The Estimation of Low-Dose Hazards by Extrapolation from High Doses

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Empirical information on the effects of low doses of ionizing radiation is beset by severe limitations. Theoretical considerations of biophysics can guide the analysis of epidemiological data by indicating certain dose-response relations or eliminating others. Thus, it can be shown that at low doses there must be proportionality between dose and effect on non-interacting cells and that one must anticipate different dose-effect relations upon exposure to markedly different types of radiation.

The assessment of the biomedical hazards of low levels of ionizing radiation has always been seriously limited by the small frequency of observable effects at doses of low-LET\(^1\) radiation that are less than about 1 gray.\(^2\) This difficulty exists not only in human radiation epidemiology, but also in experimental animal radiobiology where attempts to improve statistical precision by increasing the number of animals exposed are obviously restricted by considerations of cost or complexity. In fact the number of persons exposed to A-bombs at Hiroshima and Nagasaki was far greater than the number of animals exposed in almost any radiobiological experiment. This is equally true for the members of the expanded Life Study Sample (LSS), which is a cohort of the Japanese populations that has been selected for intensive study.

However, a comparison of statistical limitations in human and animal studies cannot be based merely on numbers. It is well known that radiation sensitivity varies greatly amongst species or even strains of animals, and in some instances it has been possible to assess rather accurately the damage produced by comparatively small radiation doses [1]. This makes it evident that it is not possible to employ observations on animals as a basis of absolute risk estimates for man. It is generally agreed that these must be based on epidemiological data obtained at high doses with extrapolations into the low-dose range guided by general findings in experimental and theoretical radiobiology. There are profound uncertainties in these projections, and

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\(^1\)The linear energy transfer (LET) is a physical quantity characterizing the rate at which ionizing particles deposit energy along their tracks. X- and gamma rays are examples of low-LET radiations; neutrons and alpha particles at conventional energies are high-LET radiation.

\(^2\)The gray (Gy) is replacing the rad as a unit of (absorbed) dose.

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they are frequently given with the proviso that they must not be extended to arbitrarily small doses. Thus, in the recent report of the Committee on the Biological Effects of Ionizing Radiation of the National Academy of Sciences (BEIR III) [2], the lowest single dose for which risk estimates for cancer induction are provided is 100 mGy.

Although extrapolations can be uncertain and therefore controversial, the rationale adduced for their justification can sometimes be shown to be either sound or faulty or at least not pertinent. However, in many cases extrapolations are based on judgments that can be neither proved nor disproved and that are frequently based on pragmatic considerations. Perhaps the best known of these is the so-called "linear hypothesis" which has been frequently invoked in connection with radiation protection.

In the sense in which the term "linear hypothesis" is usually employed, it is misnamed, because what is claimed is not merely that some portion of the dose-effect curve under consideration can be approximated by a straight line. The hypothesis goes further because it postulates that in a plot of excess effect (i.e., effect beyond that caused in the absence of radiation) versus dose one obtains a straight line that emanates from the origin. Thus, what is claimed is proportionality. This distinction is quite important because only proportionality permits the concept of a "risk coefficient" which represents the risk per unit of absorbed dose at small doses regardless of their value. Although "linearity" is one of the models considered by BEIR III, the explicit limitation of estimates to doses above 100 mGy fails to endorse proportionality or the existence of a risk coefficient. This is further emphasized by the statement that it is unknown what effects dose rates of 1 mGy per year cause in human populations.

In view of the profound significance of proportionality to radiation protection, an examination of its validity is especially appropriate. This can be based on elementary considerations of microdosimetry. Figure 1 is a schematic representation of a monolayer of some 150 cells and the track pattern produced in them by absorbed doses of 10 mGy of either neutrons or gamma rays. It is assumed that in either case the radiation energy is of the order of 1 MeV. It is immediately obvious that, at least in the case of the neutrons, the absorbed dose is an unsuitable index of the physical insult to individual cells. Most of the cells receive no energy at all, while the energy concentration in a few cells is very high. This concentration expressed as specific energy (i.e., the energy absorbed divided by the mass of the cell) is typically of the order of 0.5 Gy. It is also evident that if the dose is reduced by, say, a factor of 2 the number of cells affected will on the average also be reduced by a factor of 2, but the mean specific energy in the affected cells remains the same. It follows that whatever the biological effect under consideration, the probability of its occurrence in the cell population must be proportional to absorbed dose. The figure also indicates that at a dose of 10 mGy the cells are traversed by several electrons and that, in contrast to the pattern produced by neutrons, virtually all cells receive a finite amount of specific energy that depends on the dose. However, it is evident that at a dose that is 1 mGy or less multiple traversals must become very improbable and that at such low levels proportionality must exist for gamma radiation, also.

These considerations can be applied to radiobiological effects only if two criteria are met. One of these is that the effect in question consists of injury to individual cells or that it arises as a result of injury to individual cells. The other criterion is that each cell must be autonomous, which means that its response depends solely on the
LOW DOSE RADIATION HAZARDS

TRACK PATTERN IN 150 CELLS GENERATED BY
AN ABSORBED DOSE OF 10 mGy
(1 RAD)
CELL DIAMETER \( \approx 5 \mu m \)

a.  

b.  

1 MeV Gamma Rays  
\( \Phi(0) = 4.5 \)

1 MeV Neutrons  
\( \Phi(0) = 0.02 \)

\( \Phi(0) \) is the Event Frequency per Cell

FIG. 1. Track pattern in mammalian 150 cells generated by 10 mGy (1 rad) of (a) \( \gamma \)-rays, (b) neutrons. The cell diameter is taken to be about 5 \( \mu m \) and the energy of either radiation is near 1 MeV.

energy it has received regardless of energy absorption that may have occurred outside it (in other cells, media, etc.).

It is generally assumed that the cells of the germ plasm meet these requirements at least to a large extent. Consequently, a proportional (sometimes termed linear-no-threshold) relation between dose and genetic injury is usually assumed to hold at low doses. Although this establishes that the dose-effect curve must be a simple straight line emanating from the origin of the dose-effect plot the slope of this line remains uncertain. In no epidemiological surveys, including those at Hiroshima and Nagasaki, has it been possible to determine the incidence of genetic effects on man with statistical significance, and it has been assessed primarily on the basis of animal experimentation.

The reverse situation obtains in the case of carcinogenesis. It is well established that radiation causes cancer in man with an incidence that can be approximately estimated at high doses. However, the shape of the dose-effect curve is uncertain because it is unclear whether cancers arise as a result of the action of radiation on autonomous cells. There is evidence that at least some tumors are monoclonal, which means that they apparently arose from a single cell [3,4]. But this is not sufficient because it must also be established that such cells are autonomous. In a number of animal experiments the opposite has been found.

The absence of autonomous response can be demonstrated by the absence of proportionality at low doses. It has been impossible to determine cancer incidence at doses of X- and gamma rays that are so low that there is a negligible probability of multiple events in individual cells; however, this has been quite feasible in the case of neutrons. On the basis of the event frequencies depicted in Fig. 1 it can be calculated that a neutron dose of several hundred mGy is required before there is an appreciable probability of multiple events in the nuclei of mammalian cells. If, as
seems likely, the carcinogenic action is initiated in a volume that is smaller than the nucleus this limit would have to be even higher. However, as shown in Fig. 2, a non-proportional dependence of cancer incidence on dose has been observed even at the lower end of this dose range in mice exposed to neutrons, and in the case of mammary neoplasms in a susceptible strain of rat, absence of proportionality was demonstrated to extend to a dose as low as a few mGy.

In view of these findings, arguments based on cellular radiation response are not adequate to justify the thesis of proportionality between dose and cancer induction. The argument that epidemiological data are not inconsistent with proportionality is equally weak because various other dose-effect relations fit equally well (or poorly). Thus, in general, proportionality can be neither accepted nor rejected with any assurance. However, there are persuasive reasons to indicate that it cannot obtain for both high- and low-LET radiations over a wide range of doses.

Although Fig. 1 is drawn in such a way as to indicate physical equivalence of neutrons and gamma radiation because the track patterns are drawn for equal absorbed doses, it certainly does not depict such patterns for equal biological effect. It is well known that the relative biological effectiveness (RBE) of neutrons is substantially greater than that of X- or gamma rays, at least as far as effects on higher organisms are concerned. This means that the response of such cells cannot be proportional to the energy they receive because in that case the RBE would always have to be unity. Furthermore, the fact that equal mean energy concentrations in cell populations such as those depicted in Fig. 1 result in higher biological effectiveness

![Image](https://example.com/image.png)

**FIG. 2.** Age-corrected tumor incidence (T.I.) or average number of tumors (T.N.) vs. low doses of neutrons having energies of the order of 1 MeV. a. lung adenomas, b. lung adenocarcinomas, c. ovarian tumors, d. mammary adenocarcinoma; all in the RFM mouse [9]. e. lung tumors in the RFM mouse [8], f. mammary neoplasms in the Sprague-Dawley rat [1]. The absence of linearity shows that these tumors cannot arise as a result of autonomous cell responses.
of high-LET radiation means that the response of the mammalian cell must be supra-linear (i.e., increase with a power of the specific energy that is larger than one). It is the central tenet of the theory of dual radiation action [5] that the power is in fact equal to two, and this has been deduced from a very generally observed dependence of RBE on the reciprocal of the square root of the neutron dose. However, even if this theory is not applied, it is evident that as long as the RBE is greater than unity it must increase as a low neutron dose decreases. Thus, as already mentioned in the discussion of Fig. 1, halving of a neutron dose must result in a twofold reduction of the number of cells affected while in the case of the low-LET radiation, halving of the dose must lead to a more than twofold lessening of any effect because the mean specific energy received by all cells decreases by a factor of two.

Like the considerations relating to proportionality, those of the dependence of RBE on dose are virtually certain to apply to autonomous cells. Cellular interactions can readily modify dose-effect curves, but since such interactions are not likely to depend on radiation quality they should modify the dose-effect curves for various radiations equally, with the result that the RBE dependence on dose is preserved. This expectation has in fact been met in the two instances where adequately precise data have been obtained for the induction of neoplasms by neutron doses that are less than 100 mGy. In the case of mammary neoplasms of the rat, the dose-effect relation has negative curvature [1] and in the case of lung tumors in mice, it has positive curvature [8]. Thus, in neither case does the dose-effect relation conform to proportionality, but it nevertheless shows in both instances the same dependence of RBE on dose which has been observed in many other systems [1,5,7].

This simple qualitative analysis indicates that for those doses where single inactivation predominates, the RBE of neutrons relative to low-LET radiation must increase with decreasing dose. Consequently, it is not possible for both dose-effect curves to have the same shape and at most only one of them can indicate proportionality. The dose range in which this must be the case depends on neutron energy as well as the dimensions of the (probably subnuclear) regions in which the critical energy absorption takes place. In those cases where it was possible to reliably assess the dependence of the RBE of fission neutrons relative to low-LET radiation, the variation extends from neutron doses of the order of less than a milligray to at least several hundred milligray with corresponding gamma ray doses ranging from less than 100 mGy to at least several Gy.

The dependence of RBE on dose can be a substantial help in attempts to attain optimal statistical analysis of epidemiological data. Thus, risk estimates have been obtained for leukemia [10] as well as for all cancers [7] for both neutrons and gamma radiations by comparing mortality in Hiroshima and Nagasaki. Because of a current dispute over the dosimetry in the two cities, these estimates will not be presented here. It may, however, be pointed out that if the claim that there was essentially no neutron component in either city should be correct, this would not invalidate the basic considerations that have been presented here. It should also be realized that the linear and the quadratic approximations of dose-effect relations for neutrons and gamma radiation, respectively, resulted from optimum mathematical fitting procedures in a limited dose range. These approximations were thus not the result of a naive application of theorems that apply only to autonomous cells, and they must also not be extrapolated to doses of less than about 100 mGy of low-LET radiation. It is probable that for effects produced below this limit (and a corresponding lower limit of neutrons) the dose-effect curves for both radiations have the same shape.
However, the nature of this shape cannot be specified at this time with any assurance.

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