RADIATION INDUCTION OF BREAST CANCER IN THE RAT

(A Validation of the Linear Hypothesis
of Radiation Carcinogenesis over the Range 0-600 rads)

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INTRODUCTION

The AEC Staff Document criticized our work on radiation carcinogenesis as having ignored a large body of experimental animal data -- data they infer might have altered our estimate of 16,000 additional cancer deaths from U.S. population exposure at FRC Guidelines.(1)(2)

We, of course, always have considered, and always shall consider relevant experimental animal studies, for they do indeed provide valuable clues that may be important for radiation exposure of man.

However, our estimates were made utilizing human data, since humans are the relevant subjects of our concern. The three issues of importance, where animal data might help, are:

(a) The issue of a "safe threshold" of radiation.

(b) Linear versus non-linear dose response relationship.

(c) The issue of acute versus protracted radiation.

Actually (a) and (b) are parts of the same problem, namely, dose response relationships. In a separate report of this series we have dealt with the acute versus protracted dose delivery, and demonstrated that supposed protection through protraction of radiation, based upon excellent experimental animal data, is illusory. Those experiments are much better interpreted as simply that radiation, in protracted experiments, is delivered later in life, when the value of each rad for carcinogenesis is less.(3) Thus, any hope for "repair" of carcinogenic damage from such studies, we believe, is quite ephemeral.

The issue of dose-response relationships is one where we have already examined considerable human data. Those data certainly present no scientific evidence suggesting any safe radiation threshold.(4)(5)(6) Indeed, both the Uranium Miner data and the breast cancer data in humans suggest, if anything, that the effect per rad of radiation is even worse at low doses than at high doses. Hempelmann, in a recent evaluation of radiation-induced thyroid adenomas, indicates linearity in the dose-response curve down to 20 rads total dose, with no suggestion whatever of any safe threshold.(7) And very recently Stewart has published evidence that there is a dose-response relationship for radiation-carcinogenesis in-utero based upon the number of films taken during obstetric radiography(8). This would be in the neighborhood of 0 to 10 rads.

Overall, there is no evidence on humans that even remotely argues for any safe threshold with respect to radiation carcinogenesis. AEC Staff suggests that one should study experimental animal data concerning this issue. We agree, and indeed we have been preparing an extensive report on this very subject, including induction of cancer in various tissues. However, because of the timeliness, we shall present the first section of that report here, based upon the elegant studies of mammary cancer induction by radiation in rats by Bond and his collaborators at the Brookhaven National Laboratory. This study represents an exhaustive important series of researches. The major conclusion reached by Bond and co-workers is that the data show perfect linearity in mammary cancer induction by radiation with x-rays all the way down to 25 rads, and that there is indication of linearity, by this small extrapolation, all the way to 0 rads.(9)

It is interesting that one of the most thorough studies of experimental animal carcinogenesis leads to conclusions diametrically opposed to the AEC Staff position of safe thresholds of radiation.

While we would never be so arrogant as to extrapolate dose-response relations from rodent to man for many reasons, the absence of scaling parameters being a major one, it is of great interest to know the "ball-park" range for doubling doses for mammary cancer induction in the rat as compared to those we have presented for radiation-induction of mammary cancer in humans.(6)

The data of Bond et al show that for 400 rads of radiation, the Sprague-Dawley rats show 80% of the animals to have at least one breast cancer by the end of the observation period of 11 months. Thus, 400 rads is already a "saturation" type of dose, and hence unsuitable for dose-response relationships in an 11-month observation period. However, it is possible to study the extremely high dose region (400 rads or more) if the observations of breast cancer are made at a much earlier period of life than 11 months. Fortunately, the very thorough studies of Bond and co-workers provide data which allow calculation of mammary cancer incidence out to 6 months post-irradiation, and these observations will be used in the high-dose calculations.

In all estimates of doubling dose for radiation carcinogenesis, a prime input is the spontaneous incidence of the particular cancer under study. If that cancer is spontaneously fairly rare, a large series is required to provide a stable value for the spontaneous incidence. Bond studied 77 rats without irradiation and observed one breast cancer. The statistics of small numbers is such that the true number might be 2, or at the outside, even 3. We shall, therefore, make the calculations using the observed spontaneous incidence of 1 cancer in 77 rats, and also provide an "extreme" analysis using the value of 3 per 77 rats, as an outside limit.

The purpose of the analysis is to compare doubling doses for mammary cancer induction in rats at various parts of the entire scale of doses from 0 through 600 rads. This provides an excellent test of the doubling dose concept, and of linear theory, and furthermore can indicate whether any trends suggest any type of safe threshold. As we shall see below, any trend is opposite to a threshold. Lastly, we shall compare the doubling doses for mammary cancer induction in rats with those we have already reported for humans in Hiroshima-Nagasaki and Nova Scotia, Canada.(6)

INDUCTION OF BREAST CANCER IN SPRAGUE-DAWLEY RATS BY X-RAYS

(The 0-200 rad region)

We have taken all the prime data of Bond and co-workers relevant for our analysis and reproduced them in Table 1. We shall limit our analysis to the overall induction of mammary cancer. In our more detailed presentation of all experimental animal data, we shall later consider specific histologic types of cancer, such as adenocarcinoma and adenofibroma, as well as provide an analysis based upon total cancers induced, rather than number of rats developing cancer. As Bond et al have shown, multiple breast cancers are frequent in the irradiated animals.

TABLE 1

THE PRIME INPUT DATA FOR THE STUDY OF RADIATION-INDUCTION OF BREAST CANCER IN SPRAGUE-DAWLEY RATS (from Bond et al, Reference 8)

Category	Radiation Dose(rads)	Number of Rats studied	Number of Rats Developing Breast Cancer by 11 months	by 6 months
A	0	77	1	0
B	25	47	5	1
C	50	16	2	1
D	100	14	3	1
E	200	44	17	5
F	400	58	45	28
G	470	43	25	14
H	530	42	28	10
I	600	58	33	24

Spontaneous Breast Cancer rate in Sprague-Dawley rats (11 months of observation)

Observed, 1 cancer in 77 rats, or an incidence = $\left(\frac{1000}{77}\right)(1)$, or 13 breast cancers per 1000 rats.

Extreme estimate is 3 cancers in 77 rats, or an incidence = $\left(\frac{1000}{77}\right)(3)$ = 39 breast cancers per 1000 rats.

Categories B through E - including 25 rads, 50 rads, 100 rads, 200 rads.

Mean Dose calculation is the first step. (See data, Table 1)

$$\text{Mean Dose} = \frac{(25)(47) + (50)(16) + (100)(14) + (200)(44)}{47 + 16 + 14 + 44}$$

$$= \frac{1175 + 800 + 1400 + 8800}{121} = \frac{12175}{121}$$

$\therefore$ Mean Dose = 100.6 rads, for the overall group.

Rats developing mammary cancer = 5 + 2 + 3 + 17 = 27 out of 121 animals.

This corresponds to an incidence of $\left(\frac{1000}{121}\right)(27)$, or 223.1 rats with breast cancer per 1000 animals observed.

Doubling Dose Calculation:

	Observed data	Extreme (Outside) value
Irradiated rats	223.1 per 1000	223.1 per 1000
Spontaneous incidence	13.0 per 1000	39.0 per 1000
Excess, radiation-induced	210.1 per 1000	184.1 per 1000
Doubling Doses =	$\frac{\text{Excess}}{\text{Spontaneous}}$	$\frac{\text{Excess}}{\text{Spontaneous}}$
=	$\frac{210.1}{13.0}$	$\frac{184.1}{39.0}$
=	16.2 doubling doses	4.72 doubling doses
So, 100.6 rads =	16.2 doubling doses	4.72 doubling doses
$\therefore$ One doubling dose =	6.2 rads	21.3 rads

So, for all categories out to 200 rads, the most probable doubling dose for mammary cancer induction by radiation is 6.2 rads, with a small likelihood it could be as much as 21.3 rads.

Categories B through D - including 25, 50, 100 rads, but excluding 200 rads.

$$\text{Mean Dose} = \frac{(25)(47) + (50)(16) + (100)(14)}{47 + 16 + 14}$$

$$= \frac{1175 + 800 + 1400}{77} = \frac{3375}{77}$$

$\therefore$ Mean Dose = 43.8 rads, for the overall group.

Rats developing mammary cancer = 5 + 2 + 3 = 10 out of 77 animals. This corresponds to an incidence of $\left(\frac{1000}{77}\right)(10)$ = 130 rats with breast cancer per 1000 animals observed.

Doubling Dose Calculations:

	Observed data	Extreme (outside) value
Irradiated rats	130 per 1000	130 per 1000
Spontaneous incidence	13 per 1000	39 per 1000
Excess, radiation-induced	117 per 1000	91 per 1000
Doubling Doses =	$\frac{117}{13}$	$\frac{91}{39}$
=	9 doubling doses	2.33 doubling doses
So, 43.8 rads =	9 doubling doses	2.33 doubling doses
$\therefore$ One doubling dose =	4.9 rads	18.7 rads

So, for all categories out to 100 rads, the most probable doubling dose for mammary cancer induction by radiation is 4.9 rads, with a small likelihood it would be as much as 18.7 rads.

Categories B + C, including 25 and 50 rads only

$$\text{Mean Dose} = \frac{(25)(47) + (50)(16)}{47 + 16} = \frac{1175 + 800}{63} = \frac{1975}{63}$$

$\therefore$ Mean Dose = 31.3 rads.

Rats developing mammary cancer = 5 + 2 = 7 out of 63 animals. This corresponds to an incidence of $\left(\frac{1000}{63}\right)$ (7) = 111.1 rats with breast cancer per 1000 animals observed.

Doubling Dose Calculation:

	Observed data	Extreme (outside) value
Irradiated rats	111.1 per 1000	111.1 per 1000
Spontaneous incidence	13.0 per 1000	39.0 per 1000
Excess, radiation-induced	98.1 per 1000	72.1 per 1000
Doubling Doses =	$\frac{98.1}{13} = 7.5$	$\frac{72.1}{39} = 1.8$
So, 31.3 rads =	7.5 doubling doses	1.8 doubling doses
$\therefore$ 1 doubling dose =	4.2 rads	17.4 rads

So, for the categories out to 50 rads, the most probable doubling dose for mammary cancer induction by radiation is 4.2 rads, with a small likelihood it would be as much as 17.4 rads.

Category B alone - 25 rads Mean Dose - 25 rads.

5 cancers developed in 47 animals. This corresponds to an incidence of $\left(\frac{1000}{47}\right)(5) = 106.4$ rats with breast cancer per 1000 animals observed.

Doubling Dose Calculation:

	Observed data	Extreme (outside) value
Irradiated rats	106.4 per 1000	106.4 per 1000
Spontaneous incidence	13.0 per 1000	39.0 per 1000
Excess, radiation-induced	93.4 per 1000	67.4 per 1000
Doubling Doses =	$\frac{93.4}{13} = 7.18$	$\frac{67.4}{39} = 1.7$
So, 25 rads =	7.18 doubling doses	1.7 doubling doses
$\therefore$ 1 doubling dose =	$\frac{25}{7.18} =$ 3.5 rads	$\frac{25}{1.7} =$ 14.7 rads

We can now summarize all these doubling doses:

Categories	Mean Dose (rads)	Most Probable Doubling Dose(rads)	Extreme (outside) Doubling Dose(rads)
B+C+D+E(25,50,100,200 rads)	100.6	6.2	21.3
B+C+D (25,50,100 rads)	43.8	4.9	18.7
B+C (25,50 rads)	31.3	4.2	17.4
B (25 rads)	25.0	3.5	14.7

The data as a whole represent a beautiful confirmation of linear theory, and the doubling dose concept. Indeed, if anything, the radiation effect in producing breast cancer in rats is even more severe at low total doses than predicted by linear theory. This may be a real effect, or possibly only apparent due to mild saturation effects at the high doses.

The results are precisely the opposite of anything even remotely resembling a threshold. For a threshold to exist, the doubling doses, at low total doses, should be going toward infinity. Instead the doubling dose is decreasing to below 4 rads! Even allowing for a higher spontaneous breast cancer incidence than Bond observed, the doubling dose appears to be below 20 rads, and again behaves precisely opposite to threshold concepts. Nor should this extreme sensitivity to breast cancer induction by radiation in rats be at all surprising. Thus, from Upton's data on mice, one calculates readily, for the 0-100 rad region the following:[10]

RF Male Mice (x-rays) Myeloid Leukemia: Doubling Dose - 23.1 rads.

RF Female Mice (Co^{60} γ rays) Ovarian cancer: Doubling Dose = 17.6 rads.

Many more data will be presented in our detailed further animal studies.

INDUCTION OF BREAST CANCER BY X-RAYS

(The 400-600 rad region)

We shall now calculate the doubling dose for the very high dose region, utilizing the mammary cancer incidence (of Table 1) for up to 6 months, to avoid the saturation phenomena encountered in the 11-month observations.

Again, we need the spontaneous incidence rate as a prime input. Bond observed 0 cancers in 77 rats out to 6 months. But because of small numbers, this 0 value would not hold up in a larger series. For all radiation categories as a whole, including unirradiated animals, there were 84 rats showing breast cancer by six months of age, whereas there were 159 rats (including the 84) showing breast cancer by 11 months. Therefore, an excellent approximation is that the breast cancer incidence is $\frac{84}{159}$, or 53% as high at 6 months as at 11 months. Because cancers appear earlier in irradiated animals, in general, the use of this factor will overestimate

the spontaneous incidence at six months, and, hence, increase apparent doubling doses. Thus, the radiation effect will be underestimated, if anything.

For 11 months, we used 13 per 1000 as spontaneous incidence, and 39 per 1000 as an outside extreme.

$(0.53)(13) = 7.4$ estimated spontaneous incidence at 6 months.

$(0.53)(39) = 20.7$ estimated extreme spontaneous incidence at 6 months.

Categories F + G + H + I (400 rads, 470 rads, 530 rads, 600 rads)
(See data of Table 1)

$$\text{Mean Dose} = \frac{(400)(58) + (470)(43) + (530)(42) + (600)(58)}{58 + 43 + 42 + 58}$$

$$= \frac{23200 + 20210 + 22260 + 34800}{201} = \frac{100470}{201}$$

Mean Dose = 499.9 rads

Rats developing mammary cancer in 6 months = 28 + 14 + 10 + 24 = 76 rats out of 201 animals. This corresponds to $\frac{1000}{201}(76) = 378.1$ per 1000 as the number of rats developing breast cancer in 6 months per 1000 animals observed.

Doubling Dose Calculation:

	Best Estimate	Extreme Estimate
Irradiated rats	378.1 per 1000	378.1 per 1000
Spontaneous incidence	7.4 per 1000	20.7 per 1000
Excess, radiation-induced	370.7 per 1000	357.4 per 1000
Doubling Doses =	Excess/Spontaneous	Excess/Spontaneous
=	$\frac{370.7}{7.4} = 50.1$	$\frac{357.4}{20.7} = 17.3$
So, 499.9 rads =	50.1 doubling doses	17.3 doubling doses
∴ One doubling dose =	$\frac{499.9}{50.1} =$ 10.0 rads	$\frac{499.9}{17.3} =$ 28.9 rads

These values, 10.0 rads as best estimate and 28.9 rads as an outside value, are extremely consistent with all the data presented above for 200 rads and less. When we consider that (a) we have probably overestimated the spontaneous incidence at 6 months, and (b) there may still be some saturation effects, even at 6 months, the doubling doses may very well be approximately constant over the entire range from 0 through 600 rads.

CONCLUSIONS

1. Bond and co-workers' excellent studies of mammary cancer induction by x-rays in Sprague-Dawley rats show, as Bond and co-workers indicated, a linear dose-response relationship with no suggestion of any safe radiation threshold. Our analysis of their data is in total accord with this view. If there is any trend, it is away from a threshold and suggests a somewhat higher risk of cancer per rad as lower and lower doses are approached.

2. The best estimate of the doubling dose for mammary cancer induction by x-rays in Sprague-Dawley rats is in the neighborhood of 5 rads. It is unlikely to be higher than 20 rads.

3. These doubling doses are remarkably close to those we have reported for women in Nova Scotia and in Japan, in both of which doubling doses were in the 25 rad region, over a large range of total doses.

4. These experimental animal cancer-induction studies are in excellent accord with the linear, non-threshold model of radiation carcinogenesis which fits the human observations so well.

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