BEAGLE DOG STUDIES IN RADIATION PROTECTION

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INTRODUCTION

Beagle dogs have been used as experimental subjects in studies sponsored by the U.S. Department of Energy (DOE) and its predecessor organizations, since the establishment of the Atomic Energy Commission in 1947. Major longterm studies began with two contracts let in 1950-51 to the University of California at Davis (UCD) and to the University of Utah (UU). In 1954 the Battelle Pacific Northwest Laboratories (PNL, then contracted under General Electric Company) began inhalation studies utilizing dogs, and in 1961 the Lovelace Foundation Fission Product Inhalation Laboratory (now the Inhalation Toxicology Research Institute, ITRI) was founded. The Argonne National Laboratory (ANL) did some limited studies using the Beagle dog in the 1950's, and its current longterm external radiation studies began in 1968. The first four studies have dealt primarily with radionuclides, except for early work at UCD. Early studies at ANL were with radionuclides but they are currently committed to external radiation. Various routes of entry of radionuclides have been used; the radionuclides have been primarily fission products and/or actinides; external radiation exposures have used neutrons and x- or gamma rays.

Almost all research with Beagle dogs in DOE programs has aimed at supplying data for the purpose of strengthening the bases for radiation protection guidelines. The studies have provided information ranging from the very basics of dosimetry to the definitive description of the resulting radiololgical effects. Thus, they are defined as dose-response studies, that explore the causes of radiation damage from the molecular to the whole body levels of investigation. What will be reported in the oral presentation is a more detailed review of the use of results from Beagle dog studies that have played an important role in radiation protection.

RESULTS AND DISCUSSION

The most recent compilation of radionuclide guidelines was in 1978 by the International Commission on Radiologiocal Protection (ICRP78). In reviewing the recommendations in ICRP-30 (ICRP78) a tally was made of the number of DOE Contractor publications used in establishing individual guidelines. Numerous publications cited were from the use of rodents in radionuclide metabolism, dosimetry, and toxicity studies. Of the total, 75% of the references were from DOE supported laboratories; most of the remaining 25% were publications from studies performed outside the United States. For 12 elements, dog data constituted the basis for the numerical value used for a critical parameter in derivation of Annual Limit of Intake or Derived Air Concentration. Most uses have been for organ distribution

and retention parameters or proper assignment of compounds to inhalation classes (D, W, or Y). For 33 elements, critical parameters were based on experimental animal data and/or human data that included comparative studies in dogs.

Respiratory tract particle deposition models (lung models) use many of the results obtained from studies with Beagle dogs to assign values of half lives for transport from lung to blood. Early lung models used 120 or 360 days for the retention halflife of insoluble particles in the deep lung (NBS53, TGLD65). Currently, the value used is 500 days, and the newer models may extend this. Present dog studies of the lung retention time for insoluble plutonium will doubtless indicate a longer half life. Only a species with a lifespan like the dog may be used for this type of simulation, as its respiratory physiological properties are so much like the human. The latest lung retention data for plutonium in the dog show some trends toward a power function retention, and this may well be enforced by recent findings in the human autopsy cases being analyzed. In the latter there is plutonium in lung tissue decades after exposure.

The sophistication that has been developed for characterizing aerosol properties to describe inhalation studies has advanced the field of aerosol physics. Use of the aerodynamic diameter to quantitate deposition in the respiratory tract has become commonplace. Mercer revolutionized the ideas concerning particle solubility in the respiratory tract by relating the half life of movement to blood in terms of the particle properties (Me67). His work has been applied to many studies in which chemical characteristics of the particle inhaled and its subsequent biological behavior could be predicted through in vitro solubility studies. Such studies show promise for use of on-the-job in vitro solubility measurements on aerosol samples collected at an operation, to predict the class (D, W, or Y) of inhaled compound being considered a potential health hazard.

Dosimetry in radionuclide studies is difficult and much progress has been made over the past few decades, that has direct implications on radiation protection standards. With radionuclides, the chief experiments aimed at dosimetry have been known as distribution-excretion or dose pattern studies. These generally require sacrifice of an animal after exposure so that organ and tissue distribution of the radionuclide can be determined as a function of time. When sacrifices cover a long period post-exposure, the pattern of dosage that will give rise to the biological effect is calculated.

In addition to information for the major organ systems, the parameters associated with the tracheobronchial lymph nodes play an important part in hazards evaluation following inhalation. ICRP-26 (ICRP77) considerations of guidelines for estimating the risks and exposure limits for the tracheobronchial lymph nodes have been largely based on data from dog studies that showed high concentration, long retention times, and therefore, very high radiation doses in the nodes of dogs that inhaled insoluble radionuclides. Limited human autopsy data support the dog data in that the tracheobronchial lymph nodes appear to receive the highest radiation dose

for many inhaled insoluble radionuclides. However, data from dog studies and limited human data at that time showed no neoplastic or life shortening effects of the radionuclides in the tracheobronchial lymph nodes. Based on this information, the Commission (ICRP77) decided that irradiation of the lung is likely to be more limiting than that of lymphoid tissue for inhaled insoluble radioactive particles and that it would be satisfactory to consider the pulmonary lymph nodes and lung as one composite organ.

Biological effects studies have assumed many different approaches over the years, but almost all have depended upon an investigation by the patholoIgist using the microscope to determine cause of death. Gross tumor incidence has been the important endpoint for estimating risk from radiation exposure, with newer sophisticated methods currently being used to more definitely determine cause of death. Because the ultimate endpoint of interest is carcinogenesis, however, this has been the prime target of the longterm studies, whether from external or internal radiation. With the availability of multipurpose blood testing techniques, clinical findings have also become an integral part of the biological effects studies. Each dog on experiment receives a periodic physical examination, the clinical results of which may bear a relationship to carcinogenesis. The ultimate goal in these studies is to derive a value for the number of cancers that may be expected for each man-year-dose of radiation exposure. These are the constants of importance in calculating new guidelines.

Although it might seem that risk parameters in standard-setting are derived almost entirely from human data, these parameters are supported by a great deal of animal data. The risk factor for lung cancer employed in arriving at a weighting factor in the ICRP system is derived from human experience, but without animal data it would not even be known that plutonium or other radionuclides, could produce lung tumors. Quality factors could be derived from stopping power calculations, but if these were not supported by experimental observations in animals there would be little confidence in them. It was easier to explain the dependence on animal data for bone-seeker standards in the old ICRP system where "distribution factors" were employed; now doses are calculated to bone surfaces to avoid the direct dependence on animal data, but the results are believed because they predict what was observed to happen in animals.

The risk estimates that are now being calculated from longterm dog experiments are likely to be the only ones available that incorporate well-documented exposures to radionuclides. Within the past few years, risk factors have been obtained for beta emitters deposited in Beagle dogs by inhalation, in longterm studies at ITRI. Some of these values will be used for these radionuclides when guidelines are again updated. Values for risk have been derived for alpha emitters at the University of Utah for bone-seeking radionuclikes in the Beagle dog. Completion of the lifespan dog studies in progress at PNL and ITRI will yield more accurate values for alpha-emitters in lung, and for combinations of effects in non-respiratory tract organs. Results from the ANL low level, chronic, whole body gamma ray exposures of Beagle dogs will doubtless play an important role in establishing such risk factors for external radiation.

CONCLUSION

This has been a general overview of the derivation of radiation protection guidelines from experimental data. Beagle dog studies have been utilized as a major data source for evolution of such guidelines, and this will continue to be the case until they are completed and the final data analyzed.

REFERENCES

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Me67 Mercer, T.T. (1967), "On the Role of Particle Size in the Dissolution of Lung Burdens", Health Phys. 13 1211.

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