OSTEOSARCOMA INDUCTION BY PLUTONIUM-239, AMERICIUM-241 AND NEPTUNIUM-237: THE PROBLEM OF DERIVING RISK ESTIMATES FOR MAN

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Spontaneous bone cancer (osteosarcoma) represents only about 0.3% of all human cancers, but it is well known to be inducible in humans by internal contamination with Radium-226 (1) and Radium-224 (2). Plutonium-239, Americium-241 and Neptunium-237 form, or will form, the principal long-lived alpha particle emitting components of high activity waste and "burnt-up" nuclear fuel elements. These three nuclides deposit extensively in human bone and although, fortunately, no case of a human osteosarcoma induced by any of these nuclides is known, evidence from animal studies suggests that all three are more effective than Radium-226 in inducing osteosarcoma (3,4,5,6). The assumption that the ratio of the Risk Factors, the number of osteosarcoma expected per 10000 person/animal Gy, for Radium-226 and any other bone-seeking alpha-emitter will be independent of animal species has formed the basis of all the important studies of the radiotoxicity of actinide nuclides in experimental animals (7). The aim of this communication is to review the Risk Factors which may be calculated from the various animal studies carried out over the last thirty years with Plutonium-239, Americium-241 and Neptunium-237 and to consider the problems which may arise in extrapolating these Risk Factors to homo sapiens.

Data on osteosarcoma induction by each of the three actinide nuclides are available only for rats, but information for Plutonium-239, 238 and Americium-241 has been obtained in mice and beagles. Some of the beagle studies are not yet completed and some of the rodent data were obtained only at relatively high radionuclide doses; however, sufficient information is now available to make a provisional evaluation of the likely Risk Factors for man for the three most important actinide components of the nuclear fuel cycle.

The radiotoxicity of Plutonium-239 and Americium-241 in rats has been studied by Soviet workers (4,8) and by Taylor et al (3,9) following intravenous injection of activities which yielded an averaged radiation dose to bone of about 7 Gy. For each of these nuclides the various sets of data may be combined to yield single Risk Factors for Plutonium-239 and Americium-241 of 440 (Standard Deviation (SD) 50) and 230 (SD 30) respectively. The difference between these values is statistically significant and suggests that Plutonium-239 is 1.9 (SD 0.2) times more effective in inducing osteosarcoma than Americium-241.

Data for Neptunium-237 are much less extensive and come from studies by Soviet workers (6) and by Wirth (10). A single large US study following inhalation of Neptunium-237 yielded no osteosarcomas (11). From the Soviet and German data Risk Factors for the male and female rat combined have been calculated as 1200 (SD 150) at an average bone radiation dose of 3-5 Gy; 2900 (SD 450) at 0.7-1.0 Gy and 3700 (SD 1200) at <0.15 Gy. These results suggest that Neptunium-237 may be more carcinogenic than Plutonium-239 and that there may be a trend towards higher Risk Factors at lower average absorbed alpha doses to bone.

Studies of the relative radiotoxicity of Plutonium-239 and Americium-241 in mice have been made by the Salt Lake City Group (12,13). These studies show

no clear evidence for an effect of radiation dose to bone on the calculated Risk Factor and, for averaged doses to bone in the range 3 to 13 Gy, Risk Factors of 730 (SD 70) for Plutonium-239 and 270 (SD 50) for Americium-241 have been calculated. In this species Plutonium-239 appears to be 2.7 (SD 0.2) times more effective than Americium-241 for the induction of bone sarcoma.

The most valuable information will come from the as yet uncompleted beagle studies in the United States. However, due to the kindness of the groups in Salt Lake City and Richland in publishing extensive data on the progress of their studies it is possible to make provisional estimates of the Risk Factors for Plutonium-239, Americium-241 and Radium-226 at various dose levels. It must be emphasised that the values which will be discussed in the following paragraphs are provisional since they are based on the present author's analysis of data which have not yet been fully analysed by the original investigators.

The Risk Factors calculated for beagles are shown graphically in Figure 1. All three nuclides show Risk Factors which are significantly higher at low average alpha radiation doses to bone, as compared to higher bone doses. This effect is most marked for Plutonium-239 and is least for

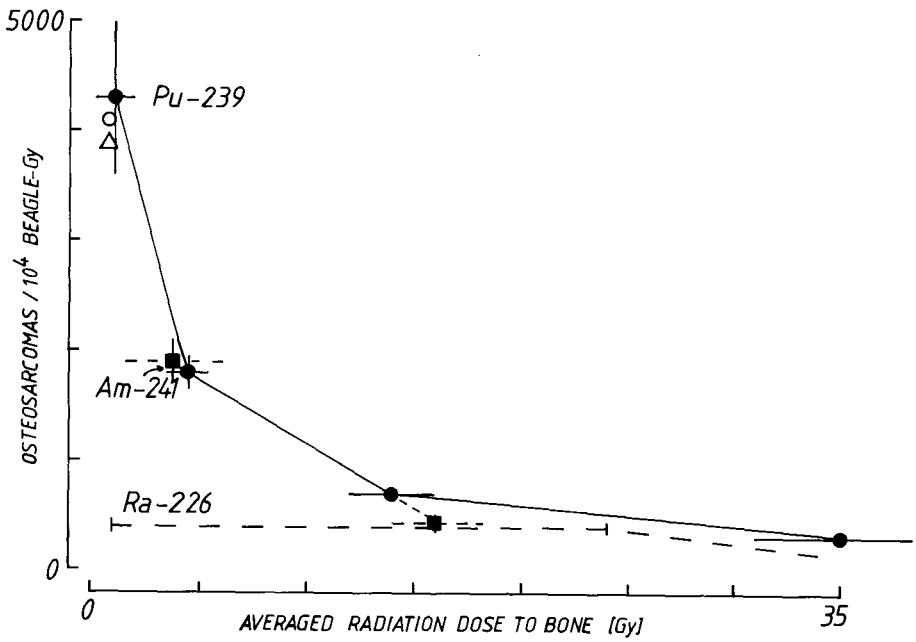

FIGURE 1 Calculated Risk Factors for osteosarcoma induction in beagles as a function of radionuclide and average alpha radiation dose to bone. Closed symbols - intravenous injection (5), open symbols - inhalation (14).

Radium-226. Particularly noteworthy are the very different ranges of bone dose over which the maximum risk is observed for the different nuclides. For Plutonium-239 the dose range is very narrow, about 0.1 to 2 Gy, as compared to about 1.5 to 6 Gy for Americium-241. For Radium-226 the calculated Risk Factor is similar (400 SD 60) up to about 25 Gy but reduces to about 170 and about 60 at average bone doses of 40 and 155 Gy respectively. At average bone doses of about 1.2 Gy Plutonium-239 appears to be about twice as carcinogenic as Americium-241 (Pu/Am = 2.3 (SD 0.2)), but at the two higher doses shown in Figure 1 this difference disappears. The risk Factor for Plutonium-239 in the bone dose range 0.1 to 2 Gy for the Utah beagles, which received single intravenous injections (5), is closely similar to those which may be calculated from the data of Park (14) for beagles which inhaled either Plutonium-239 nitrate or Plutonium-238 oxide (these values are shown as open symbols in Figure 1).

All the Risk Factors discussed above were calculated for adult animals, for young adult dogs Mays et al (7) have calculated a Risk Factor of 7700 (SD 1200) at bone doses <1 Gy, a value about double that shown in Figure 1. Thus the possibility that age may significantly affect the Risk Factor cannot be excluded.

The quite large differences in the ranges of averaged bone dose over which Plutonium-239, Americium-241 and Radium-226 apparently exhibit their maximum risk highlights the importance of a detailed understanding of the microscopic distribution of alpha particle radiation dose and the development of cell-specific dosimetry for each bone-seeking radionuclide (15). Such models are under active investigation for the above nuclides in beagles, but for Neptunium-237 it appears probable that any such cell-specific model will have to be developed from studies in rat bone, a tissue with characteristics rather different from human bone.

The data in Figure 1 show that for radiation protection purposes it is necessary to calculate the Risk Factors from animal studies involving the lowest meaningful bone dose levels available. It must also be recognised that the Risk Ratios for pairs of radionuclides may also vary with the averaged alpha dose to bone. From the human data for Radium-226 (16) at bone doses of <14 Gy, a Risk Factor of between 50 and 100 may be calculated, 4 to 8 times lower than that observed in beagles, and of the same order as the difference in the spontaneous incidence of osteosarcoma in beagle and human. Thus using the risk ratio concept, and assuming that at very low bone doses the relative carcinogenicity of Plutonium-239 and Neptunium-237 are similar in rat, beagle and man, the following Risk Factors for the three actinides in humans are proposed:

Plutonium-239, 238: 1000 to 2000 osteosarcomas/10000 person-Gy

Americium-241: 500 to 1000 osteosarcomas/10000 person-Gy

Neptunium-237: 3000 to 6000 osteosarcomas/10000 person-Gy.

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