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RADIATION RESEARCH 58, 131–140 (1974)

The Validity of Risk Estimates of Leukemia Incidence Based on Japanese Data[1]

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ROSSI H. H. AND KELLERER, A. M. The Validity of Risk Estimates of Leukemia Incidence Based on Japanese Data. *Radiat. Res.* **58**, 131–140 (1974).

On the basis of all available pertinent radiobiological evidence it must be expected that the RBE of neutrons for the induction of human leukemia is a function of absorbed dose. An analysis of epidemiological and dosimetric data obtained at Hiroshima and Nagasaki yields results that conform to this expectation. It must, therefore, be concluded that the shapes of the dose–effect curves for the two Japanese cities are different and among the simplest assumptions that may be applied a linear dose dependence for neutrons appears to be the most plausible. Risk estimates based on a linear dependence for gamma radiation must, therefore, be excessive.

INTRODUCTION

Attempts to derive numerical estimates of the incidences of deleterious effects at low doses of ionizing radiation, particularly near MPD (maximum permissible dose) levels, cannot be based on direct observation. In fact the limits are selected in such a way as to make the incidences, if not zero, at least so low that they are virtually indeterminable, and Weinberg has accordingly classified the problem as "trans-scientific" (*1*). In the absence of readily applicable information the organizations responsible for protection recommendations have taken the position that it must be assumed that any amount of radiation can be harmful, and that it is:

". . . prudent to assume a non-threshold linear relationship for dose versus effect in the region of low dose, but this does not justify the use of extrapolations to predict effects, except for gross estimates of maximum possible effects" (*2*).

Despite the caveat in the second part of this statement, risk estimates have been derived by procedures in which the minimal incidence values that can with some degree of certainty be distinguished from control values were shown to be not inconsistent with linearity, with the "risk per rad" obtained by a least square fit to a linear relation.

This method can be defended as being the simplest one that can be applied to the insufficient information. It can, however, also be criticized because the fact

[1] This investigation was supported by Contract AT-(11-1)-3243 for the U.S. Atomic Energy Commission and Research Grant CA 12536 from the National Cancer Institute.

that a particular functional relation can not be rejected on the usual 95% significance level does not in any way establish the validity of this relation.

The degree to which reputable scientific organizations can differ in these matters has recently become apparent. One position was taken in a report of the Advisory Committee on the Biological Effects of Ionizing Radiation of the Division of Medical Sciences in the National Academy of Sciences (*3*). While discussing uncertainties attendant to the linear model and voicing doubts concerning a fixed, dose independent, relative biological effectiveness (RBE) of neutrons, the committee nevertheless proceeds to derive risk estimates based on these assumptions and terms these estimates "most likely values" (p. 168). The Report of the United Nations Scientific Committee on the Effects of Atomic Radiations [(*4*), p. 403 paragraph 6] specifically rejects this approach. Whatever position is taken on the issue, it is apparent that even optimal statistical treatment of epidemiological data must leave a substantial margin for doubt because of uncertainties which relate not only to incidence but often also to the dose received (particularly in human populations). The situation can, however, be clarified if the empirical findings are examined in the light of certain general observations in radiation biophysics.

We have performed such an analysis of the leukemia incidences at Hiroshima and Nagasaki. These data represent probably the most extensive observations on the most important malignancy induced by ionizing radiation. A further significant aspect is that the data allow the comparison of different radiation qualities because the radiation in the two cities was quite different. It had a substantial component of neutrons with energies of the order of 1 MeV at Hiroshima while it consisted mostly of hard gamma rays at Nagasaki (*5*).

CELL VS. TISSUE EFFECTS

There is virtually no generally accepted knowledge of the process whereby radiation induces leukemia, and the possibility that the different pathological types are produced by radically different mechanisms cannot be discounted. In particular we do not know if any type can be induced by a unicellular mechanism, i.e., a transformation of individual noninteracting cells, or whether the process is multicellular, i.e., depends on direct or mediated interaction of a number of affected cells. The distinction is important because in the case of unicellular response one would conclude that at least in the case of neutrons the incidence is proportional to dose near MPD levels because there the probability that cells are traversed by more than one neutron secondary (proton or other nucleus) is negligible, and because single secondaries have been found to deposit sufficient energy in the cell to produce many kinds of injury including lethality with a probability that approaches unity at high LET (*6*, *7*).

On the other hand, if radiation induces leukemia by a multicellular mechanism virtually any shapes of the dose–effect curve are possible, including those in which the basic assumptions employed in radiation protection are not "prudent." We have deduced (*8*) that in the observable effect range the induction of certain experimental tumors (mammary neoplasms in the rat) involves cellular interac-

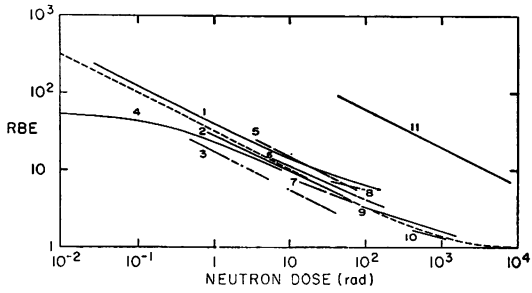

FIG. 1. Relative biological effectiveness of neutrons as a function of absorbed dose of neutrons for various biological endpoints (see Table I). The broken curve gives the shape of the RBE vs. dose relation for high and intermediate doses; it is derived from the theory of dual radiation action (*9*).

tion. This may not be the case for human leukemia, and there is indeed some evidence that the shapes of the dose–effect curves may be different (see below). There is, however, also no definitive reason for concluding that leukemia induction is a unicellular process.

THE DOSE DEPENDENCE OF RBE

While it is difficult to reach conclusions on the basic shape of the dose–effect curves either for neutrons or for gamma radiation, there is strong evidence that their shape should be different. This is equivalent to the statement that the relative biological effectiveness of neutrons as compared to gamma radiation should be a function of the level of effect or of the dose of either radiation.

Figure 1 (*9*) shows the dependence of neutron RBE on neutron dose for a variety of somatic effects on higher organisms. The curves are selected from an even larger assembly of data showing the same basic characteristic and we are not aware of any observations that are in conflict with them. All of the curves

TABLE I

REFERENCES TO INDIVIDUAL CURVES IN FIGURE 1

Author and number of curve in Fig. 1		*End point*	*Neutron energy*
Bateman *et al.* (1972)	1	Opacification of the murine lens	430 keV
	2	Opacification of the murine lens	1.8 MeV
	3	Opacification of the murine lens	14 MeV
Sparrow *et al.* (1972)	4	Mutations of *Tradescantia* Stamen Hairs (blue to pink)	430 keV
Vogel (1969)	5	Mammary neoplasm in the Sprague-Dawley rat	Fission
Biola *et al.* (1971)	6	Chromosome aberrations in human lymphocytes	Fission
Hall *et al.* (1973)	7	Growth reduction of *Vicia Faba* root, aerated	3.7 MeV
	8	Growth reduction of *Vicia Faba* root, anoxic	3.7 MeV
Field (1969)	9	Skin damage (Human, rat, mouse, pig)	6 MeV
Withers *et al.* (1970)	10	Inactivation of intestinal crypt cells in the mouse	14
Smith *et al.* (1968)	11	Various effects on seeds of *Zea Mays*	Fission

show a pronounced dependence of RBE on dose, and except for the case of the *dry* seeds of Zea Mays the main variation of RBE occurs in a dose range wider than the interval from 1–100 rad. Since in this interval the RBE varies between roughly 30 and 3, the range of x-ray doses is more than the interval between 30 and 300 rad and covers the range in which significant data were obtained at Nagasaki.

The theory of dual radiation action (*9, 10*) accounts not only for the basic phenomenon of the variation of RBE with dose, but also for the maximum slope ($-\frac{1}{2}$) of the logarithmic dose–RBE relation. Although its predictions need not to be invoked for the main argument developed here, it may be of interest that they include dose–rate dependence of x- and γ-ray effects in the range under discussion, as well as a constant RBE of at least 30 and absence of dose–rate effects at x- and γ-ray doses below a few rad (as actually found in stamen hair aberrations in *Tradescantia*). Thus below the dose range in which the Japanese data are significant the shape of the incidence curves should be the same for neutrons and gamma rays. However, apart from any consequences of the theory, all radiobiological observations indicate that at doses where meaningful Japanese data are available the RBE is a function of dose, decreasing as the dose increases. These radiobiological data imply therefore that the curve for Hiroshima should be convex upwards if the curve for Nagasaki approximates a straight line; if the curve for Hiroshima appears to be linear, the curve for Nagasaki should be concave upwards.

In general, for somatic effects on higher organisms and for the dose range under discussion one may state the following rule: If the effect of neutrons as measured on any scale is given by the function $I(D_n)$, the effect of gamma rays as measured on the same scale is $I(aD_\gamma^2)$ where D_n and D_γ are the absorbed doses of neutrons and γ-rays, and a is constant. The RBE is equal to $1/(aD_\gamma)$.

THE DATA

One of the difficulties in establishing dose–effect or dose–RBE relations for the Hiroshima and Nagasaki observations is that available dosimetric information concerns principally the dependence of tissue kerma in free air ("air dose") on distance.[2] The mean absorbed dose in the bone marrow is less than kerma, the reduction being larger for neutrons than for gamma rays and dependent in either case on body orientation. However, since it appears that the radiation spectrum changed little with distance from the epicenter of the explosion, the ratio between kerma and dose can be considered a constant. The shape of the dose–effect curve at Nagasaki (where only gamma radiation was of importance) should therefore be the same as that of the kerma–effect curve. At Hiroshima where the proportions of neutron and gamma radiation varied with distance the shapes should differ, particularly at low values where the dose–effect curve should be somewhat steeper.

The RBE is the inverse of the ratio of doses for equal effects. We are employing for the purposes of this discussion the symbol R for the corresponding kerma ratio.

[2] In the following the tissue kerma in free air will be simply referred to as kerma (K).

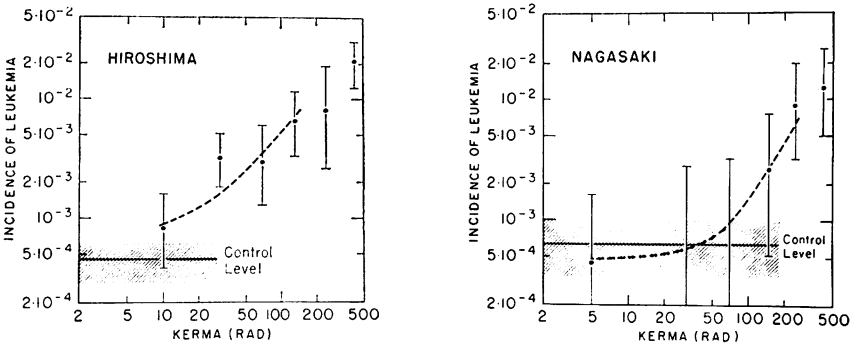

FIG. 2. Incidence of leukemia per exposed individual over the period from Oct. 1950 to Sept. 1966 vs. kerma at Hiroshima (left) and Nagasaki (right). The bars represent 95%-confidence ranges; the shaded area is the 95%-confidence region for the unirradiated population of each city. The broken curves are the result of a least squares fit as described in the text.

If the ratio of mean dose to the marrow and kerma is denoted by c, i.e., if

$$c_\gamma = D_\gamma / K_\gamma \quad \text{and} \quad c_n = D_n / K_n$$

it follows from

$$\text{RBE} = D_\gamma / D_n \quad \text{and} \quad R = K_\gamma / K_n$$

that

$$\text{RBE} = (c_\gamma / c_n) R$$

where D_γ and D_n are the respective doses for equal effect. The RBE is larger than R because $c_\gamma > c_n$, but the ratio RBE/R should be at least approximately constant.

The observed leukemia incidences at Hiroshima and Nagasaki during the observational period from October 1950 to September 1966 are shown in Fig. 2 as function of kerma. The data are taken from the study by Ishimaru *et al.* (*5*). In this compilation the populations were divided into categories which received kermas within certain ranges that were represented by nominal values. The broken lines correspond to a least squares fit which will be discussed below. The 95% confidence limits are indicated by the solid bars.

An overall fit of the data, both in Hiroshima and Nagasaki, is complicated by the unknown influence of lethality and the corresponding flattening of the curves in the range of high doses. A comparison of the kerma–effect relation in Hiroshima with that observed in Nagasaki does, however, indicate a characteristic difference, and we have therefore applied a more direct statistical analysis which is not based on the fitting of the kerma–response curves to certain equations, but instead on the comparison of the effects of each of the nominal kermas in Hiroshima with each of the nominal kermas in Nagasaki. In this way one obtains a confidence region for the kerma-dependence of the relative effectiveness, R_H, of the radiation in Hiroshima with respect to that in Nagasaki. Details of this statistical procedure are described in an earlier publication (*19*).

If K_H is a particular kerma in Hiroshima and K_N a particular kerma in Nagasaki, I_H and I_N are the observed incidences, and I_H is significantly larger than I_N, then

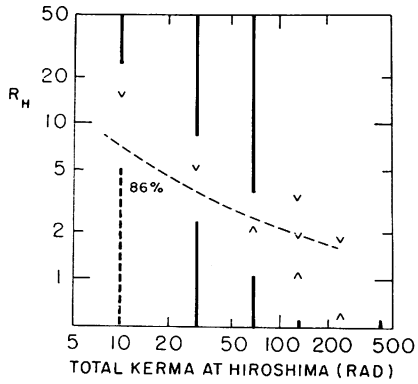

FIG. 3. Relative biological effectiveness of the radiation in Hiroshima compared to that in Nagasaki as a function of kerma in Hiroshima. The bars represent those values which can be excluded with 95% confidence; the broken bar stands for a level of significance of 86%. The broken curve is the result of the least squares fit described in the text.

the R_H at the kerma K_H must be larger than K_N/K_H. Such a result of the comparison of two doses is indicated in Fig. 3 by a solid bar which covers the range of values of R_H which are rejected, i.e., all values below K_N/K_H. Conversely, if I_N is significantly larger than I_H, R_H must be smaller than K_N/K_H, and the result is then indicated by a solid bar extending from the top of the figure downwards, so that it covers all values of R_H which must be rejected. If the difference between the incidences at K_N and K_H is not statistically significant, the result of the comparison is merely indicated by an arrow. The actual kerma relation should lie between the two sets of bars in Fig. 3.

The statistical test used for the comparison of two observed incidences is the χ^2-test for all those cases where in both groups the number of observed cases of leukemia was larger than 6; in all other cases Fisher's "exact probability test" has been applied. The two groups of survivors in the ABCC master sample which have been assigned the kermas of 31 and 69 rad of gamma rays in Nagasaki, have been combined into one group in order to make this group sufficiently large for comparison with the group of persons who were assigned the kerma of 10 rad in Hiroshima. Nevertheless, it has been found that the incidence in the Nagasaki group is lower than that in the Hiroshima group only on a level of statistical significance of 86%. To indicate this fact, the result of the comparison has been represented by a broken bar in Fig. 3.

The control incidences do not enter this analysis explicitly but might distort the limits given in Fig. 3 if there was a real difference in the background rates in the two cities. It would seem that the rates agree within statistical uncertainties. However, if the control incidence at Hiroshima had been higher than at Nagasaki, an apparent high R_H would be observed at low doses. The observed control rate was in fact higher in Nagasaki and if it were assumed that this difference is real the dependence between R_H and kerma would be even steeper than indicated in Fig. 3.

Although the possibility of a constant R_H of about 3 can only be rejected with a significance level of 86%, the trend of the data indicates an increase of R_H with decreasing neutron kerma as has also been postulated by Poston *et al.* (*20*). Furthermore, this dependence appears to be of the same form which has been found in all the various systems compiled in Fig. 1. We therefore conclude that it is not justified to use the linear approximation to represent the leukemia data in both Hiroshima and Nagasaki.

It should be noted that the direct analysis of R_H does not only have the advantage that it leads to a somewhat sharper statistical discrimination between the data in Hiroshima and Nagasaki, but that it also has the advantage of not invoking any assumptions on the overall shape of the kerma–effect relations. Such assumptions are especially problematic in the present case because one deals with considerable uncertainties both in the range of low and of high kermas. In the range of low kermas the absolute number of observed leukemia cases is very small and the statistical uncertainties are correspondingly large. In the range of high kermas on the other hand, one deals with considerable uncertainties in the assignment of kerma values. This is due to the fact that those persons who received the largest doses are a highly selected group of survivors from regions near the epicenter of the explosion where the mortality was high. The direct analysis of R_H as a function of kerma has, on the other hand, the disadvantage that it refers to the comparison of a mixture of neutrons and gamma rays in the case of Hiroshima with the gamma radiation which was prevalent in Nagasaki. It does not permit the direct estimate of the R–kerma relation for the neutrons alone compared to gamma rays; one can however state that the values of R would have to be higher than those of R_H.

A SIMPLE APPROXIMATION TO THE KERMA VS. INCIDENCE CURVES

Although the analysis of the dose-RBE dependence indicates a difference between the dose-effect curves in the two cities, their individual shapes can not be assessed in any detail. We have, however, attempted to determine the coefficients in what may be the simplest model according to which the incidence in both cities is given by the form:

$$I(K) = I_0 + aK + bK^2$$

The analysis was based on Fisher's F-distribution and has been performed separately for the two cities.[3] It is somewhat doubtful whether such an analysis is strictly applicable to the very limited amount of data, but it can be at least a general guide to the possible incidence–kerma relations.

A linear relation is found to be well within the 95% confidence region for Hiroshima where neutrons were the dominent radiation component. On the other hand the confidence domain for the Nagasaki data lies in the region of negative values of the linear component, a. This would indicate that a sufficient fit requires either a negative linear component, or a higher power than 2 of kerma in the

[3] A. M. Kellerer and H. H. Rossi, pp. 245–263 in Annual Report on Research Project, USAEC. COO-3243-2 (1973).

incidence–kerma relation. However, in view of the few points on which the analysis is based and in view of the uncertainties in the kerma values it may not be justified to draw such detailed conclusions. The essential result is that a linear relation appears unlikely for the data from Nagasaki. This is in agreement with the gross appearance of the data in Fig. 2 which suggests that the function $I(K_n)$ might have the simple form $I(K_n) = kK_n$ with the consequent relation $I(K_\gamma) = kaK_\gamma^2$. As explained above, this would be consistent with a unicellular mechanism of leukemia induction although such a process is not necessarily implied by this relation.

Accordingly one may perform a least square fit to the data in Hiroshima and Nagasaki, with a linear dependence between the incidence and the neutron component of kerma and a quadratic dependence between the incidence and the gamma-ray component of kerma. A separate assessment of the neutron component and the gamma component of the kerma in Hiroshima and Nagasaki has been given by Ishimaru *et al.* (*5*). On the basis of their values one obtains the estimated probability of 2.2×10^{-4} for leukemia during the observation period per rad of neutrons and of 8.7×10^{-8} per rad^2 of gamma radiation. In the least square fit which results in these values, only the kermas below 200 rad in the case of Hiroshima and below 300 in the case of Nagasaki have been considered. Higher dose values have been excluded because of the possible distortion of the kerma values due to selection. Another reason is that there is evidence suggesting an actual decline of incidence at high kerma (*4*).

The kerma–incidence relations which follow from the least-squares fit are inserted in Fig. 2 as broken line. The fit has been performed with the assumption of equal control values in the two cities; the common control value of leukemia prevalence obtained in this manner is 4.8×10^{-4}. As mentioned above it is uncertain whether there was in fact a real difference between the control values. If the observed difference is real an even more pronounced threshold of the curve for Nagasaki is indicated. With the estimated parameters of the linear–quadratic model, one can calculate the theoretical kerma–R_H dependence for the actual mixture of neutrons and gamma rays which occurred in Hiroshima. The resulting curve is given as a broken line in Fig. 3.

DISCUSSION

It must be stressed that the values estimated above are based on an assumption of linear dependence of leukemia incidence on neutron kerma. Although this assumption together with the generally observed dependence of the RBE of low energy neutrons on neutron dose results in better agreement with observations in the Japanese cities, it may well be only a rough approximation.

It is even more important that the relations given here not be extrapolated beyond the range in which meaningful observations were made. According to our basic theoretical approach the RBE should become constant for gamma-ray doses of the order of perhaps tens of rads with the result that below such doses the functional dependence of incidence on dose should be the same for both radiations except for a constant applied to the dose. The question whether this dependence

is linear can not be answered at this time with any degree of assurance. As mentioned above we have deduced that the induction of certain experimental animal neoplasms must be a complex multicellular process. The data which have been analyzed here do not indicate the lack of linearity in the neutron dose–effect relation that required that deduction. However, similar effects may well operate at still lower doses.

We consider the derivation of risk estimates to be beyond the objectives of this paper if only because such estimates can follow diverse philosophies. In particular one might wish to derive the estimates either with emphasis on conservativism or with the aim of attaining actual values. However, in either case the relations derived here should provide a more realistic point of departure.

The conclusions made here support the position taken by the UN Scientific Committee (*4*). They are at variance with the approach taken by the NAS Advisory Committee (*3*).

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