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DOSE-RESPONSE RELATIONSHIPS FOR FEMALE RADIUM DIAL WORKERS: A NEW LOOK

R.E. Rowland
Environmental Research Division, Argonne National Laboratory
Argonne, IL 60439, USA

ABSTRACT

The values of initial systemic intake and of skeletal dose for all of the U.S. radium cases have recently been revised. This revision was required following the demonstrations by Rundo and by Keane that humans who were exposed to radium as adults lost radium at a rate that depended on the quantity of radium originally deposited within their bodies. These new values have been used to define new dose-response relationships for both the bone sarcomas and the carcinomas arising in the paranasal sinuses and mastoid air cells induced by internally deposited radium. The population examined was employed in the U.S. dial painting industry prior to 1950 and consisted of 1530 female dial workers for whom radium body burden measurements were available. By the end of 1990, 46 cases of bone sarcomas and 19 cases of head carcinomas had been diagnosed in this cohort. The head carcinoma incidence can be adequately fitted by a simple linear function, as was found in previous analyses. The bone sarcoma cases were previously fitted by a dose-squared-exponential function. With the revised values of systemic intake, the sarcoma results could not be satisfactorily fitted with this expression. When the exponent on D was increased to larger values, excellent fits were obtained.

Introduction

In previous publications, dose-response relationships for female radium dial workers and other radium populations were derived.[1,2] These publications examined the incidence of the bone sarcomas and head (paranasal sinus and mastoid air cell) carcinomas induced by very high levels of ^{226}Ra and ^{228}Ra deposited in the human skeleton. Both average skeletal dose and the initial systemic intake were used as measures of radiation insult. When these results were published, the retention of radium in the human body was calculated by means of a power function, the Norris retention function.[3] Since then radium body burdens have been determined for more cases, several more malignancies have appeared, and the Norris function has been replaced by a retention function[4] similar to that proposed by the ICRP.[5] These changes have made it necessary to re-examine the shape of the dose-response functions.

Systemic Intake

The systemic intake, the quantity of radium that entered the blood during the period of exposure, is a time-invariant measure of the radium insult derived from a measurement of body content made long after the radium was acquired. The calculated

intake allows cases to be grouped by intake level, as is often done in laboratory animal studies. Systemic intake is the only radiation insult considered in this study.

The radium dial paint first used in the United States contained only ^{226}Ra, but later the two radium isotopes, ^{226}Ra and ^{228}Ra, were mixed to reduce the cost. To express the radium intake as a single number, a ratio of effectiveness for the two isotopes was defined. We showed[1] that, for the induction of bone sarcomas in terms of systemic intake, 1 kBq of ^{228}Ra was about 2.5 times as effective as 1 kBq of ^{226}Ra. Therefore, for the induction of bone sarcomas, the unit of systemic intake is kBq ^{226}Ra + 2.5 × kBq ^{228}Ra. In the case of the head carcinomas, which are thought to be induced by the daughter products of ^{222}Rn, only the ^{226}Ra content of the body is considered relevant, so the systemic intake is expressed in units of kBq ^{226}Ra.

The Retention of Radium in the Human Body

The publications of Rundo et al.[6] and Keane et al.[7] demonstrated that radium retention in adult humans 30-60 y after intake depends on the quantity of radium deposited within the body. This was not an unexpected result, because an effect of dose level was reported by Lloyd et al.[8] in long-term studies of radium in beagles. Dogs with high-level radium injections had higher fractional retentions than those receiving lower doses. Lloyd et al.[8] attributed this effect in the beagle to radiation damage to the bone remodeling processes at high radium concentrations. Such a dose effect was also proposed by Rundo et al.[6] and Keane et al.[7] for the human radium cases.

To determine the initial systemic intake, one must calculate back, by means of an accepted retention equation, from the time when the body burden was measured to the time when radium was acquired. Stehney et al.[9] found that the average radium subject was measured about 40 y after first exposure to radium. Thus, apparently slight differences between two different radium retention functions can make large differences in the intake calculated from the measured body content.

Rowland[4] used the data of Rundo et al.[6] and Keane et al.[7] to define a modified retention function for low levels of radium in humans. The retention function proposed in the ICRP 20 document on human metabolism of the alkaline earths[5] in man was the logical starting point. The ICRP 20 document defined a parameter λ as the rate of apposition and resorption in compact bone, gave the value of λ as 2.5% y^{-1}, and stated that λ seemed to be a property of bone itself rather than a property of one of the radioelements in bone. However, in the ICRP 20 retention equation for radium, λ was given the value of 1.5% y^{-1}.

Schlenker et al.[10] subsequently modified certain parameters in the ICRP 20 equation to account better for the distribution of radium between soft tissue and bone. Rowland,[4] working from the modification of Schlenker et al.,[10] set λ at 2.5% y^{-1} and

derived a revised retention function for radium applicable to intake levels that do not result in radiation damage to bone. This function has now been used as the starting point for the recalculation of the intake and skeletal dose values for all of the U.S. radium cases. It should be noted that all of the previously published values of intake and skeletal dose were calculated by means of the power function retention equation proposed by Norris et al.[3]

The Study Population

For this report all female dial workers with body burden measurements who entered the industry before 1950 were examined; a total of 1530 such cases were found. In this cohort, 46 women were found to have had bone sarcomas, and 19 had one of the head carcinomas; 3 of these women experienced both a bone sarcoma and a head carcinoma. The follow-up of these cases terminated at the end of 1990.

A previous analysis of dose response for bone sarcomas in the female radium dial workers[2] made use of the 42 bone sarcomas that had then appeared among the 1468 women first exposed to radium before 1950 for whom body content measurements were available. The previous analysis of head carcinoma induction in the female dial workers[1] was based on 759 women exposed before 1930, who experienced 17 of these malignancies.

The Bone Sarcomas

The 46 bone sarcomas in our cohort of 1530 women had appearance times ranging from 7 to 63 y (mean ± s.d. = 28 ± 14 y). The lowest combined radium intake associated with a bone sarcoma was 3.70 MBq (100 μCi). This malignancy, diagnosed in 1981 in a dial worker who began painting dials in 1918, was thus detected 63 years later. The highest combined intake associated with a bone sarcoma was 234 MBq (6330 μCi), in a dial worker who started painting dials in 1917 and was diagnosed 10 y later.

In Table 1 the dial worker cases are arranged by intake levels in units of kBq ^{226}Ra + 2.5 × kBq ^{228}Ra. As was the case in previously published analyses,[1,2] the intake range covered several orders of magnitude. In the format of previous analyses, each decade of intake was divided into three groups defined by the numbers 1-2.5, 2.5-5, and 5-10. Previous analyses used μCi as the unit of intake, but here kBq are used. The intake level for the cases in each group is expressed as a weighted mean as follows:

$$\text{weighted mean} = \frac{\sum D_i y_i}{\sum y_i} \qquad (1)$$

Here D_i and y_i are the systemic intake and years at risk, respectively, for each individual in the intake group. Also included in Table 1 are the number of cases, the

number of person-years at risk, and the number of bone sarcomas for each group. Person-years at risk are calculated from the date of original employment to the date of death, diagnosis of a bone sarcoma, or end of follow-up, less an assumed 5-y development period from tumor induction to earliest possible diagnosis.[1]

Table 1. Case distribution, person-years of risk, and bone sarcoma experience by systemic intake level.

Systemic Intake			Number of		
Range (kBq)	Range (μCi)	Weighted Average (kBq)	Cases	Person-Years at Risk	Bone Sarcomas
≥ 50000	≥ 1351	73310	21	235	6
25000 - 49999	675.7 - 1350	37850	21	411	16
10000 - 24999	270.3 - 675.6	15100	51	2005	22
5000. - 9999.	135.1 - 270.2	7651	45	2237	1
2500. - 4999.	67.57 - 135.0	3498	53	3133	1
1000. - 2499.	27.03 - 67.56	1637	76	4166	0
500.0 - 999.9	13.51 - 27.02	702.2	76	4200	0
250.0 - 499.9	6.757 - 13.50	364.9	93	4861	0
100.0 - 249.9	2.703 - 6.756	153.3	168	8574	0
50.00 - 99.99	1.351 - 2.702	71.69	139	6459	0
25.00 - 49.99	0.676 - 1.350	36.40	167	7505	0
10.00 - 24.99	0.270 - 0.675	17.18	153	6589	0
<10.00	<0.270		467	21826	0
			1530	72101	46

The Head Carcinomas

The 19 head carcinomas in the measured female dial workers (Table 2) had appearance times of 19 to 59 y (mean ± s.d. = 41 ± 10 y). The lowest ^{226}Ra intake associated with a head carcinoma in this cohort was 2.9 MBq (78 μCi). This malignancy occurred in a woman who started painting dials in 1922 and was diagnosed 51 y later. The highest intake associated with a head carcinoma was 36.6 MBq (998 μCi), in a woman who started painting dials in 1918 and was diagnosed 39 y later.

Table 2. Case distribution, person-years of risk, and head carcinoma experience by systemic intake level.

Systemic Intake			Number of		
Range (kBq)	Range (μCi)	Weighted Average (kBq)	Cases	Person-Years at Risk	Head Carcinomas
≥ 25000	≥ 675.7	35110	14	166	3
10000 - 24999	270.3 - 675.6	11790	29	813	6
5000. - 9999.	135.1 - 270.2	7523	45	1625	6
2500. - 4999.	67.57 - 135.0	3648	47	1966	4
1000. - 2499.	27.03 - 67.56	1564	65	2887	0
500.0 - 999.9	13.51 - 27.02	731.9	62	3172	0
250.0 - 499.9	6.757 - 13.50	362.1	76	3601	0
100.0 - 249.9	2.703 - 6.756	154.2	210	9847	0
50.00 - 99.99	1.351 - 2.702	72.35	165	7096	0
25.00 - 49.99	0.676 - 1.350	36.68	188	7711	0
10.00 - 24.99	0.270 - 0.675	17.41	159	6192	0
<10.00	<0.270		470	19508	0
			1530	64584	19

In Table 2 the dial worker cases are arranged by ^{226}Ra intake levels in kBq. The same numerical intake level ranges are used as in the bone sarcoma analysis. All other quantities are the same as in Table 1 except for person-years at risk. Here a 10-y development time is assumed to be required between induction of the head carcinoma and the earliest possible diagnosis.[1]

Dose-Response Relationships

Various logical forms of a general dose-incidence expression,

$$I = (\alpha D + \beta D^2)e^{-\gamma D}, \qquad (2)$$

including the complete expression and simplifications obtained by leaving out the term containing the D, or the D^2, or the $e^{-\gamma D}$, were fitted to the data and subsequently tested by a χ^2 statistic. Here the incidence, I, is in malignancies per person-year, and α, β, and γ are constants to be found by the fitting procedure. Each equation was fitted to all data points with D greater than 10 kBq (12 points for the sarcoma data, 11 points for the carcinoma data). For the χ^2 analysis, the lower intake levels, where no malignancies were observed, were combined into a single intake group by summing the expected numbers calculated for the individual levels. When necessary, groups were further combined so that no group contained an expected number of less than three malignancies.[11] The weighted squares of the differences between the observed and the expected numbers of malignancies were calculated after the groups had been combined. The number of degrees of freedom was equal to the number of groups after combining, less the number of fitted parameters. The fitting procedure was applied to all the data points, and the goodness of fit was evaluated after the groups were combined.

The Sarcomas

No acceptable fits to the sarcoma data were found for any logical form obtained from the general equation by the above procedure. To be acceptable the coefficients α, β, and γ would have to be positive, and the χ^2 analysis would have to result in a p value equal to or greater than 0.05.

Examination of the data suggested that the data might be fitted by a function that rose more rapidly than the square of the intake. To test this idea, the function

$$I = \beta D^{\delta} e^{-\gamma D} \qquad (3)$$

was fitted to the data. Here β, γ, and the exponent, δ, were to be obtained from the fitting routine. In this case a satisfactory fit ($p = 0.13$) was found with the exponent equal to 3.15; the fitted function is

$$I = 2.132 \times 10^{-15} \times D^{3.15} \times e^{-7.055 \times 10^{-5} \times D}. \quad (4)$$

When the exponent, δ, was preselected, any value for the exponent between 2.7 and 4.1 was found to provide an acceptable fit to the sarcoma data set.

The general equation above, Eq. 2, and all its simplifications are based on the assumption that the fitted function goes through the origin; that is, when the intake is zero, the incidence is zero. When this restriction was lifted, so that the function to be fitted was

$$I = \text{Constant} + (\alpha D + \beta D^2)e^{-\gamma D}, \quad (5)$$

and the same simplifications were tried, no acceptable fits to the sarcoma data were found. However, when the exponent on D was changed from 2 to the value found above, 3.15, an acceptable fit was obtained. The fit was

$$I = -1.443 \times 10^{-4} + 2.142 \times 10^{-15} \times D^{3.15} \times e^{-7.056 \times 10^{-5} \times D}. \quad (6)$$

Setting the incidence, I, equal to zero and solving for D gives an intercept value of 2739 kBq (74 μCi). This fit to the data is shown in Fig. 1. On the scale shown in Fig. 1, little difference can be seen between Eqs. 4 and 6.

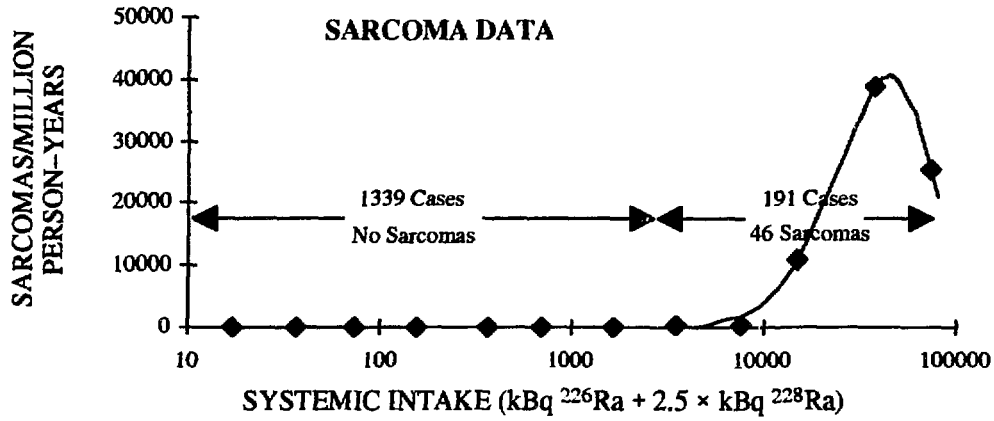

Figure 1. The dose-response function for bone sarcomas shown in Eq. 6 is plotted in units of bone sarcomas per million person-years versus combined systemic intake in kBq. The solid diamonds are the observed data points for the 12 intake groups from Table 1.

The Carcinomas

Various logical forms of the general dose-incidence expression, Eq. 2, were also fitted to the carcinoma data and tested by a χ^2 statistic. In contrast to the findings for the bone sarcoma data, several forms of this basic equation were fitted to the head carcinoma

data; these fits are listed in Table 3. The linear, linear-exponential, and dose-squared-exponential functions provided acceptable fits. The linear and the dose-squared-exponential fits are shown in Fig. 2.

Table 3. Acceptable fits to the carcinoma data.

Function	Coefficients	p value	Intercept
	Forced through the origin; when D = 0, then I = 0.		
$I = \alpha D$	$\alpha = 5.24 \times 10^{-7}$	0.22	0
$I = \alpha D e^{-\gamma D}$	$\alpha = 5.89 \times 10^{-7}$ $\gamma = 3.72 \times 10^{-6}$	0.10	0
$I = \beta D^2 e^{-\gamma D}$	$\beta = 1.03 \times 10^{-10}$ $\gamma = 5.57 \times 10^{-5}$	0.88	0
	Fitted with a constant to determine an intercept.		
I = Constant + αD	Const. = -9.22×10^{-5} $\alpha = 5.28 \times 10^{-7}$	0.55	175 kBq (4.7 μCi)
I = Constant + $\alpha D e^{-\gamma D}$	Const. = -2.68×10^{-4} $\alpha = 6.36 \times 10^{-7}$ $\gamma = 5.51 \times 10^{-6}$	0.24	422 kBq (11 μCi)

The fits in Fig. 2 are both forced through the origin; that is, the equations define the incidence as zero at zero intake. If this condition is removed and Eq. 5 is used as the function to be fitted, somewhat different results are obtained. These results are also listed in Table 3. Only the linear and the linear-exponential functions provided acceptable fits, suggesting the existence of a threshold. The apparent threshold values of 175 kBq (4.7 μCi) for the linear fit and 422 kBq (11 μCi) for the linear-exponential fit are quite small and statistically not significant.

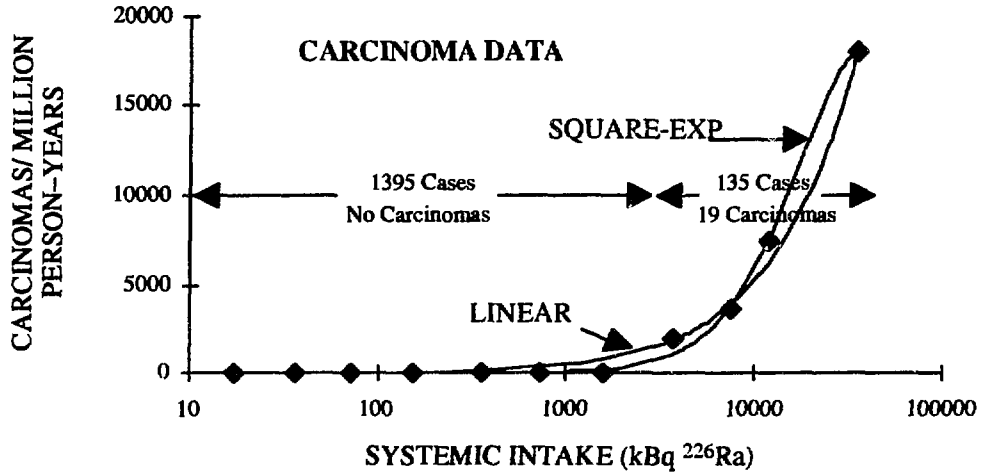

Figure 2. Two dose-response functions for head carcinomas from Table 3, the linear and the dose-squared-exponential function, are plotted in units of head carcinomas per million person-years versus systemic intake in kBq. The solid diamonds are the observed data points for the 11 intake groups from Table 2.

The 19 head carcinomas observed in this cohort are insufficient to allow us to differentiate between the various proposed response functions. In such a situation, it is probably best to accept the simplest result, the linear non–threshold function, in spite of the fact that a more complex function, the dose-squared-exponential function, appears to give a better fit to the data.

Discussion

The revised systemic intake values have altered the shapes of the dose-response functions from those found in earlier studies. The most evident change is in the fits to the bone sarcoma data. Past studies[1,2] showed that the sarcoma data could be fitted by a non-threshold function based on the square of the systemic intake, but not by a linear non-threshold function. The recalculated systemic intake values cannot be fitted by a dose-squared function, but they demonstrate a steep dose-response behavior that can be fitted with a larger value for the exponent. A mechanistic justification for such a form of a dose-response function remains to be found.

As a consequence of the threshold-like appearance of the dose-response functions for the bone sarcomas, very few of these malignancies are predicted at low intake levels. The head carcinomas, which do not demonstrate such a rapid drop with dose, are predicted to be more abundant than the bone sarcomas at low intake levels. This is in contrast to the observed frequency of the two malignancies at high intake levels; more than twice as many bone sarcomas (46) as head carcinomas (19) were observed in this cohort. This same pattern was observed for the entire population of cases with measured radium body burdens studied in the United States, for which the distribution is 64 sarcomas to 32 carcinomas among 2383 individuals exposed to radium from various sources. The dose-response functions derived here should be applied only over the range of intake values within which the malignancies were observed.

Conclusions

The recalculation of the intake levels for the measured radium cases has changed the distribution of radium-induced malignancies. The overall effect has been to raise the intake levels for the cases with lower intakes and to reduce them for the cases with higher intakes. This effect, while it is noticeable for the head carcinomas, does not result in significant changes to the previously published dose-response functions. The effect is more significant for the bone sarcomas and has resulted in a very steep dose-response relationship. Whether this result is actually a demonstration of a threshold or simply an indication of a very low probability of sarcoma induction below 2700 kBq remains to be seen.

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