OSTEOSARCOMA INDUCTION IN THE BEAGLE DOG WITH ALPHA-EMITTING RADIONUCLIDES (^{239}Pu, ^{228}Th, ^{228}Ra, ^{226}Ra)

(a) Further Validation of the Linear Hypothesis of Radiation Carcinogenesis

(b) Absence of Any Suggestion of Safe Radiation Threshold for Bone Cancer Induction

by

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INTRODUCTION

Recently we indicated that the cancer induction data for radium-exposed persons were consistent with radiation induction of bone cancer at a doubling dose of 25 rads (1)(2). In our studies of this question we could find no evidence supporting any safe radiation threshold anywhere in the range of 0 through 50,000 cumulative rads. Our analysis was never intended to try to prove that a threshold was impossible, but rather that no evidence for any such threshold has ever been presented (3). Further, the 25 rad doubling dose used in analysis of the radium-exposed persons was consistent with the bone sarcoma and (sinus + mastoid) carcinoma occurrence data over the entire range, 0-50,000 rads.

It is of interest, therefore, to know whether an epidemiologically more satisfactory population sample is available for confirmation of our analysis. Archer has shown quite amply why the radium-exposed persons cannot be regarded as epidemiologically satisfactory (4). It appears that no other human data are available, fortunately, for this purpose so we must turn to experimental animal data. The extensive, long range experiments of the Utah group on the Beagle do provide epidemiologically suitable material for analysis of the problem in a reasonably long-lived animal. Mays and co-workers have recently provided an up-to-date summary of all their experiences with osteogenic sarcoma in Beagles with four separate alpha-emitting radionuclides, ^{239}Pu, ^{228}Th, ^{228}Ra, and ^{226}Ra, and such data are of direct relevance (5). Therefore, the analysis below is concerned with the evidence resulting from those studies. As will be seen in detailed consideration, all four radionuclides are alarmingly effective in osteogenic sarcoma induction in the moderate dose range, and suggest markedly lower doubling doses than the 25 rads used to test the Evans data on humans.

DOUBLING DOSE ESTIMATES FOR OSTEOGENIC SARCOMA INDUCTION

(The Utah Beagle Data of Mays and co-workers)

Spontaneous Occurrence of Osteogenic Sarcoma in Beagles

As has been demonstrated in several previous publications, (2)(6)(7)(8)(9), the key input parameter required for doubling dose

estimation is the spontaneous occurrence rate of the particular cancer under study. For, the doubling dose is defined as that radiation dose which produces an excess of cancer equal to the spontaneous occurrence rate. Mays and co-workers have estimated that spontaneous osteosarcoma in the Beagle is responsible for only 1 to 100 deaths per 100,000 dogs (5)(10). This value is, of course, for Beagles living out the median life span of ~ 12-13 years. In a rigorous analysis of the radiation-induction of osteosarcoma, where many of the Beagles die of osteosarcoma at times even below $\frac{1}{2}$ the natural life span, the required spontaneous occurrence would be that for the age at which the radiation-induced osteosarcomas occur. Such spontaneous occurrence data are not available. Therefore, by using the life-time spontaneous data, we shall be underestimating the hazard of radiation-induction of osteosarcoma, - that is we will be overestimating the doubling dose. Within any set of data for a particular radionuclide, this error will be minimum, so that doubling doses over a wide range of radiation dose will be fairly reasonable. We shall choose the highest value reported by Mays et al, namely 100 per 100,000 as the spontaneous occurrence of bone sarcoma. Again, this means we shall be underestimating the radiation induction of cancer. Use of any lower value in the range reported by Mays would lead to radiation hazards shocking even to the many hardened students of the problem. Thus, we shall be conservative, and minimize the hazard of radiation induction of cancer in the Beagles exposed to various alpha-emitting, bone-seeking radionuclides. All data below are from Mays and co-workers (5).

^{239}Pu (Plutonium)

Data are reported by Mays and co-workers for osteosarcoma induction in Beagles by ^{239}Pu at various injected doses. At doses of 0.296 μCi/kg of ^{239}Pu or higher, the incidence of bone sarcoma is essentially 100% so the data are of saturation variety and hence of no value in studying dose-response relationships. Ideally, the data should be available for radiation-induced osteosarcoma over a range of doses where well under 50% of the exposed animals develop this cancer. Certainly for inferences concerning radiation protection standards the truly relevant data would be

for osteosarcoma induction for far below 50% of exposed dogs. For testing concepts of linearity of dose-response (which translates into constancy of doubling dose for osteosarcoma induction) the data of Mays et al do allow examination of a fairly wide range of doses for several alpha-emitting radionuclides.

Our utilization of the linear hypothesis of radiation-carcinogenesis assigns a constant fractional increase of the spontaneous cancer rate per rad delivered. That dose which produces a radiation-induced excess occurrence equal to the spontaneous occurrence we refer to as one doubling dose.

The data of Mays and co-workers for ^{239}Pu are presented in Table I.

TABLE 1

(Data of Mays et al, Table I, Ref. 5.)

OSTEOSARCOMA DEATHS IN BEAGLES EXPOSED TO ^{239}Pu

Injected ^{239}Pu (μCi/Kg)	Total dogs exposed	Osteosarcoma deaths	Averages for dogs with osteosarcoma: Years Inj→death	Rads at 1 year	Rads 1 yr before death	Rads at death
0.0157	12	4	9.92	9	78	86
0.0477	12	8	8.14	28	183	208
0.0951	12	10	7.15	55	313	362

We are inclined to agree with Mays et al that the dose in rads at 1 year before death due to osteosarcoma is probably closest to the dose involved in actual induction of the osteosarcoma. Hence, throughout all calculations, we shall use the value of rads at 1 year before death to estimate doubling doses. The general principles and results of calculation will be presented in detail for ^{239}Pu, and the results in tabular form, for all the other radionuclides.

0.0157 μCi/Kg ^{239}Pu

4 osteosarcomas in 12 animals

corresponds to 33,300 per 100,000 dogs

Spontaneous occurrence 100 per 100,000 dogs

Excess, radiation-induced = 33,200 per 100,000 dogs

$$\text{Number of doubling doses} = \left(\frac{\text{Excess}}{\text{Spontaneous}}\right)$$

$\therefore$ Doubling doses are $\frac{33,200}{100}$, or 332 doubling doses

Radiation dose 1 year before osteosarcoma death = 78 rads.

$\therefore$ 78 rads represents 332 doubling doses

or, 1 Doubling Dose = $\frac{78}{332}$, or 0.23 Rads from ^{239}Pu.

0.0477 μCi/Kg ^{239}Pu

8 osteosarcomas in 12 animals

corresponds to 66,700 per 100,000 dogs

Spontaneous occurrence 100 per 100,000 dogs

Excess, radiation-induced = 66,600 per 100,000 dogs

Number of doubling doses = $\frac{66,600}{100}$, or 666 doubling doses.

Radiation dose at 1 year before osteosarcoma death = 183 rads.

$\therefore$ 183 rads represent 666 doubling doses

or, 1 Doubling Dose = $\frac{183}{666}$, or 0.27 Rads from ^{239}Pu.

0.0951 μCi/Kg ^{239}Pu

10 osteosarcomas in 12 animals

corresponds to 83,300 per 100,000 dogs

Spontaneous occurrence 100 per 100,000 dogs

Excess, radiation-induced = 83,200 per 100,000 dogs

Number of doubling doses = $\frac{83,200}{100}$, or 832 doubling doses.

Radiation dose at 1 year before osteosarcoma death = 313 rads

$\therefore$ 313 rads represents 832 doubling doses

or, 1 Doubling Dose = $\frac{313}{832}$, or 0.38 Rads from ^{239}Pu.

Considering (a) that saturation effects are most likely operating in the highest dose category (10 out of 12 animals dying of osteosarcoma) and (b) that the earlier deaths at high doses should have required use of a somewhat lower spontaneous occurrence rate, it can be stated with emphasis:

1. These data represent a remarkable confirmation of linear theory of radiation-induction of osteosarcoma over the dose range studied (78-313 rads from ^{239}Pu).
2. Doubling dose is essentially constant.

The extremely low doubling dose for osteosarcoma induction by ^{239}Pu is startling. There exist good reasons to believe that the doubling dose, while truly very low, is not quite as low as the above calculations indicate. Mays has pointed out that the rad dose is calculated assuming distribution of the plutonium alpha particles over the entire skeletal mass (5). However, Mays points out, as do others, that ^{239}Pu is primarily a surface seeker, being primarily concentrated in the endosteum, next in the periosteum, and to a lesser extent, depending upon particle size, in the bone marrow. Presumably the ~ 50% of the α particle energy dissipated in the mineral skeleton is wasted, with respect to osteosarcoma induction. It is completely conceivable that the true dose to relevant tissue for osteosarcoma induction is 10 X higher than that presented by Mays et al for overall skeleton. It would appear doubtful that the relevant tissue dose is 50 X higher than the average skeletal dose. Using these limits, the following are set out for possible doubling doses for osteosarcoma induction (Table 2).

TABLE 2

RANGE OF DOUBLING DOSES FOR OSTEOSARCOMA INDUCTION IN BEAGLES BY ^{239}Pu

Dose level (^{239}Pu) µCi/Kg	Averaging over entire skeletal mass Rads	10 X Averaging over entire skeletal mass Rads	50 X Averaging over entire skeletal mass Rads
0.0157	0.23	2.3	11.5
0.0477	0.27	2.7	13.5
0.0951	0.38	3.8	19.0

Not only do the Utah Beagle data indicate consistency with linear theory of osteosarcoma induction, and essential constancy of doubling dose over a wide range of delivered doses, but also they indicate it is remote for the true doubling dose to be as high as 25 rads to the relevant tissue (average). Certainly these data argue strongly against purported thresholds in the 0-1000 rad range. The Utah Beagles are experiencing a 300 fold or more increase in osteosarcoma incidence in the general neighborhood of purported "safe threshold" doses.

^{228}Th (Thorium)

Thorium behaves similarly to plutonium in the sense of being a bone surface seeker rather than a bone volume seeker. Mays and co-workers provide data for ^{228}Th usable up to 0.0919 μCi/Kg. At higher doses essentially all Beagles developed osteosarcoma or died early of radiotoxicity. Their relevant data are reproduced in Table 3.

TABLE 3

(Data of Mays et al, Table 1, Ref. 5)

OSTEOSARCOMA DEATHS IN BEAGLES EXPOSED TO ^{228}Th.

			Averages for dogs with osteosarcoma			
Injected ^{228}Th (μCi/Kg)	Total dogs exposed	Osteosarcoma deaths	Years Inj→death	Rads at 1 year	Rads 1 yr before death	Rads at death
0.0152	12	4	8.75	46	130	132
0.0302	12	7	6.17	91	236	247
0.0919	12	11	3.19	285	503	618

The calculation of doubling doses for osteosarcoma induction by ^{228}Th is carried through precisely in the same manner as presented above for ^{239}Pu. The results are summarized in Table 4.

TABLE 4

DOUBLING DOSES FOR OSTEOSARCOMA INDUCTION IN BEAGLES BY ^{228}Th

Injected ^{228}Th μCi/Kg	Rads at 1 yr before death	Total dogs exposed	Osteo-sarcoma deaths	Osteo-sarcoma per 100,000	Spontaneous per 100,000	Number of doubling doses	One doubling dose (Rads)
0.0152	130	12	2	16,700	100	166	0.49
0.0302	236	12	5	41,700	100	416	0.57
0.0919	503	12	11	91,700	100	916	0.55

Again, an extremely low-doubling dose (~ 0.5 rads) is obtained for ^{228}Th as with ^{239}Pu. The data are in excellent harmony with linear theory (constancy of doubling dose) over a four fold range of doses. As Mays pointed out, ^{228}Th is a surface seeker too, so the true dose to relevant tissue for osteosarcoma induction must be higher than calculated. It is conceivable, therefore that the true doubling dose may well be 10 X higher, or approximately 5.0 rads. It is doubtful that it would be 50 X higher, which would correspond to 25 rads. When consideration is given to energy differences in alpha particles for Pu^{239} versus ^{228}Th and its daughters, and to the uncertainty concerning redistribution of thorium daughters, the two fold difference in doubling dose between ^{239}Pu and ^{228}Th may well disappear. What is relevant is that both are indeed extremely potent carcinogens in the purported "safe threshold" region.

^{228}Ra (Radium)

Radium, in contrast with both plutonium and thorium, is regarded as a volume seeker rather than a surface seeker in bone. Since most suggestions indicate the relevant cells for osteosarcoma induction to be in the surface region (although not specifically identifiable at this time) our expectation immediately would be an appreciably higher doubling dose for radium nuclides than for plutonium or thorium nuclides. Mays' data for the ^{228}Ra nuclide (MsTh) are presented in Table 5.

TABLE 5

(Data of Mays et al, Table 1, Ref. 5.)

OSTEOSARCOMA DEATHS IN BEAGLES EXPOSED TO ^{228}Ra

Injected ^{228}Ra (μCi/Kg)	Total dogs exposed	Osteosarcoma deaths	Averages for dogs with osteosarcoma: Years Inj→death	Rads at 1 year	Rads 1 yr before death	Rads at death
0.148	12	4	8.07	42	455	501
0.309	12	5	6.17	100	810	966
0.973	12	8	4.08	348	1630	2250

The calculated doubling doses for osteogenic sarcoma induction are presented in Table 6.

TABLE 6

DOUBLING DOSES FOR OSTEOSARCOMA INDUCTION IN BEAGLES BY ^{228}Ra

Injected ^{228}Ra μCi/Kg	Rads at 1 yr before death	Total dogs exposed	Osteo-sarcoma deaths	Osteo-sarcoma per 100,000	Spontaneous per 100,000	Number of doubling doses	One doubling dose (Rads)
0.148	455	12	4	33,300	100	332	1.4
0.309	810	12	5	41,700	100	416	1.9
0.973	1630	12	8	66,700	100	666	2.4

Again, we are faced with extremely low doubling doses for osteosarcoma induction, this time by ^{228}Ra, namely ~ 1.5-2.5 rads. Considering the early deaths in the high dose group and the fact that this means a lower spontaneous rate should have been used, the data are completely in harmony with linear theory (essentially constant doubling doses). Since ^{228}Ra is a volume seeker primarily, there would appear little reason to expect the average dose to relevant cells to be appreciably higher than the average skeletal dose reported here by Mays and co-workers. It is therefore doubtful that the true doubling dose of ^{228}Ra could be as high as 20 rads, and is probably closer to the values in Table 6.

^{226}Ra (Radium)

Mays and co-workers also studied the osteosarcoma induction by the long-lived radionuclide of radium, ^{226}Ra. The relevant data are presented in Table 7.

TABLE 7

(Data of Mays et al, Table 1, Ref. 5.)

OSTEOSARCOMA DEATHS IN BEAGLES EXPOSED TO ^{226}Ra

			Averages for dogs with osteosarcoma			
Injected ^{226}Ra (μCi/Kg)	Total dogs exposed	Osteosarcoma deaths	Years Inj→death	Rads at 1 year	Rads 1 yr before death	Rads at death
0.166	12	1	11.25	84	458	488
0.339	12	4	9.63	166	810	874
1.07	12	11	6.28	561	1940	2190

The calculated doubling doses are in Table 8.

TABLE 8

DOUBLING DOSES FOR OSTEOSARCOMA INDUCTION BY ^{226}Ra

Injected ^{226}Ra μCi/Kg	Rads at 1 year before death	Total dogs exposed	Osteo-sarcoma deaths	Osteo-sarcoma per 100,000	Spontaneous per 100,000	Number of doubling doses	One doubling dose (Rads)
0.166	458	12	1	8,300	100	82	5.6
0.339	810	12	4	33,300	100	332	2.4
1.07	1940	12	7	58,300	100	582	3.3

The doubling doses for osteosarcoma induction by this radionuclide, ^{226}Ra, are also extremely low (2.4 to 5.6 rads). The 5.6 rads is based upon the group with 1 osteosarcoma death, and hence the highest statistical uncertainty. It is to be noted that the doubling dose for ^{226}Ra, though extremely low, is approximately twice that for ^{228}Ra, a shorter-lived radium nuclide. Mays and co-workers have provided some reasonable suggestions for the greater carcinogenicity of ^{228}Ra compared with ^{226}Ra. First, the α particle range is greater for ^{228}Ra than for ^{226}Ra, so more α particles escape bone substance and are able to irradiate the probably relevant target cells. Second, there may be translocation of some of the daughter products of ^{228}Ra to sites where a greater carcinogenic effect may be possible than for the radium parent nuclide retained in bone volume. In any event, the most striking feature both of the ^{226}Ra and ^{228}Ra findings is the doubling dose for osteogenic sarcoma induction being less than 5 rads, with very remote prospects indeed that it could be as high as 25 rads.

Conclusions

Analysis of the data of Mays and co-workers shows that for all four α-emitting, bone seeking radionuclides, ^{239}Pu, ^{228}Th, ^{228}Ra, and ^{226}Ra, the observed doubling doses are under 5 rads in all cases, based upon average skeletal dose. The apparently much lower doubling doses for the two surface-seeking nuclides, ^{239}Pu and ^{228}Th than for the two volume-seeking nuclides, ^{228}Ra and ^{226}Ra, are in all probability due, as Mays

suggests, to the relative underestimate for the surface seekers of the relevant dose to the tissue which yields osteosarcomas.

These monumental experiments, involving careful, exhaustive, long-term observation of Beagles provide a beautiful confirmation of the linear theory of radiation carcinogenesis, over the dose range available, with the expected essential constancy of doubling doses, within experimental error. Further, the data indicate the doubling doses to be in the same low region as that which proved to fit the human radium exposure data (25 rads).

Above all, the Beagle data certainly should sound the final death-knell for threshold-hoping in the 0-1000 rad region for osteosarcoma induction.

Instead of "safe thresholds", the data show some 50 to 300 fold increase in osteosarcoma production in this dose range.

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