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STUDIES OF RADIUM-EXPOSED HUMANS II:

FURTHER REFUTATION OF THE R. D. EVANS' CLAIM THAT "THE LINEAR, NON-THRESHOLD MODEL OF HUMAN RADIATION CARCINOGENESIS IS INCORRECT"

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INTRODUCTION

We have recently refuted Evans' claim that the "linear, non-threshold model of human radiation carcinogenesis is incorrect". Our refutation was based upon an analysis using residual radium burden in the Evans and Hasterlik series of cases.(1)(2)(3)

Recently Evans has published a paper indicating that he prefers analysis to rest upon cumulative rads or cumulative rad-years to the skeleton instead of upon residual radium burden(4). We like and accept Dr. Evans' suggestion that cumulative rad-dose represents a better basis for analysis than does residual radium burden. Therefore, this report is an analysis of all the Evans' observations on radium-exposed persons based upon cumulative rads of exposure.

As the analysis presented below will justify, we state the following:

1. We reject the Evans' claims even more strongly than before.

2. The linear, non-threshold model of human radiation carcinogenesis from 0 cumulative rads through 50,000 cumulative rads is in excellent accord with the observations.

3. The linear, non-threshold model proves acceptable even for doses 10,000 times those relevant for setting FRC Guidelines.

PRELIMINARY DISCUSSION

Why This Report is Required

The sophisticated worker in this field of human radiobiology may wonder why we should address ourselves at all to the analysis of the data concerning the radium-exposed humans. This does require an answer here.

Such important and highly competent bodies as the International Commission on Radiological Protection have, for years, rejected the Evans' claims of "safe thresholds" and"non-linearity" as being unsupportable by the evidence he has presented. Further, in the important JCAE Hearings "Radiation Exposure of the Uranium Miners", several eminent workers in this field rejected Evans' claims most effectively, including Morgan[10], Snyder[11], Archer[12], and Parker[13]. It seemed hardly credible that after such effective refutation, the matter might still come up again for necessary refutation. But it has.

After the convincing serial refutations of Evans referenced above, Evans has recently produced a paper[4] which indicates that if a more appropriate description of dose is used, such as cumulative rads or cumulative rad-years, then the evidence strongly supports his contentions. We have demonstrated here that this is in no way true and that all the Evans' claims are totally indefensible scientifically. When a man who has contributed so effectively and extensively, as has Robley Evans, states that on a new basis of calculation, the story is different, it is imperative that his claims be carefully considered and analyzed. It was possible his new interpretation might be correct. But, by careful analysis, we are now convinced it is erroneous.

There exists, however, an even more compelling reason why the radium-exposed human story must be laid to rest for what it is. Recently we presented evidence indicating that radiation carcinogenesis in humans, in all probability, includes all forms of cancer rather than certain rare cancers or leukemia.

Further, we suggested that each rad contributes a fractional increase in risk of cancer - a fraction of the spontaneous occurrence rate of a particular form of cancer. This, of course, grossly magnifies the extent of the radiation hazard. Our generalizations concerning human carcinogenesis will ultimately stand or fall on scientific merits. As we study the problem in progressively increasing depth, we feel more confident than ever that our generalizations will stand, with only minor revisions at most.

The Division of Biology and Medicine (AEC) has, in our opinion, erroneously interpreted our presentations as an attack upon atomic energy in general and upon the Atomic Energy Commission, in particular. We were surprised beyond belief by this reaction of the Division of Biology and Medicine, for we had fully expected them to welcome our findings as potentially important inputs to a scientific dialogue of the greatest portents for human health of this and future generations. In what we regard as a rather poor effort to discredit the "Gofman-Tamplin findings", the Division of Biology and Medicine has recently "exhumed" the radium story as definitive proof of a "safe practical threshold" of human radiation exposure. We are dismayed to see this occur. We would expect that the ICRP is even more dismayed, but they will surely speak for themselves. Let us quote from two recent documents, widely circulated by DBM-AEC, which herald the "safe threshold" concept. The first comes from Dr. John Storer, a former Associate Director of DBM, who stated the following in a critique he wrote of the Gofman-Tamplin work[14]. We quote Storer directly:

"For example, in the case of induction of bone tumors in the radium dial painters, the conclusion should be inescapable that there is an effective dose below which tumors do not appear".

Dr. Storer, with DBM, stands opposed to the following: Morgan, Snyder, Archer, Parker, the ICRP, Gofman and Tamplin.

The second is in a recent DBM-AEC Staff Report, also widely circulated (including Associated Press dispatches).[15] Quoted directly:

"There is evidence for an effective or practical threshold yet no allowance has been made for levels of radiation below which cancer cannot be causally related".

While it is difficult to make sense out of this statement from the DBM Staff Paper, it is meant, in all likelihood, to refer to Evans' "demonstration" of an effective or practical threshold.

Clearly, the Division of Biology and Medicine of the AEC didn't accept all the prior, effective refutations of the Evans' claims. They are widely circulating these claims as proof of safe radiation thresholds, in an apparent effort to influence the forthcoming Federal Radiation Council Review of Radiation Exposure Standards. DBM-AEC should be encouraged to challenge scientifically any statements we make. But we fear that recourse to a widely discredited hypothesis derived from radium exposures may, unfortunately, have the effect of diminishing the weight given to any substantive arguments that DBM may have forthcoming. We hope this will not be the case.

So, because Evans has recently refurbished his own hypothesis and because DBM has "exhumed" the same hypothesis as being "inescapable", it has become necessary for us to address ourselves again to this important area. That is why this detailed analytical report has been written.

The Linear Hypothesis and the Use of the Radium Studies at all

As we have stated in the text, there are numerous reservations one should have for drawing any conclusions from the studies of radium-exposed persons. Every epidemiologist knows the treacherous pitfalls of using human data where an appreciable fraction of the population under study is lost to analysis. Overt biases can be pin-pointed in such situations; the hidden ones are even more to be feared.(See Archer (12)) The MIT studies of radium-exposed

persons is a classic in the annals of epidemiology of the situation where drastic biases may be present. It represents a great contribution to many aspects of human radiation exposure, but we doubt very much that it ever should have been used at all for epidemiologic purposes. The ICRP shares this view, we believe. Any capable epidemiologist examining the clinical material available would probably reach the same conclusion.

Why then should one even bother to go through the labor of testing the linear hypothesis on such a poor epidemiological sample. Part of the answer lies in the fact that it is available. Fortunately, epidemiological material in this area is only available through the ignorance or unfortunate, often rash, actions of man and society. If some of the crude outlines of dose-response curves can be ascertained through the study of this material, one can assuredly temper conclusions with an ever-present awareness of the epidemiological pitfalls.

Part of the answer lies in the fact that, overtly and covertly, the MIT studies have been used to justify permissible radiation doses as "safe". Even with the epidemiologic pitfalls, it is therefore valuable to be able to demonstrate within the data themselves that certain interpretations made and widely advertised are not correct.

While we have shown here that the linear hypothesis fits the MIT data over a range from 0 to 50,000 rads, we would be wary about over-extending the meaning of our findings. We are dealing with treacherous epidemiologic material. Our analysis of a 25 rad doubling dose being good from 0 through 50,000 rads does not exclude a gently curving dose-response curve. The doubling dose may be even lower than 25 rads in the higher dosage ranges until finally the "overkill" region is reached at extreme doses where the doubling dose increases above 25 rads. People can develop multiple cancers, but they can only die once. Since we are dealing with a fatal disease, bone sarcoma (and a glance at Robley

Evans' plots shows this), we know that linear theory must break down somewhere in the high dose range. When people get to 30-100% incidence rates of fatal bone sarcoma, this disease alone, or this one plus some of the other fatal diseases, preclude(s) further response with still further increase in dose in the very high ranges. Therefore, at extreme dosages, where everyone gets killed, the doubling dose can rise steeply, even approaching infinity. We would hope, fervently, that no one will be so rash as to misinterpret an "infinite" doubling dose at 50,000 to 100,000 rads as evidence for a safe radiation threshold in that dose region.

THE RADIUM DIAL PAINTERS AND IATROGENIC CASES

Evans has divided his cases into two large subgroups:

(a) The radium dial-painters plus iatrogenic cases

(b) The Chemists exposed to radium.

The circumstances of acquisition of radium burden differ for the two groups, so that Evans' division of the cases into these subgroups is reasonable. We shall analyze both groups of cases starting with group (a) The radium dial painters plus iatrogenic cases.

In Table 3 (Reference 4), Evans presents the various exposure groups below 1200 cumulative rads as groups (a) through (f). In Table 5 (Reference 4) Evans presents the various subjects suitable for epidemiological appraisal as Class 1-5, ranging from cumulative rad values of 1200 through 50,000. We shall, therefore, analyze all these groups (a through f of Table 3 and Class 1-5 of Table 5) since we believe Evans' subdivisions are quite reasonable and appropriate.

Two kinds of cancers have occurred in the radium-exposed persons, bone sarcomas and carcinomas of the (sinuses plus mastoid). We shall address ourselves, appropriately, to each type of cancer separately in detail.

TABLE 1

Age Specific Annual Death Rates for Malignant Neoplasms of Bone*

USA Vital Statistics (1966)(7)

	MALES			FEMALES		
Age Span (years)	Population at risk	Deaths	Death Rate cases/100,000	Population at risk	Deaths	Death Rate cases/100,000
20-24	6,625,000	55	0.83	6,981,000	16	0.23
25-29	5,632,000	24	0.43	5,840,000	10	0.17
30-34	5,326,000	10	0.19	5,527,000	14	0.25
35-39	5,717,000	15	0.26	5,987,000	17	0.28
40-44	6,021,000	24	0.40	6,371,000	18	0.28
45-49	5,633,000	46	0.82	5,978,000	32	0.54
50-54	5,189,000	52	1.00	5,498,000	46	0.84
55-59	4,490,000	93	2.07	4,839,000	63	1.30
60-64	3,757,000	110	2.93	4,174,000	52	1.25
65-69	2,901,000	107	3.69	3,476,000	84	2.42
70-74	2,261,000	98	4.33	2,929,000	92	3.14
75-79	1,564,000	81	5.18	2,124,000	75	3.53
80-84	847,000	66	7.79	1,230,000	53	4.31

*This category is what we shall, in Table 2 and in the text, refer to as bone sarcomas.

TABLE 2

Age Specific Annual Death Rates of Bone Sarcomas in USA

Males, Females, and Average of Males and Females

Age Span (years)	Age Specific Annual Death Rates, in cases/100,000		
	Males	Females	Average $\frac{M+F}{2}$
20-24	0.83	0.23	0.53
25-29	0.43	0.17	0.30
30-34	0.19	0.25	0.22
35-39	0.26	0.28	0.27
40-44	0.40	0.28	0.32
45-49	0.82	0.54	0.68
50-54	1.00	0.84	0.92
55-59	2.07	1.30	1.69
60-64	2.93	1.25	2.09
65-69	3.69	2.42	3.06
70-74	4.33	3.14	3.74
75-79	5.18	3.53	4.36
80-84	7.79	4.31	6.05

We shall explore whether the linear hypothesis, namely a constant doubling dose for radiation-induction of cancer, is consistent with all the Evans' data, or whether his claimed "threshold" is required.

An analysis of this problem requires several inputs:

1. The expected spontaneous incidence of bone sarcoma and of (sinus + mastoid) carcinoma.
2. The expected radiation-induced cancer incidence.

Item 1, the expected spontaneous incidence of bone cancers can be obtained from U.S. Vital Statistics data.

Item 2, the radiation-induced cancer can be estimated as follows:

(1) We shall use the linear hypothesis that the risk of cancer (per rad) is the same for very low doses all the way up to 50,000 cumulative rads[5]. Since this covers a range up to 10,000 times as large as is relevant for FRC Guidelines, this will provide a drastic challenge for the linear hypothesis. Evans says the linear hypothesis is incorrect. By our drastic test, we shall give him every benefit in evaluation.

(2) We shall, over this entire range up to 50,000 rads, use 25 cumulative rads as the doubling dose for bone sarcoma or for cancer of the nasal sinuses and mastoid, or a 4% increase in risk of radiation-induction of cancer per rad. In our published "laws" of radiation-carcinogenesis we suggested 1% per rad, but indicated it might well be higher[5][6]. Our reason for using 4% here is partly to credit the widely-held concept that high LET radiation is more damaging than low LET radiation.

Item 1: The Expected Spontaneous Incidence of Bone Sarcoma and of (Sinus + Mastoid) Carcinoma

Two forms of cancer are at issue here. The first is bone sarcoma. The second is carcinoma of the sinuses and mastoid. From U.S. Vital Statistics data the appropriate values for bone sarcoma are available and are presented

in Table 1. It will be noted that the values for males are slightly higher than for females. For the calculations below we shall average the male and female incidence rates, as shown in Table 2. Evans does not present the male and female data separately, and this is why we average them. It is our impression that the radium dial painters had more females than males in the group, so our use of the average tends to favor the Evans' hypothesis. We are, at every step, trying to shade all uncertainties in favor of Evans' hypothesis. In any event, the final results would not differ in any significant detail whether we used the male incidence data, the female incidence data, or the average, which we are using.

The incidence data for carcinoma of the nasal sinuses and mastoid are, as Evans states, not well known, except that these cancers are extremely rare spontaneously. Spratt and coworkers have estimated that cancer of the maxillary antrum is probably less than 1 case per 200,000 annually[8]. These cancers are so rare that the U.S. Vital Statistics do not list them separately. A reasonable estimate would be that (sinus + mastoid) cancers are $\frac{1}{2}$ as frequent as bone sarcomas in the population-at-large, considering the data of Spratt and the U.S. Vital Statistics. We shall use this estimate. This estimate is entirely consistent with the estimate by Stewart for England and Wales, prepared for ICRP Publication 11, April 3, 1967.

Item 2: The "Expected" Radiation-Induced Cancers

In the groups of especial interest in this entire analysis (Evans' Class a through f - Table 3, Reference 4), Evans presents the following parameters:

Years Since Exposure (average) = 47 years (Figure 5, Reference 4)

Average Age in 1967 = 73 years (Figure 5, Reference 4)

Thus, by subtraction, 73-47, we deduce the average age where exposure to radium begins is 26 years.

Further, Evans presents in Table 2 (Reference 4) the following estimates of how much of the cumulative rad exposure was to be expected in the first 10 years of exposure and in the first 40 years of exposure. These data are reproduced here (from Table 2, Reference 4).

"Typical Dosage Parameters for 1μCi ^{226}Ra residual, 40 years after a brief acquisition" (Evans)

	Male (7 Kg)	Female (5 Kg)
Cumulative rads in first 10 years	970 rads	1360 rads
Cumulative rads in first 40 years	2300 rads	3220 rads

Inspection of these data shows that most of the cumulative rad dose was acquired after 10 years. Here we shall make a drastic move to give the Evans' "threshold" hypothesis a large advantage. We shall assume that all the cumulative rads were acquired instantaneously. In this way we will overestimate the number of cancers expected in the years after exposure. Since the Evans' hypothesis, either of "practical or absolute" thresholds of "safe" radiation dose, rests upon a supposed discrepancy between "expected" and "observed" cancers, it should be clear that everything we do to increase the "expected" cancers will favor the Evans' hypothesis. As will become evident from the analysis below, even this extreme gesture leaves the Evans' concept unsupportable.

From the Evans' data it appears, as Evans states, that the latency period before cancer occurs is longer the lower the cumulative rads delivered. Inspection of Evans' Figure 5 (Reference 4) indicates that for low cumulative rad values latencies in excess of 20 years may occur. We agree that it is reasonable to assume longer latency period at the lower dosages. Therefore, we shall use the following expected latency periods.

Dose Range	Average Latency Period
0-100 rads	25 years
100-1200 rads	20 years
1200-2500 rads	15 years
>2500 rads	10 years

One could manipulate such latencies a few years either way, and be perfectly consistent with observational material. The only real issue is to show the longer latency period at low doses.

Now, we can proceed with the analysis, based upon cumulative rads, for all the Evans' groups, a through f, and Class 1 through 5 of Table 5 (Reference 4). We shall start with the bone sarcomas, and, after completion of this analysis, go on to the (sinus + mastoid) carcinomas.

Bone Sarcoma: Expected Spontaneous Cancers

Utilizing the data of Table 2, we shall first estimate the spontaneous expected bone sarcomas for persons between 26 years of age and 73 years of age. These will be expressed as cases expected spontaneously per 100,000 persons. Later, to estimate total expected sarcomas we shall add the calculated radiation-induced cases.

TABLE 3

Expected Spontaneous Bone Sarcomas from 26 through 73 years of age

(Number of Cases per 100,000 persons)

Age Span (in years)	Annual Incidence (from Table 2)	No. of years in Age Span	Total Incidence for Age Span
26-29	0.30	4	1.20
30-34	0.22	5	1.10
35-39	0.27	5	1.35
40-44	0.32	5	1.60
45-49	0.68	5	3.40
50-54	0.92	5	4.60
55-59	1.69	5	8.45
60-64	2.09	5	10.45
65-69	3.06	5	15.30
70-73	3.74	4	14.96
Sum for Age Span 26-73 years			62.41

Thus, over the entire 47-year span of time, we can expect, from spontaneous occurrence, the development of 62.4 sarcomas of bone per 100,000 persons at risk.

"Expected" Radiation-Induced Sarcomas of Bone

As stated above, we shall use strict linear theory, with 25 rads as the doubling dose for α radiation-induced sarcoma of bone, or a 4% increase in risk per rad. The latency periods will be those tabulated above. We shall demonstrate in detail the calculated expectancy of radiation-induced cancers for each dosage group.

The 0-100 Cumulative Rad Dosage Group

For this group we have assumed an average latency period of 25 years. Therefore, for such a group, starting at 26 years of age, the bone sarcomas would start appearing at age 51 years and keep appearing each year thereafter, with 25 rads as doubling dose, to 73 years of age (where the study group was as of 1967). Therefore, to estimate the radiation-induced contribution, we must first know the spontaneous rate of bone sarcoma occurrence between 51 and 73 years of age. Then we know, from the definition of doubling dose that 25 rads produces a number of sarcomas of bone equal to this spontaneous rate. For doses above or below 25 rads, we calculate how many doubling doses there are, and then estimate the radiation-induced contribution directly. All of this will be illustrated in detail in the calculations below. The calculated spontaneous expected sarcomas are as follows for the age span 51 years through 73 years (Table 4).

TABLE 4

Expected Spontaneous Cases (For the period beyond latency)

(Latency: 25 years, 0-100 rad-dose group)

(Incidence expressed in cases/100,000 persons)

Age Span (years)	Annual Incidence (from Table 2)	No. of years in Age Span	Total Incidence for Age Span
51-54	0.92	4	3.68
55-59	1.69	5	8.45
60-64	2.09	5	10.45
65-69	3.06	5	15.30
70-73	3.74	4	14.96
Sum for 51-73 years			52.84

So we have 52.84 sarcomas of bone as the spontaneous occurrence in 100,000 persons over the age span 51-73 years. If 25 rads is the doubling dose, this means, for such a group, every 25 rads adds 52.84 sarcomas of bone per 100,000 persons in this overall age span.

We now proceed serially through all the other dosage groups, with their respective latency periods.

The 100-1200 Cumulative Rad Groups

For this group we have used a latency period of 20 years. Therefore, for such a group, starting at 26 years of age, the bone sarcomas would start appearing at age 46 years, and keep appearing each year thereafter, with 25 rads as the doubling dose, to 73 years of age (where the study group was in 1967). The spontaneous rate of bone sarcoma is needed here too.

TABLE 5

Expected Spontaneous Cases (For the Period beyond latency)

(Latency: 20 years, 100-1200 rad-dose group)

(Incidence expressed in cases/100,000 persons)

Age Span (years)	Annual Incidence (from Table 2)	No.of years in Age Span	Total Incidence for Age Span
46-49	0.68	4	2.72
50-54	0.92	5	4.60
55-59	1.69	5	8.45
60-64	2.09	5	10.45
65-69	3.06	5	15.30
70-73	3.74	4	14.96
Sum for 46-73 years			56.48

So we have 56.48 sarcomas of bone as the spontaneous occurrence per 100,000 persons over the entire age span 46-73 years.

The 1200-2500 Cumulative Rad Group

For this group we have used a latency period of 15 years. Therefore, for such a group, starting at 26 years of age, the bone sarcomas would start appearing at age 41 years, and keep appearing each year thereafter, with 25 rads as the doubling dose, to 73 years (where the study group was in 1967). The expected spontaneous bone sarcoma incidence for 41-73 years is in Table 6.

TABLE 6

Expected Spontaneous Cases (For the Period beyond latency)

(Latency: 15 years, 1200-2500 rad-dose group)

(Incidence expressed in cases/100,000 persons)

Age Span (years)	Annual Incidence (from Table 2)	No.of years in Age Span	Total Incidence for Age Span
41-44	0.32	4	1.28
45-49	0.68	5	3.40
50-54	0.92	5	4.60
55-59	1.69	5	8.45
60-64	2.09	5	10.45
65-69	3.06	5	15.30
70-73	3.74	4	14.96
Sum for 41-73 years			58.44

So we have 58.44 sarcomas of bone as the expected spontaneous occurrence per 100,000 persons over the age span 41-73 years.

The > 2500 Cumulative Rad Group (2500-50,000 cumulative rads)

For this group we have used a latency period of 10 years. Therefore, for such a group, starting at 26 years of age, the bone sarcomas would start appearing at 36 years of age and keep appearing each year thereafter, with 25 rads as the doubling dose, to 73 years (where the study group was in 1967). The expected spontaneous bone sarcoma incidence for 36-73 years is in Table 7.

TABLE 7

Expected Spontaneous Cases (For the Period beyond latency)

(Latency: 10 years, > 2500 rad-dose group)
(Incidence expressed in cases/100,000 persons)

Age Span (years)	Annual Incidence (from Table 2)	No.of years in Age Span	Total Incidence for Age Span
36-39	0.27	4	1.08
40-44	0.32	5	1.60
45-49	0.68	5	3.40
50-54	0.92	5	4.60
55-59	1.69	5	8.45
60-64	2.09	5	10.45
65-69	3.06	5	15.30
70-73	3.74	4	14.96
Sum for 36-73 years			59.84

So, we have 59.84 sarcomas of bone as the expected spontaneous occurrence per 100,000 persons over the age span 36-73 years.

We can now proceed with the consideration of all the Evans' categories of radium dial painters plus iatrogenic cases.

FORMAL ANALYSIS OF BONE SARCOMA IN THE EVANS' CATEGORIES

Class (a): 170 dial painters plus iatrogenic cases

Dosage range ≥ 1 rad to < 50 rads. Median dose 25 cumulative rads.

Total bone sarcomas expected = Spontaneous + Radiation-Induced.

Spontaneous bone sarcomas (from 26-73 years) from Table 3,

= 62.41 per 100,000 persons.

Therefore, for 170 persons, spontaneous expected = $\frac{62.41}{100,000} \times 170 = 0.106$ cases.

Radiation-Induced Cases. (Use Table 4, Latency period 25 years)

Spontaneous cases, beyond latency, = 52.84/100,000.

For 25 rads as doubling dose radiation-induced would be = 52.84/100,000.

Actual rads for this class = 25 rads. Therefore, 52.84/100,000 = radiation-induced cases.

For 170 persons, radiation-induced cases = $\frac{52.84}{100,000} \times 170 = 0.090$ cases.

Total Bone Sarcomas Expected = spontaneous + radiation-induced

= 0.106 + 0.090 = 0.196 cases

Cancer cannot occur as fractional cases. We can observe 0 cases, 1 case, 2 cases, etc.

For an expectancy of 0.196 cases, there are 80 chances out of 100 of observing 0 cases. This happened, in accord with probabilities.

Conclusion: Excellent consistency with linear theory out to 50 rads.

No evidence of any safe threshold below 50 rads.

No reason to accept any of Evans' claims.

Class (b): 28 radium dial painters plus iatrogenic cases

Dosage range ≥ 50 rads to < 100 rads. Median dose 75 cumulative rads.

Total bone sarcomas expected = Spontaneous + Radiation-Induced.

Spontaneous bone sarcomas (from 26-73 years) from Table 3,

= 62.41 per 100,000 persons.

Therefore, for 28 persons, spontaneous bone sarcomas expected

$$= \frac{62.41}{100,000} \times 28 = 0.017 \text{ cases}$$

Radiation-Induced Cases. (Use Table 4, Latency period 25 years)

Spontaneous cases, beyond latency = 52.84/100,000.

For 25 rads as doubling dose, radiation-induced cases would be 52.84/100,000.

For 75 rads (median dose of this class), radiation-induced

$$= \frac{75}{25} \times 52.84 \text{ per } 100,000 = \frac{158.5}{100,000}$$

For 28 persons, radiation-induced cases $= \frac{(158.5)(28)}{(100,000)} = 0.044$ cases

Total Bone Sarcomas Expected = spontaneous + radiation-induced

= 0.017 + 0.044 = 0.061 cases.

There are 94 chances out of 100 of observing 0 cases. This happened.

Conclusion: Excellent consistency with linear theory out to 100 rads.

No evidence for any safe threshold below 100 rads.

No reason to accept <u>any</u> of Evans' claims.

Class (c): 41 radium dial painters plus iatrogenic cases

Dosage range ≥ 100 rads to < 300 rads. Median dose 200 cumulative rads.

Total bone sarcomas expected = Spontaneous + Radiation-Induced.

Spontaneous bone sarcomas (from 26-73 years) from Table 3,

= 62.41 per 100,000 persons.

Therefore, for 41 persons, spontaneous bone sarcomas expected

$$= \frac{62.41}{100,000} \times 41 = 0.026 \text{ cases.}$$

Radiation-Induced Cases. (Use Table 5, Latency period 20 years)

Spontaneous cases, beyond latency, = 56.48/100,000

For 25 rads as doubling dose, radiation-induced cases would be 56.48/100,000

For 200 rads (median dose of this class), radiation-induced

$$= \frac{200}{25} \times \frac{56.48}{100,000} = 451.8 \text{ per } 100,000 \text{ persons}$$

For 41 persons, radiation-induced cases $= \frac{451.8}{100,000} \times 41 = 0.185$ cases

Total Bone Sarcomas Expected = spontaneous + radiation-induced

$$= 0.026 + 0.185 = 0.211 \text{ cases}$$

There are 79 chances out of 100 of observing 0 cases. This happened.

Conclusion: Excellent consistency with linear theory out to 300 rads.

No evidence for any safe threshold below 300 rads.

No reason to accept <u>any</u> of Evans' claims.

<u>Class (d): 17 radium dial painters plus iatrogenic cases</u>

Dosage range ≥ 300 rads to < 600 rads. Median dose 450 cumulative rads.

Total bone sarcomas expected = Spontaneous + Radiation-Induced.

Spontaneous bone sarcoma (from 26-73 years) From Table 3,

$$= 62.41 \text{ per } 100,000 \text{ persons.}$$

Therefore, for 17 persons, spontaneous bone sarcomas expected

$$= \frac{62.41}{100,000} \times 17 = 0.011 \text{ cases.}$$

Radiation-Induced Cases. (Use Table 5, Latency period 20 years)

Spontaneous cases, beyond latency, = 56.48/100,000

For 25 rads as doubling dose, radiation-induced cases would be 56.48/100,000

For 450 rads (median dose of this class), radiation-induced

$$= \frac{450}{25} \times \frac{56.48}{100,000} = 1016.6 \text{ cases per } 100,000 \text{ persons}$$

For 17 persons, radiation-induced cases $= \frac{1016.6}{100,000} \times 17 = 0.173$ cases.

Total Bone Sarcomas Expected = spontaneous + radiation-induced

= 0.011 + 0.173 = 0.184 cases.

There are 82 chances out of 100 of observing 0 cases. This happened.

Conclusion: Excellent consistency with linear theory out to 600 rads.

No evidence for any safe threshold below 600 rads.

No reason to accept any of Evans' claims.

Class (e): 6 radium dial painters plus iatrogenic cases

Dosage range ≥ 600 rads to < 1000 rads. Median dose 800 cumulative rads.

Total bone sarcomas expected = Spontaneous + Radiation-Induced.

Spontaneous bone sarcomas (from 26-73 years) from Table 3,

= 62.41 per 100,000 persons.

Therefore, for 6 persons, spontaneous bone sarcomas expected

$$= \frac{62.41}{100,000} \times 6 = 0.004 \text{ cases.}$$

Radiation-Induced Cases (Use Table 5, Latency period 20 years)

Spontaneous cases, beyond latency, = 56.48/100,000

For 25 rads as doubling dose, radiation-induced cases would be 56.48/100,000

For 800 rads (median dose of this class), radiation-induced

$$= \frac{800}{25} \times \frac{56.48}{100,000} = 1807.4 \text{ cases per } 100,000 \text{ persons.}$$

For 6 persons, radiation-induced cases $= \frac{1807.4}{100,000} \times 6 = 0.108$ cases

Total Bone Sarcomas Expected = spontaneous + radiation-induced

= 0.004 + 0.108 = 0.112 cases.

There are 89 chances out of 100 of observing 0 cases. This happened.

Conclusion: Excellent consistency with linear theory out to 1000 rads.

No evidence of any safe threshold below 1000 rads.

No reason to accept any of Evans' claims.

Class (f): 5 radium-dial painters plus iatrogenic cases

Dosage Range ≥ 1000 rads to < 1200 rads. Median dose 1100 cumulative rads.

Total bone sarcomas expected = Spontaneous + Radiation-Induced.

Spontaneous bone sarcomas (from 26-73 years) from Table 3,

$$= 62.41 \text{ per } 100{,}000 \text{ persons.}$$

Therefore, for 5 persons, spontaneous bone sarcomas expected

$$= \frac{62.41}{100{,}000} \times 5 = 0.003 \text{ cases}$$

Radiation-Induced Cases. (Use Table 5, Latency period 20 years)

Spontaneous cases, beyond latency, = 56.48 per 100,000 persons

For 25 rads as doubling dose, radiation-induced cases would be 56.48/100,000

For 1100 rads (median dose of this class), radiation-induced

$$= \frac{1100}{25} \times \frac{56.48}{100{,}000} = 2485.1 \text{ cases}/100{,}000$$

For 5 persons, radiation-induced cases $= \frac{2485.1}{100{,}000} \times 5 = 0.124$ cases

Total Bone Sarcomas Expected = spontaneous + radiation-induced

$$= 0.003 + 0.124 = 0.127 \text{ cases}$$

There are 87 chances out of 100 of observing 0 cases. This happened.

Conclusion: Excellent consistency with linear theory out to 1200 rads.

No evidence of any safe threshold below 1200 rads.

No reason to accept <u>any</u> of Evans' claims.

<u>Combined Analysis of All Classes (a) through (f)</u>

There is an easy way to determine whether taking all classes together will in any way help the Evans' hypothesis.

(a) First, we can proceed to calculate the probability of observing 0 cases for all the groups combined. Since each group is independent of the others, the probability of observing 0 cases in <u>all</u> the groups is the simple product of the individual probabilities.

Thus, (a) x (b) x (c) x (d) x (e) x (f)

$$\text{Combined Probability} = \frac{80}{100} \times \frac{94}{100} \times \frac{79}{100} \times \frac{82}{100} \times \frac{89}{100} \times \frac{87}{100}$$

= 38 chances out of 100 of observing 0 cases. This happened.

Obviously, this is well within the realm of chance. Indeed, if anyone draws any comfort out of the fact that 38/100 is below 50/100, he simply doesn't understand statistical probabilities. Even more, it so happens that sitting on the upper edge of the combined (a) through (f) group is a case of bone sarcoma at 1200 cumulative rads. No one even dreams that the assignment of dose is good to 50 rads out of 1200. Thus, had we used 1201 rads as the cutting line instead of 1200 rads, we would have

Combined probability of observing 0 cases = 38/100

probability of observing 1 case $\simeq$ 62/100

One case was observed.

So, we can again state:

Conclusion: Excellent consistency with linear theory from 0-1200 rads.

No evidence for any safe threshold from 0 to 1200 rads.

No reason to accept any of Evans' claims.

The High Dose Region - Test of the Linear Theory

In refuting the purported evidence for a safe "threshold" of radiation all the way out to 1200 rads of cumulative radiation, we have estimated the expected spontaneous + radiation-induced cases based upon linear theory. We shall now add, group by group, the extremely high dose groups where a large number of cancers were observed. We shall thereby have an opportunity to assess the linear theory into the very high dose range.

In Table 5 of Reference 4, Evans presents the data for his Class 1-5 cases, designated as statistically suitable cases with a very high incidence of bone sarcoma plus (sinus + mastoid) carcinoma. We shall accept this group for analysis, even though we have many epidemiological reservations about all of the Evans' cases. (see Discussion above) Provided such reservations are kept in mind, the analysis can proceed. Reproduced here are Evans' data for Class 1-5 subjects. (Table 8)

TABLE 8

No. of Subjects	Dose Range (cumulative rads)	Median Dose	No. of Bone Sarcomas	No. of Sinus + Mastoid Carcinomas
12	1200-2500	1850	4	0
22	2500-5000	3750	3	2
12	5000-10000	7500	2	1
8	10000-20000	15000	1	2
5	20000-50000	35000	0	2
Total 59			10	7

In this part of our analysis, we are concerned only with the bone sarcomas. We shall return to the separate problem of the (mastoid + sinus) carcinomas later.

Class 1: Calculated Contribution of Spontaneous + Radiation-Induced Bone Sarcomas

12 radium dial painters plus iatrogenic cases.

Dosage range ≥ 1200 to < 2500 rads. Median dose 1850 rads.

Total bone sarcomas = Spontaneous + Radiation-Induced.

Spontaneous bone sarcomas (from 26-73 years) from Table 3

= 62.41 per 100,000 persons.

Therefore, for 12 persons, spontaneous bone sarcoma = $\frac{62.41}{100,000} \times 12 = 0.007$ cases.

Radiation-Induced Cases (Use Table 6, Latency period 15 years)

Spontaneous cases, beyond latency, = 58.44 cases per 100,000 persons.

For 25 rads as doubling dose, the radiation-induced cases would be

= 58.44/100,000 persons

For 1850 rads (median dose for this class), radiation-induced is

$$\frac{1850}{25} \times \frac{58.44}{100,000} = 4324.6 \text{ per } 100,000.$$

Therefore, for 12 persons, radiation-induced bone sarcomas

$$= \frac{4324.6}{100,000} \times 12 = 0.52 \text{ cases.}$$

Total bone sarcomas expected = Spontaneous + Radiation-induced

= 0.003 + 0.52 = 0.523 cases

Now we can total up all the expected from 0 rads out to 2500 rads.

Expected Class	a	= 0.196
"	b	= 0.061
"	c	= 0.211
"	d	= 0.184
"	e	= 0.112
"	f	= 0.127
Class	1	= 0.523
Total Expected out to 2500 rads		1.414 Observed 4 cases.

In the statistics of small numbers, this difference is not provably significant, and its spurious nature becomes evident as we bring in the remaining data in the high dose ranges.

Class 2: 22 radium dial painters iatrogenic cases

Dosage range ≥ 2500 to < 5000 rads. Median dose 3750 cumulative rads.

Total bone sarcomas = Spontaneous + Radiation-Induced.

Spontaneous, as above, = 62.41 per 100,000 persons.

Therefore, for 22 persons, spontaneous = $\frac{62.41}{100,000} \times 22$ = 0.014 cases.

Radiation-Induced Cases (Use Table 7, Latency period 10 years)

Spontaneous cases, beyond latency = 59.84/100,000 persons.

For 25 rads as doubling dose, the radiation-induced cases would be

= 59.84/100,000 persons.

Therefore, for 3750 rads (median dose for this class) radiation induced is

$$\frac{3750}{25} \times \frac{59.84}{100,000} = 8976 \text{ per } 100,000.$$

For 22 persons, radiation-induced = $\frac{8976}{100,000} \times 22$ = 1.97 cases.

Total cases = Spontaneous + Radiation-Induced

= 0.014 + 1.97 = 1.984 cases

Now, we can again total all the expected - this time from 0 out to 5000 rads.

Expected, Class a through f + Class 1 = 1.414
Class 2 = 1.984
3.398, or 3.40 cases expected

Observed = 4 + 3 = 7 cases total.

The observed is still slightly higher than predicted, but not significantly so. Of much greater relevance is completion of the analysis to include the remaining cases.

Class 3: 12 radium dial painters iatrogenic cases

Dosage range ≥ 5000 to < 10000 rads. Median dose 7500 cumulative rads.

Total bone sarcomas = Spontaneous + Radiation-Induced.

Spontaneous, as above, = $\frac{62.41}{100,000} \times 12 = 0.007$ cases.

Radiation-Induced Cases (Use Table 7, Latency period 10 years)

Spontaneous cases, beyond latency, = 59.84/100,000 persons

For 25 rads as doubling dose, the radiation-induced cases would be

= 59.84/100,000 persons.

Therefore, for 7500 rads (median dose for this class) radiation-induced is

$$\frac{7500}{25} \times \frac{59.84}{100,000} = 17952 \text{ per } 100,000$$

So, for 12 persons, radiation-induced cases = $\frac{17952}{100,000} \times 12 = 2.15$ cases.

Total cases = Spontaneous + Radiation-Induced

= 0.007 + 2.15 = 2.157 cases

Now, we can total all the expected - this time from 0 rads out to 10,000 rads.

Class a-f + Class 1 + Class 2 = 3.40 cases expected
Class 3 = 2.16 cases expected

All Classes out to 10,000 rads= 5.56 cases expected

All Classes out to 10,000 rads = 4 + 3 + 2 = 9 cases observed.

Again, the difference is not significant, and the values are coming closer together.

Class 4: 8 radium dial painters + iatrogenic cases

Dosage range ≥ 10000 to < 20000 rads. Median dose 15000 cumulative rads.

Total bone sarcomas = Spontaneous + Radiation-Induced.

Spontaneous, as above, = $\frac{62.41}{100,000} \times 8 = 0.005$ cases.

Radiation-Induced Cases (Use Table 7, Latency period 10 years)

Spontaneous cases, beyond latency = 59.84/100,000 persons.

For 25 rads as doubling dose, the radiation-induced would be

= 59.84/100,000 persons.

For 15000 rads (median dose for this class), radiation-induced is

$$\frac{15000}{25} \times \frac{59.84}{100,000} = 35,904 \text{ per } 100,000 \text{ persons}$$

So, for 8 persons, radiation-induced bone sarcomas $= \frac{35,904}{100,000} \times 8 = 2.87$ cases.

Total cases expected = Spontaneous + Radiation-Induced

= 0.005 + 2.87 = 2.88 cases.

Now we can total all the expected - this time from 0 rads out to 20,000 rads.

Class a-f + Class 1 + Class 2 + Class 3 = 5.56
Class 4 = 2.88

All Classes out to 20,000 rads = 8.44 cases expected

All Classes out to 20,000 rads = 4 + 3 + 2 + 1 = 10 cases observed.

These expected and observed values are nearly identical.

Class 5: 5 cases of radium dial painters + iatrogenic cases

Dosage range > 20,000 to < 50,000 rads. Median dose 35,000 cumulative rads.

Total bone sarcomas = Spontaneous + Radiation-Induced.

Spontaneous, as above, $= \frac{62.41}{100,000} \times 5 = 0.003$ cases.

Radiation-Induced Cases (Use Table 7, Latency period 10 years)

Spontaneous cases, beyond latency = 59.84/100,000 persons

For 25 rads as doubling dose, the radiation-induced would be

= 59.84/100,000 persons.

For 35,000 rads (median dose for this class) radiation induced is

$$\frac{35,000}{25} \times \frac{59.84}{100,000} = 83,776 \text{ per } 100,000.$$

So, for 5 persons, radiation-induced cancer $= \frac{83776}{100,000} \times 5 = 4.19$ cases.

Total cases = Spontaneous + Radiation-Induced

= 0.003 + 4.19 = 4.193 cases

Now we are in a position to obtain Grand Totals, including all the High Dose Domain plus the Low Dose Domain.

Expected, Class a-f + Class 1 + Class 2 + Class 3 + Class 4 = 8.43 cases
Class 5 = 4.19 cases

(0 to 50,000 rads) Grand Total, Expected = 12.62 cases

(0 to 50,000 rads) Grand Total, Observed = 10 cases

Realizing the statistical error in this small number of observed cases, this agreement is nothing short of fantastic!

Simple linear theory, using a doubling dose of 25 rads (for α radiation), over a tremendous range, 0-50,000 rads, has accomplished the following:

(a) Demonstrated that no evidence whatever for a safe threshold exists anywhere from 0 to 50,000 rads.

(b) Given excellent agreement in predicting the dose response curve giving agreement with observed bone sarcomas in the high dose domain.

(c) Demonstrated that no reason whatever exists to accept any of Evans' hypothesis.

We are indeed surprised that linear theory can explain the observations over a dose domain 10,000-fold higher than that relevant for setting FRC Guidelines. While this analysis clearly shows Evans cannot possibly demonstrate a threshold, it is possible that a slight curvature in the high part of the dose-effect curve cannot be ruled out. For example, possibly 30 rads might be the doubling dose out to 1000-1500 rads followed by a gentle curvature to 20 rads as doubling dose. We suspect not even the staunch advocates of strict linear theory would consider this much of a concession. We certainly concede this possibility.

At the same time, this analysis demonstrates again the wide usefulness of the doubling dose concept in human radiation carcinogenesis.

FORMAL ANALYSIS OF (SINUS + MASTOID) CARCINOMAS IN THE EVANS' CATEGORIES

We can now proceed to the analysis of the sinus + mastoid carcinomas, studying the radium dial painters plus the iatrogenic cases.

As a best estimate for the spontaneous incidence of (sinus + mastoid) cancers, we shall everywhere use $\frac{1}{2}$ the incidence of bone sarcomas. This was explained above. Since many of the calculations are identical with those for bone sarcoma, all that will be needed is the factor of $\frac{1}{2}$ to correct for spontaneous incidence.

In accordance with our general laws for radiation carcinogenesis in humans, we shall, of course, retain the doubling dose of 25 rads (for α radiation) for (sinus + mastoid) carcinoma induction.

Class (a): The 170 radium dial painters plus iatrogenic cases

Dosage range $\geq$ 1 to $<$ 50 rads. Median dose 25 cumulative rads.

Spontaneous expected (sinus + mastoid) Cancers = $\frac{1}{2}$ Bone Sarcomas Expected

$= \frac{1}{2} \times 0.106 = 0.053$ cases

Radiation-Induced Cases (Table 4, Latency period 25 years)

The estimate for bone sarcomas, radiation-induced was 0.090 case

Therefore, radiation-induced (sinus + mastoid) carcinomas = $\frac{1}{2} \times 0.090 = 0.045$

(Sinus + Mastoid) Total = Spontaneous + Radiation-Induced Carcinomas

$= 0.053 + 0.045 = 0.098$ Expected Cases.

There are 90 chances out of 100 of observing 0 cases. This happened.

Class (b): 28 radium dial painters + iatrogenic cases

Dosage range $\geq$ 50 to $<$ 100 rads. Median dose 75 cumulative rads.

As was noted for class (a), the nature of the calculation is such that the final expected for (sinus + mastoid) cancers = $\frac{1}{2}$ that calculated for bone sarcomas.

So, from previously, Total Expected Bone Sarcomas = 0.061 cases

Therefore, total expected (Sinus + Mastoid) Cancers = $\frac{1}{2} \times 0.061 = 0.030$ cases

There are 97 chances out of 100 of observing 0 cases. This happened.

Class (c): 41 radium dial painters plus iatrogenic cases

Dosage range ≥ 100 to < 300 rads. Median dose 200 cumulative rads.

From previously, total expected bone sarcomas = 0.211 cases.

Therefore, total expected (sinus + mastoid) cancers = $\frac{1}{2}$x0.211 = 0.105 cases.

There are 89 chances out of 100 of observing 0 cases. This happened.

Class (d): 17 radium dial painters plus iatrogenic cases

Dosage range ≥ 300 to < 600 rads. Median dose 450 cumulative rads.

From previously, total expected bone sarcomas = 0.184 cases.

Therefore, total expected (sinus + mastoid) cancers = $\frac{1}{2}$x0.184 = 0.092 cases.

There are 91 chances out of 100 of observing 0 cases. This happened.

Class (e): 6 radium dial painters plus iatrogenic cases

Dosage range ≥ 600 to < 1000 rads. Median dose 800 dumulative rads.

From previously, total expected bone sarcomas = 0.112 cases.

Therefore, total expected (sinus + mastoid) cancers = $\frac{1}{2}$x0.112 = 0.056 cases.

There are 94 chances out of 100 of observing 0 cases. This happened.

Class (f): 5 radium dial painters plus iatrogenic cases

Dosage range ≥ 1000 rads to < 1200 rads. Median dose 1100 cumulative rads.

From previously, total expected bone sarcomas = 0.127 cases.

Therefore, total expected (sinus + mastoid) cancers = $\frac{1}{2}$x0.127 = 0.063 cases.

The findings on each class a through f, for (sinus + mastoid) cancer, are like they were for bone sarcoma, leading to:

Conclusion: Excellent consistency with linear theory out to 1200 rads.

No evidence whatever for a safe threshold out to 1200 rads.

No reason to accept <u>any</u> of Evans' claims.

Combined Analysis for (Sinus + Mastoid) Cancer for Classes (a) through (f)

Proceeding just as we did for bone sarcoma, we can now estimate the combined probability of observing 0 cases in all the classes combined.

Probability = (a) x (b) x (c) x (d) x (e) x (f)

$$= \frac{90}{100} \times \frac{97}{100} \times \frac{89}{100} \times \frac{91}{100} \times \frac{94}{100} \times \frac{94}{100}$$

= 62 chances out of 100 is probability of observing 0 cases.

0 cases were observed.

Conclusion: Excellent consistency with linear theory with combined groups.

No evidence for any safe threshold with combined groups.

No reason whatever to accept any Evans' claims.

The High Dose Region: Tests of Linear Theory Using (Sinus + Mastoid) Cancer

Class 1: 12 radium dial painters + iatrogenic cases

Dosage range ≥ 1200 to < 2500 rads. Median dose 1850 rads.

Total bone sarcomas expected = 0.523 cases.

Therefore, total (sinus + mastoid) cancers = $\frac{1}{2}$x0.523 = 0.261 cases

Now we can total expected (sinus + mastoid) cancers from 0 through 2500 rads:

Class a	= 0.098	cases
b	= 0.030	"
c	= 0.105	"
d	= 0.092	"
e	= 0.056	"
f	= 0.063	"
Class 1	= 0.261	"

Total Expected (sinus + mastoid) 0.705 cases

Observed to 0-2500 rads = 0 cases

The expected and observed are not significantly different this far into the high dose range.

Class 2: 22 radium dial painters + iatrogenic cases

Dosage range ≥ 2500 to < 5000 rads. Mean dose 3750 cumulative rads.

Total bone sarcomas expected = 1.984 cases.

Therefore, total expected (sinus + mastoid) cancers = 0.992 cases.

Now we can again total all the expected - this time out to 5000 rads.

Class a - f + Class 1 + 2 = 1.697 expected cases (sinus + mastoid) cancers

" + " = 0 + 2 = 2 Observed (sinus + mastoid) cancers

These are not provably different - out to 5000 rads.

Class 3: 12 radium dial painters + iatrogenic cases

Dosage range ≥ 5000 to < 10000 rads. 'Median dose - 7500 cumulative rads.

Total expected bone sarcomas = 2.157 cases.

Therefore, total expected (sinus + mastoid) cancers = 1.078 cases.

Now we can total all expected cases - out to 10000 rads.

Class a-f + Class 1 + Class 2 = 1.697 cases
Class 3 = 1.078 cases

All Classes out to 10,000 rads= 2.775 cases expected (sinus+mastoid) cancers

Class a-f + Class 1 + 2 + 3 = 2 + 1 = 3 cases observed.

These are not provably different - out to 10,000 rads.

Class 4: 8 radium dial painters + iatrogenic cases

Dosage range ≥ 10000 to < 20000 rads. Median dose 15000 cumulative rads.

Total bone sarcomas expected = 2.88 cases

Therefore, total expected (sinus + mastoid) cancers = 1.44 cases

Now we can total all expected cases - out to 20000 rads.

Class a-f + Class 1 + 2 + 3 = 2.775 cases
Class 4 = 1.44 cases

Class a-f + Class 1-4 = 4.215 expected cases (sinus+mastoid) cancers

Class a-f + Class 1-4 = 3 + 2 = 5 observed cases.

These are not provably different - out to 20000 rads.

Class 5: 5 cases of radium dial painters + iatrogenic cases

Dosage range > 20000 to < 50000 rads. Median dose 35000 cumulative rads.

Total expected bone sarcomas = 4.19 cases

Therefore, expected (sinus + mastoid) cancers = 2.09 cases.

Now, we are in a position to obtain Grand Totals, including all the High Dose Domain.

Expected (Sinus+Mastoid) Cancers, Class a-f + Class 1-4 = 4.215 cases
Class 5 = 2.09 cases

Grand Total, expected (sinus+mastoid) cancers = 6.305 cases

Grand Total, observed = 7 cases.

We can regard this as fabulously good agreement.

Thus, just as for the bone sarcomas, complete analysis of the (sinus + mastoid) cancer data shows:

(a) Complete consistency with linear theory from 0-50000 rads in predicting total number of cases.

(b) Excellent consistency in the lower dose domain (below 1200 rads) and demonstrating that there is no evidence supporting a threshold.

(c) Linear theory accords with data, using a single value for doubling dose, 25 rads, from 0 cumulative rads to 50,000 cumulative rads.

THE THOROTRAST CASES OF MARINELLI

Evans draws comfort from the observations of Marinelli on some 2000 persons who have carried Thorotrast deposits for 20-25 years[9]. He estimates their burdens of skeletal α-emitters to correspond to cumulative rad values between 30 and 80 rads. Let us quote Evans directly:

"These burdens would correspond to a cumulative rad value of about 30-80 rads, and on the linear non-threshold hypothesis illustrated by curve 3 in Figure 10 (Reference 4), should be responsible for some 15 to 40 cases of sarcoma compared with the observed value of 1 or possible 2."

We shall accept Dr. Evans' calculation of cumulative rad burdens. However, we haven't the vaguest notion why he picked a "strawman" curve such as his curve 3, Figure 10 (Reference 4). That linear curve is much too steep. We certainly agree with Evans that his curve 3 gives too high a value.

Let us go through the Thorotrast data with our simple linear theory using the 25 rad doubling dose, which has proved to agree so beautifully with Evans' data. As a first approximation, we shall assume all the ages, etc. were as in the Evans" series, although a refined treatment can readily be performed.

For most of our data, a rounded spontaneous value, beyond latency, is $\sim$ 55 bone sarcomas per 100,000 persons.

For 25 rads doubling dose, this means 55 bone sarcomas per 100,000. Let us use Evans' calculated rad limits 30-80 rads.

For 30 rads, radiation-induced sarcomas = $\frac{30}{25}$ x 55/100,000 = 66/100,000

For 2000 persons, expected radiation-induced sarcomas = $\frac{66}{100000}$ x2000 = 1.32 cases.

For 80 rads, radiation-induced would be $\frac{80}{30}$ x 1.32 = 3.5 cases.

Now, the total follow-up period in the Thorotrast series is less than the radium series, so we know that the estimates above are too high. So we calculate, as a first approximation:

For 30 rads < 1.32 bone sarcomas expected

For 80 rads < 3.5 bone sarcomas expected.

This is clearly in accord with Evans' statement that 1 or possibly 2 cases were observed. Our linear model is in no disagreement whatever with the Thorotrast data.

THE CHEMISTS EXPOSED TO RADIUM

The radium dial painters and iatrogenic cases we have analyzed above. Evans presents an additional 139 cases labelled "Chemists and Miscellaneous" who received exposures in the domain 0-1200 cumulative rads. The cumulative rad dosages, reproduced from Table 3, Reference 4, are as follows:

"Chemists and Miscellaneous"
All doses in cumulative rads

Class	No. of persons	Dosage Range	Median Dose
a	106	≥1 to <50	25
b	6	≥50 to <100	75
c	20	≥100 to <300	200
d	0	≥300 to <600	450
e	7	≥600 to <1000	800
f	0	≥1000 to 1200	1100
Total	139		

No cancers were observed in any of these cases. Let us now ascertain whether this suggests any threshold or non-linear response.

We shall assume,

(a) Linear response over entire domain.

(b) 25 rads as the doubling dose for bone sarcoma, as before.

As Evans points out, the chemists were older, on the average, when they were exposed and, further, they received their dose over an extended period of time.

Thus, to be rigorous, we should credit this group with a longer effective latent period than the dial painters and, hence, a shorter average period to be developing bone sarcoma. If, therefore, we lean over backwards to favor the Evans' hypothesis, we can assume that all the cumulative rads were acquired instantaneously, and that the same number of years were available for sarcoma development as in the dial painters plus iatrogenic cases. These approximations tend to raise the expected cancers and, hence, favor Evans in a domain where 0 cancers were observed.

Let us now calculate the expected numbers of cancers for this group of 139 total cases.

Spontaneous Bone Sarcomas Expected

Spontaneous bone sarcomas = 62.41/100,000

So for 139 cases, spontaneous bone sarcomas = $\frac{62.41}{100000} \times 139 = 0.087$ cases

Radiation-Induced Bone Sarcomas

Average dose, in cumulative rads, for entire group

$$= \frac{(106)(25) + (6)(75) + (20)(200) + (7)(800)}{139}$$

$$= \frac{2650 + 450 + 4000 + 5600}{139} = 91.4 \text{ cumulative rads.}$$

Use the data of Table 4 (which is for 0-100 cumulative rads)

52.84 cases per 100,000 is the spontaneous bone sarcoma occurrence, beyond the latency.

For 25 rads as doubling dose, then 25 rads will produce 52.84 radiation-induced cases per 100,000 persons.

For 91.4 cumulative rads,

Radiation-induced bone sarcomas is $\frac{91.4}{25}$ x 52.84/100,000 = 193.2 per 100,000

Therefore, for 139 persons, radiation-induced bone sarcomas

$$= \frac{193.2}{100000} \times 139 = 0.269 \text{ cases.}$$

Total Expected = Spontaneous + Radiation-Induced

$$= 0.087 + 0.269 = 0.346 \text{ cases.}$$

There are 65 chances out of 100 of observing 0 cases. This happened.

Note: Had we treated this group more rigorously, instead of favoring Evans' hypothesis on several points, the calculated chance of observing 0 cases would have been between 80-90 out of 100. But, 65 out of 100 is good enough to say:

(a) Excellent consistency with the linear theory of radiation-carcinogenesis in man.

(b) No evidence whatever for any safe threshold out to 1200 rads.

(c) No reason whatever to accept <u>any</u> of Evans' claims.

This exhausts the various radium-exposed persons to be analyzed.

<u>CUMULATIVE RADS AND CUMULATIVE RAD-YEARS</u>

Evans bases his analyses upon cumulative rads, but suggests cumulative rad-years is even better. It certainly should be! Thus, if we had a series of persons who have received 2000 cumulative rads to the skeleton and we look at them one year later (long before the latency period is over), we would find essentially no cancers. This is no surprise.

<u>Our</u> analysis takes both cumulative rads <u>and</u> cumulative rad-years into account, for it <u>credits</u> the cumulative rads with a risk of cancer induction for <u>each year of life beyond the latency period.</u>

CONCLUSION

In his paper (Reference 4), Evans admonishes the adherents of the linear, non-threshold hypothesis as follows: (Direct quote)

"Those compilers who publish risk-estimates based upon a linear non-threshold model and their reading of the MIT and ANL-ACRH Ra and MsTh data are perhaps unaware of the mathematical odds against their proposed numbers."

We shall accept the appellation of being two such "compilers" and, further, shall compliment Dr. Evans sincerely for the massive and excellent data he has provided.

And we say to Dr. Evans,

"No, Dr. Evans, the mathematical odds are not at all against us. At every step in the analysis we find the mathematical odds completely consistent with our predictions versus observation. We suggest, furthermore, that if you, Dr. Evans, try a realistic linear model such as ours, you'll be most pleased with the agreement with the data -- out to 50,000 rads".

Lastly, we must quote from our previous report where we demonstrated, using Residual Ra Burden, the lack of validity of Evans' insistence that "the linear non-threshold model is incorrect".

"If it is true that NCRP, ICRP and AEC, as Evans suggests, used these studies to decide permissible burdens of radium, plutonium, and strontium-90, they would be well advised to cease and desist from any such further use".(1)

This statement is even more relevant now that we have analyzed Evans' recent claims.

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