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R. E. Rowland

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R. E. Rowland
Radiological and Environmental Research
Argonne National Laboratory
Argonne, Illinois

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Abstract

Extensive experience has shown that a number of radionuclides—including ^{32}P , ^{131}I , ^{222}Rn , ^{224}Ra , ^{226}Ra , ^{228}Ra , and ^{232}Th —and their decay products can induce malignancies when deposited in the human body. However, the relationship between the quantity of isotope deposited and the probability of subsequent induction of a malignancy is less clear. For some of these radionuclides, we do not have accurate estimates of the body contents of the exposed populations (and hence of the dose), and in no case do the body burdens or total doses extend over more than a small portion of the range of interest to us.

The hypothesis that the risk is linear with dose, independent of the dose rate, may be defensible in obtaining conservative estimates for use in guiding public policy. Verification of linearity, however, should be sought by studying only populations whose doses ranged over several orders of magnitude—e.g., from studies of radium in man. Current ^{224}Ra results can be described by a risk proportional to either the first or the second power of dose, but a first-power law does not adequately describe the current ^{226}Ra – ^{228}Ra results. Thus these studies cast doubt on the validity of linear risk estimates for bone-seeking alpha-emitting radionuclides in man.

Internal emitters
Radium
Malignancy
Thorotrast

The effects of internally-deposited radioisotopes are of vital importance to us today, for, as we enter a nuclear era, the human body will have the possibility of acquiring a host of new radioisotopes. Now, of course, internally-deposited radioisotopes are not new to mankind; ^{14}C , ^{40}K , ^{226}Ra , and ^{228}Ra exist in all of us as a consequence of the natural levels of these isotopes in our environment. We know, however, essentially nothing about the effects of these particular isotopes on man at environmental levels, let alone the effects of the new radioisotopes that are entering our environment.

There are two major problems that face those who investigate the internal emitters in man; first, the dosimetry is usually extraordinarily complex, and second, for ethical and practical reasons one cannot test the effects of such noxious agents by experiment. The second of these forces the investigator to take advantage of human experience which took place unexpectedly, perhaps decades earlier, so that often not only does he not know the levels of radiation involved, but even the identities of the exposed individuals. Nevertheless, the need to know is so overwhelming that our efforts must be so directed that all possible information can be derived from the scattered cases of internal radioisotope contamination.

It is my intention to consider the somatic effects of the internal emitters, and to accept as proven the hypothesis that the major long-term somatic effect of radiation on man is cancer. The question before us then relates to the risk of malignancy; how is the incidence related to the dose delivered to the sensitive cells at risk? I will also assume that while a

a linear hypothesis is and perhaps must be used for radiation protection purposes, it is our desire here today to deduce the shape of the dose-response function from the data itself.

The problems associated with the internal emitters are well illustrated by the studies of Conard and his associates of the Marshallese who were exposed on Rongelap Island in 1954 (1). Eighty-two people were exposed; 64 on Rongelap received an estimated whole body gamma dose of about 175 rad and 18 others on a nearby island about 69 rad. Over and above this whole body dose the inhalation of iodine isotopes and consumption of iodine-contaminated food resulted in total thyroid doses of the order of 135 to 335 rads in adults to as high as 1200 to 1400 rads in small children. Twenty years later, 28 people have developed thyroid abnormalities, three of which are malignant. In addition, one 19-year-old boy died of acute myelogenous leukemia in 1972 which may well have been due to his radiation exposure (Conard, private communication).

In this study we find the classic problems of the internally-deposited radionuclides. First, in addition to the internal iodine dose, there was also an external total body gamma dose. Second, neither the external gamma nor the internal iodine doses are accurately known. Third, the population is small. Fourth, the range of dose values is narrow—this is an important point to which I will return later. Fifth, there were malignant effects, but they did not occur for quite a few years after the event, and, since only 20 years have elapsed since the exposure, it is not unlikely that more malignancies may appear in the future.

The problems associated with this study of the Marshallese are common to most studies of the effects of internal emitters in man. These include difficult dosimetry, the fact that the population under study is always too small (and, incidentally, being human, the members may elect not to be part of any follow-up, thereby playing havoc with our statistics!), the range of dose values over which there is significant experience is limited, and the follow-up time by necessity is the lifetime of the exposed individual.

From Conard's studies of the Marshallese we can obtain quantitative estimates of the risk of thyroid malignancy from exposure to radioiodine, but only if we assume a linear relationship between dose and effect.

Are there any exposed populations which provide the required number of cases, well-documented dosimetry, and wide range of dose values so that risk estimates can be made without recourse to a preconceived dose-response function? Consider the studies of Thorotrast in man. Several excellent follow-up studies are underway, particularly in Portugal, Denmark, Japan, and more recently, Germany (2). The population under study is quite large, of the order of several thousand individuals, making it perhaps the largest internal-emitter study. There is a high incidence of liver tumors in this group, particularly haemangioendotheliomas, yet the only risk estimates that can be made are those based on a linear hypothesis. The quantities of Thorotrast administered ranged only from about 10 ml to 100 ml, with most cases receiving doses in the range of 15 ml to 75 ml. This implies too narrow a dose range for us to deduce the shape of a dose response function,

and therefore we must base the calculation of risk on an assumed shape for this function.

The studies I am most intimately acquainted with are the studies of radium in man, and it should come as no surprise that I consider them to have the best probability of fulfilling the above requirements. The study of ^{224}Ra in Germany by Spiess and Mays is a good starting place (3). These investigations have identified some 1811 individuals who received ^{224}Ra in the period 1944—51. Of these 898 have been followed-up, or almost 50% of the series. The doses calculated from the injection records range from 6 to 5750 rads, calculated as the average dose to the total skeleton. The highest dose in the series is thus almost a factor of 1000 greater than the lowest, so considerable leverage exists for determination of the shape of a dose-response curve.

Unfortunately (and there is always an "unfortunately" in internal-emitter studies) the exposed population included children of all ages as well as adults, and the highest doses were found in the lowest age groups. Spiess and Mays have broken the study into two segments, based on age, and reported their results for all juveniles and separately for adults. I have chosen to combine their data into one single group, and have used 815 cases for which complete injection data and follow-up history have been published for my presentation today.

The breakdown of the cases into dose ranges is shown in Table I.

The end point used for analysis in Table I is the bone tumor, 47 of which have been identified in the 815 cases used in this analysis. One

wonders about the other 50% of the injected population. Do they represent the same distribution of doses? Do they contain the same number of bone tumors? Or is it possible that most of the tumor cases have been included in the study group? This is a rather likely possibility, which would have the result of biasing upward our risk estimates. Since we don't know the answers to these questions, they will serve to stand as warnings, and we will proceed under the assumption that the data are valid as given.

These data are shown in graphical form in Fig. 1 with a linear dose-response function which has been fitted by the method of least squares. I've taken one liberty with the data here, for my own convenience. Since I am going to use a number of figures of the same type I have chosen to use the same scale on each of these illustrations. Therefore, to spread the ^{224}Ra dose values out on a scale actually designed for ^{226}Ra dose values, each dose has been arbitrarily multiplied by the factor 3.5. You should recognize that this procedure in no way changes the shape of the distribution.

These data points can also be fitted with a dose-squared-exponential-function, which has worked well with the ^{226}Ra population, and such a fit is illustrated in Fig. 2 using semilogarithmic coordinates.

The fitted dose-response function provides us with the desired measure of risk. This set of data, even though it covers a range of doses varying by a factor of about 1000, does not effectively discriminate between the two functions I have chosen to test. It is obvious that more cases are needed, particularly in the dose region between 10 and 100 rads.

Table II shows the fitted functions, and Table III shows the predicted number of tumors, under the listed conditions for several low doses. It is readily apparent that, given a significant number of cases between 50 and 100 rads, it should be possible to clearly distinguish between these two functions. Spiess and Mays have pointed out that there exists a yet-unstudied series of 1000 to 2000 ^{224}Ra cases in Germany in which the average skeletal dose is calculated to be 56 rads (3). Therefore, given the time and effort, it should be possible to obtain from these cases a definitive resolution to this question of the shape of the dose-response function for ^{224}Ra under these conditions of administration.

Let us now examine the study of the effects of radium on man in this country, a study with which I am very familiar. Unfortunately both ^{226}Ra and ^{226}Ra mixed with varying quantities of ^{228}Ra were acquired internally by those exposed to radium in this country. It is possible for us to document very accurately the internal burden of ^{226}Ra in man both during life and, from suitable samples, after death. ^{228}Ra , however, can today only be accurately measured after death, for, as a consequence of its 5.7 year half life, and the fact that those who acquired it did so some 50 years ago, very little remains in the body today. We, in assigning doses, add the contribution from ^{228}Ra to the ^{226}Ra dose. Thus, tacitly, we assume equality, rad for rad, for the emissions from the two different decay schemes, an assumption that may not be tenable. Doing so results in assigned doses to our population that range from 1 rad to 44,000 rads. For my discussion today I have arbitrarily used only those cases with doses of 30 or more rads,

so that the dose range considered varies by a factor of the order of 1500 from highest to lowest dose.

The current status of the radium population under study today by the Center for Human Radiobiology at Argonne National Laboratory is shown in Table IV.

Of the 3803 names of potentially-exposed individuals known to us, we have studied only 1572, or 41%. These cases were exposed by all routes—dial painting, medical injections, and laboratory work—over the period from the discovery of radium until today. Yes, even today radium dial painting goes on, but let me hasten to add, apparently under well-controlled conditions. Thus, while we can and do examine the results from this entire population, it is appropriate to divide the group into various segments. One segment constitutes a well-defined population of employees of three dial painting plants, who worked prior to 1938, and all of whose names were obtained from employment lists. You might be interested to know that some of these fifty-year-old lists just came into our hands within the last few years. As shown in Table IV, we have located and studied 377 of the 720 listed individuals, or 52% of them, and this group had 25 of the known 54 bone tumors in our population. Since many of these cases were known to us as a consequence of their malignancies, one might suggest that such tumor cases should be eliminated from this group until we achieve close-to-complete coverage of the entire population. If we do this, however, the number of bone tumors in this series is markedly reduced.

The effect is shown even more clearly in Table V. Here the cases are divided into dose groups, first for the total population, then the listed population, and finally, the number of acceptable tumors remaining if those found on the basis of symptoms are eliminated. You will note that it is the high dose tumors that are eliminated; these were often added to the study by selective exhumation of known tumor cases.

In Fig. 3 the bone tumors in the total population under study are fitted with a dose-response function of the dose squared exponential form. In Fig. 4 this same curve is shown, but the data points are now from the listed population of the three dial painting plants. Three sets of points are shown. The X's are the observed tumor frequencies in the population. The *'s are the frequencies left when we remove the cases found as a consequence of their malignancy. This procedure, unfortunately, almost completely removes the bone tumors at high doses. The O's indicate lower limit to the bone tumor fraction, based on two assumptions. The first assumption is that the dose distribution in the unmeasured cases is identical to that in the measured cases. The second is that, for each dose interval, there are no bone tumors in the unmeasured population. However, we know of 16 more bone tumors in the unstudied portion of this population. Therefore, at this time all we can say is that the true distribution most likely lies somewhere between the points indicated by the X's and the O's. It is undoubtedly pure coincidence, but the dose-response function derived from the total population appears to fall within these two distributions.

It is not possible to get a meaningful linear fit for a dose-response function to these radium data, either the bone tumor fraction from the entire study or from the selected employees of the three dial painting plants. The dose-squared exponential function derived from the entire population, since it fits the selected population adequately, is our best estimation for the bone tumor risk from internally-deposited ^{226}Ra or mixed ^{226}Ra and ^{228}Ra acquired from the dial painting industry. The function fitted to the bone tumor data is shown in Table VI.

This function predicts 30 bone tumors in 1000 cases, each with a skeletal dose of 1000 rads, exposed under the described conditions. If we use this risk at this level, we can compare the expected number of such tumors at lower doses, depending upon whether, below this level, the dose-response function is linear or continues to follow a dose-squared exponential. These predictions are shown in Table VII.

I've now described, briefly, due to time limitations, the status of the two radium studies currently underway, and my estimates of the bone tumor risks derived from each. Would it be possible to extend our knowledge by combining the two studies? I consider it appropriate at this session on Human Radiobiology to indulge in some speculation, and if we wish to extract information on the risk of malignancy, some speculation is required. Let us consider how the dose to the skeleton from ^{224}Ra and its daughters might be related to that from ^{226}Ra and ^{223}Ra and their daughters. Spiess and Mays have done so, pointing out that we probably should compare the dose delivered to the first 10 micra of soft tissue adjacent to bone (3).

From their calculations of the dose to this 10 micra layer we learn that, when the ^{226}Ra and ^{228}Ra dose is expressed as the average skeletal dose, then the average skeletal dose for ^{224}Ra must be multiplied by a factor of 14.2 to obtain a set of comparable dose levels. That is, the dose to the 10 micra layer from the skeletal content of ^{226}Ra that yields an average skeletal dose of 1000 rads is the same as the dose to this layer from the quantity of ^{224}Ra that delivered $\frac{1000}{14.2}$ or 70 rads to the skeleton.

However, if we multiply all the ^{224}Ra dose levels by this factor of 14.2, we find that a plot of the two sets of data on the same set of coordinates is meaningless. This may indicate that the dose from the relatively short exposures from ^{224}Ra in this series (from a few weeks to a few years) cannot be compared to the originally high, then subsequently lower lifetime dose from ^{226}Ra in a dial painter. On the other hand, it might also hint that our calculations of the doses are not correct. My colleague, John H. Marshall, is now actively investigating this latter possibility.

We can, however, compare the two sets of data empirically, and this I have done in Fig. 5. Here are the two sets of data plotted together after the ^{224}Ra data have been multiplied by the factor 3.5. I think you will agree with me that the two sets of data fit remarkably well, and you now see why I chose to use this particular factor when presenting the ^{224}Ra data.

If we now can find a theoretical basis for a combination of this nature, it might be possible to consider combining the two studies into one

enlarged population. It would be premature to do more than suggest this possibility now. However, it is tempting, for the essentially doubled population would provide greater predictive power for the shape of a dose-response function than either study by itself.

My purpose has been to point out where we are today in our attempts to quantitate the risk of malignancy from internal emitters. It appears that only from the two large radium studies will we ever have a large enough population with a significant spread in doses to attempt to formulate risk estimates from the population itself; that is, by letting the data itself define the shape of the dose response relationship.

I have taken care to point out the weaknesses of these current studies; their far-from-completeness of follow-up, their built-in tumor bias that will only disappear as we approach 100% follow-up; and, as a consequence of the long latent period in man, the time it takes to complete these studies. I do not wish to leave you, however, only with a negative impression of these studies. It may well be that only these studies have the power to show the true shape of a dose-response relationship in man. For this reason alone these most difficult and complex studies must continue, with their greatest emphasis directed toward achieving 100% follow-up of well-defined groups. Only by achieving this primary goal will we ever be able to relate dose to risk. However, if we can determine this relationship for radium in man, then we should be able to extrapolate, from properly formulated models, the risk to man as a function of dose from those isotopes of the future—plutonium,

americium and the other transuranic elements, isotopes we hope will never contaminate man at high enough levels to show effects.

References

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Table I

²²⁴Ra CASES [Spiess and Mays, 1971 (4)]

Dose range (rads)	Average dose (rads)	Cases	Sarcomas	Sarcoma fraction
2000—5750	3332	21	8	0.381 ± 0.135
1000—1999	1352	72	19	0.269 ± 0.061
500— 999	692	121	9	0.074 ± 0.025
200— 499	313	221	8	0.036 ± 0.013
96— 199	139	205	3	0.015 ± 0.008
6— 89	54	<u>175</u>	<u>0</u>	0.0 ± 0.006
		815	47	

Table II
RISK ESTIMATES FOR ^{224}Ra IN MAN

Conditions:

Multiple injections over periods from weeks to a few years

Calculated for period 19—25 years after first injection

Risk calculated as:

Fraction of cases with a bone tumor as a function of dose

Dose calculated as average to mineralized skeleton

Linear hypothesis: $F = 1.5 \times 10^{-4} \cdot D$

Dose-square-exponential: $F = 3.7 \times 10^{-7} \cdot D^2 e^{-D/1400}$

Table III
BONE TUMORS PREDICTED FROM ^{224}Ra

Dose (rads)	Linear function tumors/1000 cases	Dose-squared-exponential tumors/1000 cases
100	15	3.5
50	7.5	0.9
10	1.5	3.6×10^{-2}

Table IV

STATUS OF THE RADIUM STUDIES, APRIL 1974

Population	Known	Studied	Number with doses >30 rads	Malignancies	
				Bone	Head
Total	3803	1572	621	54	26
Listed employees of three dial-painting plants before 1938	720	377	235	25	7
Above less cases found as a consequence of malignancies			221	11	4

Table V
U.S. ^{226}Ra AND ^{228}Ra CASES

Dose range (rads)	<u>Total Population</u>		<u>Listed Population: 3 Dial Plants</u>		
	Cases	Bone tumors	Cases	Bone tumors	Less cases found by symptom
10000—44400	42	15	20	11	1
5000— 9999	44	15	16	6	3
2500— 4999	57	13	25	6	5
1000— 2499	59	10	20	2	2
450— 999	55	1	22	0	0
30— 449	364	0	132	0	0

Table VI
RISK ESTIMATES FOR ^{226}Ra IN MAN

Conditions:

Exposure in dial painting industry

Calculated for period 35—59 years after first exposure

Risk calculated as:

Fraction of cases with a bone tumor as a function of dose

Dose calculated as average to mineralized skeleton

$$F = 3.7 \times 10^{-8} D^2 e^{-D/4970}$$

Table VII
BONE TUMORS PREDICTED FROM ^{226}Ra AND ^{228}Ra

Dose (rads)	Linear function tumors/1000 cases	Dose-squared-function tumors/1000 cases
1000	30	30
500	15	8.4
100	3	0.4

Figure Legends

- Fig. 1. Fraction of cases in each dose range with bone tumors plotted as a function of average skeletal dose from ^{224}Ra and daughters. The actual dose values have each been multiplied by the arbitrary factor 3.5 to spread the dose levels. The error bars represent one standard deviation in tumor fraction. A linear dose-response function has been fitted to the data points.
- Fig. 2. Fraction of cases in each dose range with bone tumors plotted as a function of average skeletal dose from ^{224}Ra and daughters. The actual dose values have each been multiplied by the arbitrary factor 3.5 to spread the dose levels. The error bars represent one standard deviation in tumor fraction. A dose-squared-exponential function has been fitted to the data points.
- Fig. 3. Fraction of the cases in each dose range with bone tumors plotted as a function of average skeletal dose from ^{226}Ra and ^{228}Ra . The error bars represent one standard deviation. The fitted dose response function is of the form $F = \text{const} \times D^2 \times e^{-D/D_0}$.
- Fig. 4. Fraction of the listed cases in three U. S. dial painting plants with bone tumors in each dose range plotted as a function of average skeletal dose. X represents the fraction when all bone tumors are included. * represents the fraction when cases found

as a consequence of a malignancy are removed. O represents the fraction when the number of cases in each dose range are doubled, to account for the unmeasured cases, on the assumption that there will be no more bone tumors in each range. The true fraction probably lies somewhere between the X's and the O's.

Fig. 5. Superimposed tumor fractions for ^{224}Ra and $^{226,228}\text{Ra}$ as a function of average skeletal dose. O shows the tumor fractions for $^{226,228}\text{Ra}$ series, fitted (----) by $F = \text{const} \times D^2 \times e^{-D/D_0}$. X shows the ^{224}Ra series, similarly fitted (—).

12

5
12

Fig 2

EARLY DIAL PAINTING INDUSTRY

Ra-224 & Ra-226 CASES COMPARED