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POSSIBLE USES OF ANIMAL DATABASES FOR FURTHER STATISTICAL EVALUATION AND MODELING

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INTRODUCTION

There is a continuing need to understand dose-response relationships for ionizing radiation in order to protect the health of the public and nuclear workers from undue exposures. However, relatively few human populations are exposed to doses of radiation high enough to cause observable, long-term health effects from which to derive dose-response relationships. This is particularly true for internally deposited radionuclides, where much effort has been devoted to epidemiological studies of the few types of exposures available, including lung cancers in uranium miners from the inhalation of the radioactive decay products of ^{222}Ra, liver cancers in patients injected with Thorotrast X-ray contrast medium containing ^{232}Th, bone cancers in radium dial painters who ingested ^{226,228}Ra, and bone cancers in patients who received therapeutic doses of ^{224}Ra. These four types of exposures to internally deposited radionuclides provide a basis for understanding the health effects of many other radionuclides for which a potential for exposure exists. However, potential exposures to other radionuclides may differ in many modifying factors, such as route of exposure, population differences, and physical, chemical, and elemental forms of radionuclides. The only means available to study many of these modifying factors has been in laboratory animals, and to then extrapolate the results to humans. This requires that a human epidemiological study be linked to a laboratory animal study with a similar exposure, in order to understand species differences in dose response.

Many studies have been performed in animals which mimic potential exposures of people in order to understand how factors modify radiation dose-response relationships. Insights into the mechanisms of these modifying factors can be best understood by investigators from those laboratories collaborating to analyze these studies. Joint analyses for internally deposited radionuclides which have specific target organs can best be formulated as a combined analysis of radionuclides which cause health effects in the same target organ. Thus, analyses can be formulated for radionuclides that have lung, bone, or liver as their target organ. In this report, the example of bone cancer will be used because of the large number of studies of modifying factors for bone cancer available from studies in U.S. and European laboratories.

The establishment of archives for laboratory radiobiological studies in animals provides a means for investigators to know what data are available to link their studies to available human epidemiological studies. The archives provide access to detailed information necessary for comparisons, but not suitable for publication. The archives facilitates formal modeling and statistical testing of results by providing a repository whereby investigators can retrieve data from a large variety of studies in a common format. Other papers in this workshop describe the specific facilities of the archives.

BONE CANCER

Another report recently described linkages of laboratory animal data from the U.S. Archives for bone cancer in dogs to human epidemiological studies of radium dial painters who ingested $^{226,228}Ra$ and patients who received therapeutic doses of ^{224}Ra (1). Figure 1 illustrates how these linkages may be extended to include some of the studies from the European Archives. These studies provide direct linkages to the human epidemiological studies in rodents exposed to ^{226}Ra and ^{224}Ra at several different laboratories (2). Modifying factors can be studied based upon these direct linkages with human data. By comparing studies in the European and U.S. Archives, extrapolations to humans of the effects of modifying factors on dose-response relationships can be strengthened by verifying the effects in multiple species.

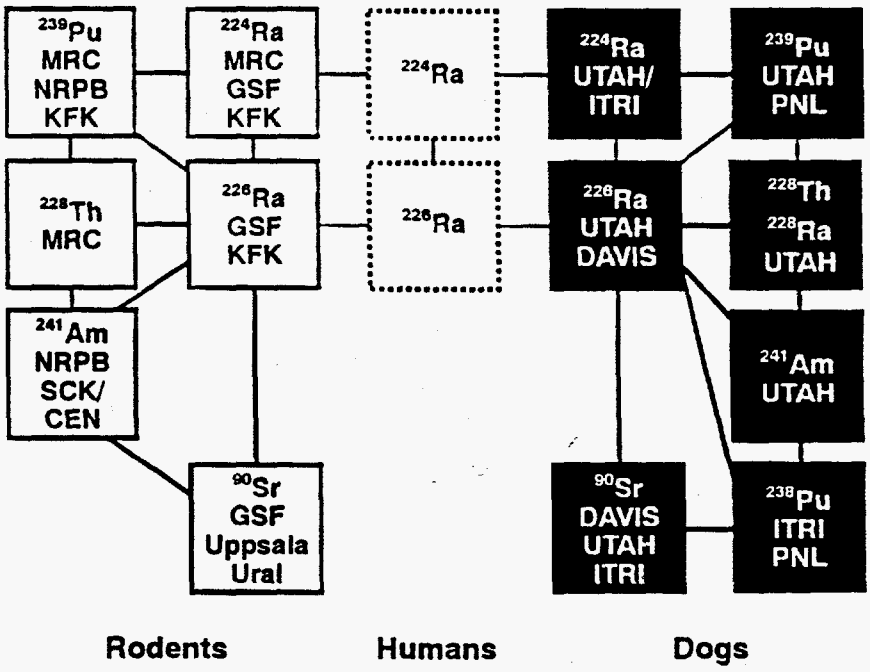

Figure 1: Some possible linkages for studies of bone cancer between the human epidemiological studies and laboratory animal studies from the U.S. and European Archives. Such linkages as these provide ways to extend available human data to other potential exposure situations for which few or no human data exist (GSF=Forschungszentrum für Umwelt und Gesundheit in Neuherberg; KFK=Kernforschungszentrum Karlsruhe; Uppsala=Swedish University of Agricultural Science in Uppsala; Ural=Ural Research Center of Radiation Medicine in Chelyabinsk; SCK/CEN=Studicenter voor Kernenergie/Centre d'Étude de l'Energie Nucléaire in Mol; MRC=Medical Research Council in Didcot; NRPB=National Radiological Protection Board in Didcot; Utah=University of Utah; Davis=University of California at Davis; PNL=Battelle Pacific Northwest Laboratory; and ITRI=Inhalation Toxicology Research Institute).

To illustrate the possibilities for using these studies, an example is given of an analysis of the effect of LET and route of exposure based upon studies of bone tumor induction in Beagle dogs performed at the ITRI from inhaled $^{238}PuO_2$ (3) and inhaled

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$^{90}SrCl_2$ (4), and at the University of Utah from injected ^{90}Sr (5). The study of inhaled $^{238}PuO_2$ included 144 dogs with doses from 0.06-8.7 Gy; 93 dogs developed bone tumors with doses from 0.2-6 Gy, and there were 7 dogs with doses below 0.2 Gy (median 0.1 Gy). The study of inhaled $^{90}SrCl_2$ included 60 dogs with doses from 5-200 Gy; 30 developed bone cancers with doses from 26 to 200 Gy, and there were 17 dogs with doses below 26 Gy (median 8 Gy). The study of injected ^{90}Sr included 85 dogs with doses from 0.7-160 Gy; 19 developed bone cancer with doses from 18 to 160 Gy, and there were 40 dogs with doses below 18 Gy (median 4 Gy).

The bone cancers were analyzed with a proportional hazards model to estimate the relative risk (6). This type of analysis describes how the age-specific tumor rates are altered by radiation dose. The change with radiation dose is described by a relative risk function. The function for the relative risk used in this study was $1 + \alpha d + \beta d^{\gamma}$ (d is the the average skeletal dose in Gy) for each radionuclide, and differences between radionuclides were tested using likelihood ratios. There were no significant differences between the two routes of exposure of inhalation and injection of ^{90}Sr (Fig. 2). There was a large difference between ^{90}Sr and ^{238}Pu, and because the estimated exponent, γ, was different for the two radionuclides (4.1 for ^{90}Sr and 2.1 for ^{238}Pu), the relative difference between the two radionuclides decreased with increasing dose. The relative differences in Figure 2 should not be confused with the quality factor for α-emitters used in radiation protection, because the doses in Figure 2 are based upon average skeletal dose and not the endosteal cell dose used in radiation protection. The linear term, αd, was not significant for any of the studies, which indicates an effective threshold for bone tumors. The failure to observe a linear response at lower doses was not due to a lack of statistical power in these studies, because of the relatively large number of dogs at lower doses, particularly in the ^{90} Sr studies.

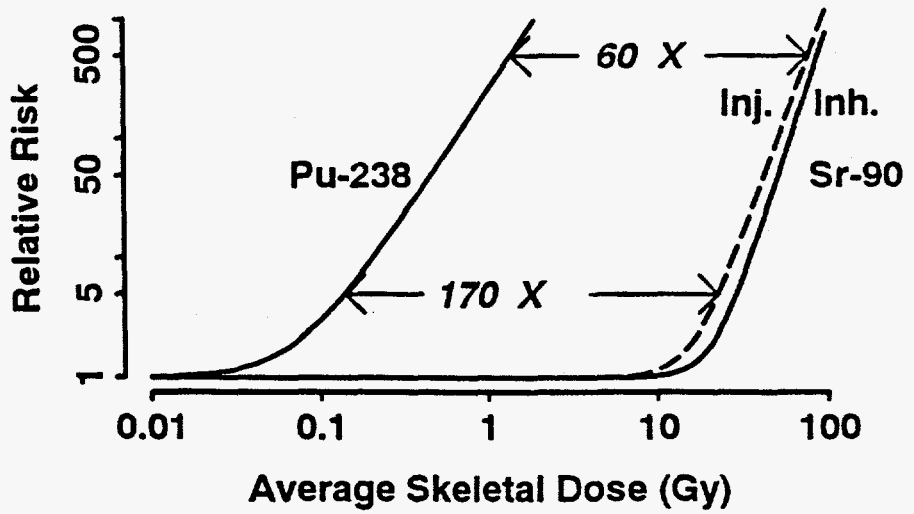

Figure 2: Estimates of the relative risk in a proportional hazards model for bone cancer in dogs that inhaled $^{238}PuO_2$ at ITRI, dogs that inhaled $^{90}SrCl_2$ at ITRI, and in dogs injected with ^{90}Sr at Utah. The increase in average skeletal dose for a relative risk of 5 and 500 between inhaled $^{238}PuO_2$ and injected ^{90}Sr is shown.

CONCLUSIONS

Cooperative analyses by investigators in different laboratories have a large potential for strengthening the conclusions that can be drawn from individual studies. When information on each animal is combined, then formal tests can be made to demonstrate that apparent consistencies or inconsistencies are statistically significant. Statistical methods must be carefully chosen so that differences between laboratories or studies can be controlled or described as part of the analysis in the interpretation of the conclusions.

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