 13.3 MBq/kg body weight. For dogs that lived more than 5 years, the cumulative absorbed beta doses were 24, 60, 18 and 92 Gy per MBq ^{144}Ce LTRB/kg body weight for lung, liver, skeleton and nasal cavity, respectively (1,2).

Fourteen dogs exposed at the highest levels died of acute effects during the first two years. Eight of these died from bone marrow aplasia during the first 44 days after exposure, and 6 had pulmonary, hepatic or marrow injury that caused death at 138 to 510 days after exposure. Except for one case of osteosarcoma in a vertebra, deaths with cancer in various organs did not begin until 4.5 years after exposure. All ^{144}Ce-exposed dogs and all but one control dog are dead as of 9/30/83. A summary of important late biological effects is given in Table 1.

DISCUSSION

The biological effects seen in this study reflect the patterns of deposition, retention and dosimetry of ^{144}Ce after inhalation in a relatively soluble form. During the first week after inhalation exposure, after rapid clearance of the naso-pharyngeal and tracheobronchial regions by way of the gastrointestinal tract, the pulmonary-deposited ^{144}Ce constituted the main part of the long-term retained burden. Most of this ^{144}Ce was translocated during the first week, primarily to the liver and skeleton. High local concentrations were also noted in the nasal turbinates, either from ^{144}Ce deposited there at the time of exposure or translocated there after absorption from the pulmonary region (1,4).

Although the most prevalent early effect of inhaled ^{144}Ce was bone marrow aplasia in the dogs exposed at the highest level, early effects were also seen in the lung and liver. Dogs that survived this early phase had non-eventful clinical

TABLE 1. Summary of Biological Effects Seen in Dogs that Inhaled $^{144}CeCl_3$ or the Associated Control Dogs

Diagnosis	Number[a]	Death Days PE	Cumulative Dose to Organ Involved, Gy
Early Effects (< 2 yr.)			
Exposed Dogs			
Pulmonary Injury	3	138-375	86-170
Hepatic Injury	2	309-336	160-190
Bone Marrow Aplasia	9	21-510	6.1-58
Late Effects (> 2 yr.)			
Exposed Dogs			
Neoplastic Disease			
Lung	4	1632-5139	11-62
Liver	10	1759-5485	10-240
Skeleton	1	799	81
Sinonasal	7	1632-4085	40-250
Bone Marrow	2	1806-1811	9.4-37
Other	8	2935-5498	
Non-neoplastic Disease	11	874-5120	
Control Dogs			
Neoplastic	7	2545-5366	0
Non-Neoplastic	7	3065-5974	0
Alive	1		0

[a]One dog had both a pulmonary adenoma and squamous cell carcinoma of the nasal cavity and one dog had both a bronchial adenocarcinoma and a squamous cell carcinoma of the nasal cavity.

courses except for a single case of vertebral osteosarcoma until cancers began to appear beyond four years after exposure.

Cancers or benign neoplasms were observed in all four organs or tissues receiving the largest relative doses: lung, liver, bone, and nasal epithelium. In the lung, 3 adenocarcinomas and an adenoma were seen. In the liver, there were 7 hemangiosarcomas, 1 hepatocellular carcinoma, 1 bile duct carcinoma and 1 bile duct cystadenoma. One osteosarcoma of bone was seen. Two cases of myelogenous leukemia were observed. In the nasal cavity, 1 hemangiosarcoma and 6 squamous cell carcinomas were seen. One of these latter tumors was found *in situ*. Cancers found in other organs were also observed in control dogs and are currently assumed to not be associated with the radiation exposures.

The malignant tumors listed above were used to calculate lifetime risk of cancer in each organ or tissue (Table 2). The risk of cancer from ^{144}Ce in the dog's liver is 2 to 3 times greater than that in the lung or sinonasal epithelium. The calculated bone cancer risk is the lowest value in Table 2, but it may also be least reliable because only one bone cancer was observed.

TABLE 2. Comparison of Estimated Lifetime Risks for Chronic Irradiation from Internally-Deposited ^{144}Ce in Dogs and People

Organ or Tissue	Lifetime Cancers/10^4 Gy	
	ICRP	Dogs[a]
Lung	20	34 (4-64)
Bone Marrow	20	27 (0-66)[b]
Liver	10	84 (61-107)
Sinonasal	10?	31 (16-46)
Bone	5	14 (4-42)[b]

[a]Lifetime risk (95% confidence interval)

[b]Based on average bone dose

How do these data apply to possible human exposures? The current ICRP exposureguidelines for internally-deposited radionuclides account for a number of different organs that may be at risk, depending upon the dose patterns associated with the radionuclide form inhaled (5). For this approach to be successful, it is necessary to estimate both the risk of cancer in each heavily irradiated tissue and the doses received by each of these tissues. Currently, dosimetry calculations are not available for the sinonasal area. Analyses of all sinonasal cancers seen in dogs exposed to beta-emitting radionuclides in a soluble form at the ITRI have shown that use of the average skeletal dose to approximate dose to nasal tissues is not a useful method especially for lanthanide radionuclides (3). This is an area that needs further attention by standards-setting bodies.

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REFERENCES

1. Boecker, B. B. and Cuddihy, R. G. (1974): *Radiat. Res.*, 60, 133.
2. Benjamin, S. A., Boecker, B. B., Chiffelle, T. L., Hahn, F. F., Hobbs, C. H., Jones, R. K., McClellan, R. O., Pickrell, J. A. and Redman H. C. (1973): Radionuclide Carcinogenesis, 181, AEC Symposium Series 29, CONF 720505, NTIS.
3. Boecker, B. B., Hahn, F. F., Cuddihy, R. G., Snipes, M. B. and McClellan, R. O. (1983): To be published in the Proceedings of the Twenty-Second Hanford Life Sciences Symposium, "Life-Span Radiation Effects Studies in Animals: What Can They Tell Us?", Richland, WA, September 27-29, 1983.
4. Benjamin, S. A., Boecker, B. B., Cuddihy, R. G and McClellan, R. O. (1979): *J. Natl. Cancer Inst.*, 63, 133.
5. International Commission on Radiological Protection (1979): *Ann. ICRP*, 2, 1.