Proc. Natl. Acad. Sci. USA
Vol. 88, pp. 8666–8670, October 1991
Medical Sciences

A different perception of the linear, nonthreshold hypothesis for low-dose irradiation

(radiation protection/low-level radiation/radioepidemiology/thresholds)

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Communicated by Eugene P. Cronkite, July 15, 1991

ABSTRACT **Two equally useful dosimetric quantities, both of which are called dose, are used in toxicology. With radiation measurement, only one—the energy per unit mass D—is called dose. The other—the total energy in the irradiated system—is here distinguished from D by assigning it the name collective energy, ε. The collective energy is a more complete statement of dose because it is the product of the energy concentration D and the mass irradiated m. Especially in radioepidemiology, in which ε is the total energy imparted to all persons irradiated, the quantity m must be specified because it is situation specific and thus highly variable. At present, radioepidemiological dose–response curves are given only in terms of the toxicological model—i.e., the fraction (probability) of radiation-attributable cancers occurring as a function of D. Because this relation does not involve the number of persons at each value of D, it fosters the illusion that any dose, no matter how small, can result in cancer. However, we show that if the dose–response relationship is expressed in terms of the absolute number of attributable cancers as a function of ε, cancer occurs, on average, only if the collective energy exceeds a relatively large minimum value, the magnitude of which will be estimated. Therefore, we conclude that the nonthreshold aspect of the linear hypothesis is misleading and quite probably invalid. For example, in or around a facility in which exposure of humans to relatively low values of D occurs, attributable cancers are most unlikely to appear unless the ε to the irradiated population exceeds this minimum value.**

Dose–response curves for ionizing radiation were first developed to predict its acute, early effects on normal organs and mammals (humans) and on cancers in connection with radiotherapy. These relationships determined the fraction (probability) of persons responding quantally as a function of absorbed dose [a quantal response is a definably either/or change of state such as an irreversible level of injury, the appearance of a cancer, or death (1)]. The purpose and usefulness of these functions was to estimate these probabilities, thus permitting the radiotherapist to prescribe a dose, or course of doses, that would maximize the probability of controlling the tumor while minimizing the chance of unacceptable collateral damage to normal tissues that were unavoidably irradiated. The curves corresponded to those used generally in toxicology and therapeutic medicine—i.e., they had a threshold and were nonlinear.

Subsequent findings in cell systems and in human radioepidemiological studies suggested that cancer could result from relatively small absorbed doses. However, it was evident that at least the initial portion of the dose–response curve was often consistent with a linear, nonthreshold relationship. Nonetheless, the identical variable quantities developed earlier in connection with the toxicological model were carried over directly to describe the linear, nonthreshold relationships (2, 3). It is the function based on this model that led to the linear, nonthreshold hypothesis, referred to here as the linear hypothesis, generally interpreted to mean that any amount of radiation, no matter how small, can cause a cancer.

Our principal objective in this communication is not necessarily to question the proportionality of the radioepidemiological variables or even the slope of the dose–response curves but rather to evaluate the appropriateness and consequences of using a toxicological–medical model to represent radioepidemiological data. Does this practice directly provide the information needed in public health? Can the same data be represented by a different functional relationship, more relevant to radioepidemiology? Would such a function support the linear hypothesis, particularly with regard to the nonthreshold thesis that attributable cancer will appear even with very small amounts of radiation?

The meaning of the concept of dose is central to these questions, as is the difference in this meaning when dose is considered in relation to the individual person (patient) who constitutes the focus of medicine and toxicology and when it is applied to a defined population regarded as a single biological entity, which is the focus of public health including radioepidemiology. These issues will be discussed first.

Two equally useful dosimetric quantities are used in medicine and toxicology, each of which is called dose. Only one, the mass concentration of agent D, is here termed dose.‖ The other, the total amount of agent in the dosed system, is distinguished from D by calling it the total amount of agent, ε. The two are related by m, the total mass of the system—i.e.,

$$\varepsilon = mD. \qquad [1]$$

The relationship is general and applies to any agent or substance administered.

The concentration form of dose D is incomplete because a value for concentration alone does not express the absolute amount of an agent in any system. The more complete expression of dose to the system is ε, which takes into account both of the quantities, D and m.

An example will usefully illustrate the difference between the two quantities and the designation of mass by implication; the administration of a soluble anesthetic agent to an animal is a convenient choice. The dose prescribed may appear in terms of D only—e.g., in mg/kg—without specification of m. However, it is generally understood that there is an implied

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‖D is here called dose because of this usage in radiation dosimetry. By historical precedent, and as defined in general and medical dictionaries, dose is the total amount administered, ε, and not the concentration D.

mass or weight to be used to obtain ε: that of the specific animal, organ, or other biological system involved. Therefore, ε, and not D alone, determines the system's response to the anesthetic.

With regard to radiation, for which energy is the active agent, the concentration and the more complete form of dose are the absorbed dose, D, and the total collective energy in the system, ε,** respectively. In therapeutic radiology and for early, acute effects in general, the absorbed dose may be used alone because it is implied (and generally understood) that the mass is that of the tumor bed or other biological entity irradiated. For this reason, absorbed dose alone has been and continues to be useful in radiotherapy.

Nonetheless, it was understood early in radiotherapy that the total energy in the system mass also plays an important role in determining the severity of effect, particularly on the normal tissues unavoidably included in the beam. Accordingly, the total energy to these normal systems is approximated in the form of kg·Gy or joules (J), the value of which is minimized to avoid unacceptable damage to normal tissues.

In cancer radioepidemiology, the system we focus on is not the patient, but rather a specific population of normal individuals who have been irradiated as the result of an event such as an atomic bombing, a large radiation accident such as at Chernobyl, or a year's occupational exposure in an industrial plant. Here also it is necessary to obtain ε for the entire system. However, in radioepidemiology it is not only the size (mass) of the total system irradiated that varies widely with the type and severity of the event, but also the spectrum of doses and the number and masses of persons in each dose interval.

Thus, in applying Eq. 1, not just one dose (interval) but many must be specified. Also, the mass of persons corresponding to any dose interval cannot be implied but must be provided specifically. Only with such detailed specification can the total energy ε, and thus the severity of effect on the entire population or subgroups, be obtained.

The unit most appropriate for the quantity collective energy is the J. However, the unit person·Gy may be used as an alternative, provided that the number and mean mass of persons in each dose interval are specified so that conversion to J is possible. In fact, this alternative unit is already being used in hazard analysis and in record keeping for radiation protection. Therefore the significance of the quantity collective energy is already implicitly recognized.

MATERIALS AND METHODS

Sources of Data. The data used in the present analyses are based on the excess incidence of cancer of all types found in studies of atomic bomb survivors (4, 5). Of the two sets of data provided, for leukemia and for all other forms of cancer, the latter were chosen because of the larger number of cancers. A composite of data from the two published reanalyses (4, 5), in which newer dose estimates were used (6), was used to develop the familiar dose–response curve shown in Fig. 1. The radiation involved was essentially all penetrating γ rays, with a small contribution from fast neutrons. Absorbed dose is used here for simplicity even though the shielded kerma was used in the original papers. Similarly, uniform whole-body irradiation is assumed to apply. Current and not projected values for attributable cancer were used.

Ambiguities in Fig. 1. The coordinates of the curve in Fig. 1 are the fraction (probability) of persons with cancer, N_{ca}/N_D, vs. absorbed dose, in which N_{ca} is the number of

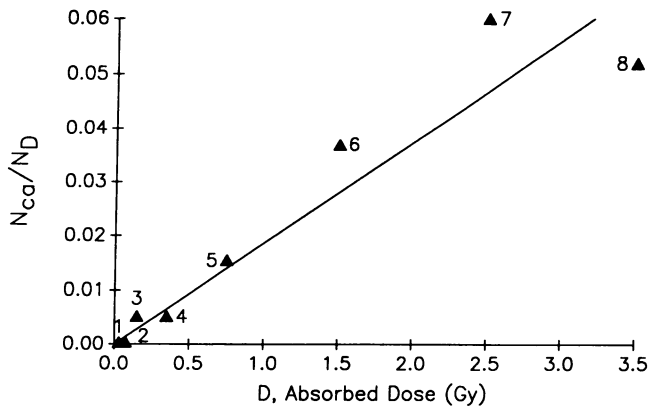

FIG. 1. Dose–response curve for all cancers except leukemia, derived from data on survivors of the atomic bombings in Japan. All data points are numbered in order of increasing absorbed dose (Gy) so that the relative positions of these points can be readily compared with those in Fig. 2.

radiation-attributable lethal cancers (i.e., persons who died from cancer), and N_D is the number of persons irradiated (dosed). This is a toxicological representation of the data, with coordinates identical to those used for the threshold functions developed for early, acute effects of irradiation.

The curve in Fig. 1 uses only the energy density or concentration form of dose D and thus provides no information on the number (mass) of persons at each value of D. For example, the group having the smaller of two values of D could have either a smaller or a larger value of ε compared to the other group, depending on the number of persons at each D value. From Fig. 1 alone, it is not possible to determine the absolute number of attributable cancers to be expected in the population of survivors in this or any other similarly exposed population; the number or mass of the irradiated persons at each data point must be taken into account (see table in Fig. 2).

We can now examine whether the dosimetric quantity ε, into which the mass is incorporated directly, would describe the radioepidemiological data more adequately than does dose and would be more appropriate for making predictions. To do this, the same data used for the function in Fig. 1 were used to formulate the relationship shown in Fig. 2, in which the absolute number of attributable cancers, N_{ca}, is shown as a function of the collective energy ε. For purposes of calculating values of ε, the average body weight of the atomic

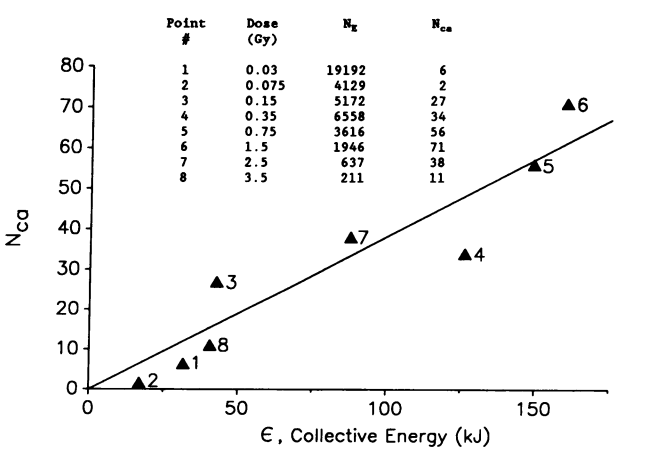

FIG. 2. Same data used in Fig. 1, plotted as the absolute number of excess cancers occurring in a population vs. the collective energy ε (in kJ) absorbed in that population. The absorbed dose, the number of people exposed, and the number of observed cancers are given for each of the (numbered) data points. Note that the order of the points differs from that in Fig. 1 (see text).

**Although the symbol ε is used by the International Commission on Radiation Units and Measurements to denote the amount of energy imparted, it is discussed only in the context of masses of microscopic dimensions.

bomb survivors was assumed to be 55 kg. Accordingly, one person·Gy is 55 J.

Because the curve in Fig. 2 is essential to the primary objective of this paper—i.e., to examine the validity of the nonthreshold aspect of the linear hypothesis—we will discuss the application of this radioepidemiological function in detail.

Comparison of the Two Curves. Although the curves in Figs. 1 and 2 are similar in that both may be assumed to be consistent with linearity, they differ conceptually. Some of these differences are as follows:

The curve in Fig. 1 does not incorporate the absolute number (mass) of persons at any point, as does every point on the curve in Fig. 2.

The curve in Fig. 1 suggests that extrapolation would estimate the probability of a cancer at levels of D below which there was an actual excess. The curve in Fig. 2 does not suggest any such downward extension; because no attributable cancers occurred below some definite value of ε, there is no justification for extrapolation to imply otherwise.

The epidemiological function in Fig. 2 permits the prediction, for any given value of collective energy, of the absolute number of attributable cancers that should be observed. This prediction can be made from the toxicological curve in Fig. 1 only if the fraction responding is multiplied by the population size, thus defining a different ε for each value of D.

All points on the curve in Fig. 1 are independent of mass; all points in Fig. 2 are highly dependent on mass. Thus, because the masses of the exposed subgroups at each dose point usually differ greatly (e.g., shown in the table in Fig. 2), the relative positions of the points in Fig. 2 differ from those in Fig. 1. The sequence of points in the figures differs, and some of the lower points in Fig. 1 are among the higher in Fig. 2 and vice versa.

The significance of the relative position of each point is made more explicit in Fig. 3, in which the curve in Fig. 2 is extended down to the region near the limit of one excess cancer. To demonstrate a potential flaw in such downward extrapolation of the curves in either Fig. 1 or 2, consider a very small extrapolated absorbed dose point in Fig. 1—e.g., below data point 1—and the associated number of persons exposed. When the value of person·Gy is computed and converted to J, the same point might well appear at the location of point A in Fig. 3. Because the number of cancers can take only integer values, this extrapolated point would have no significance.

It is tempting to assume that such a fractional value from extrapolation of the curve in Fig. 1 could become meaningful when applied to a larger population; i.e., if one simply included more irradiated persons. But if this were to be done, point A in Fig. 3 would not remain where it is; it would move higher on the curve because additional collective energy would have been included. This finding implies that the curve in Fig. 2 will essentially always be truncated at the lower end, with no meaningful data points or extensions of the curve below the point at which attributable cancers actually occur.

This last, additional difference further strengthens the value of the curve in Fig. 2 for radioepidemiological purposes and also bears heavily on the threshold aspect of the linear hypothesis. Accordingly, it is discussed next.

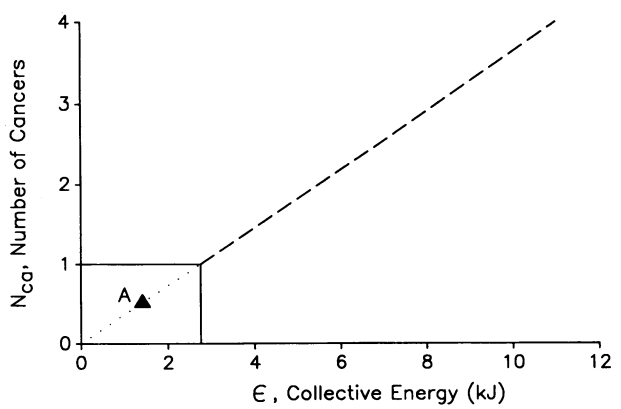

FIG. 3. Initial portion of curve in Fig. 2 constructed by linear extension of the curve to levels well below the lowest actual data point. Rectangular area near the origin formed by the 3 kJ required for one cancer is the region below which extrapolation has no meaning because the number of cancers can assume only integer values. The point marked A is discussed in the text.

RESULTS

A Minimum Energy Requirement for Excess Cancer. The slope of the curve in Fig. 2 permits the calculation of an expectation value for the minimal amount of energy required for one attributable cancer, a quantity we shall denote by ε_0. This slope is one excess cancer per 2.75 (nominally 3) kJ, so that a minimum of $\approx$3 kJ of energy is required for one attributable cancer to appear. (This value for ε_0 is a mean, derived from all data points on the curve.)

Fig. 4, which was constructed from the same data as Figs. 1 and 2, shows that this minimal energy requirement holds over a wide range of doses; i.e., ε_0 is invariant with absorbed dose. Some statistical dispersion occurs around the mean value of ε_0, particularly at the lower three points. However, if the data for these three are combined, the resulting point would lie very close to the horizontal line drawn (not shown in Fig. 4).

Interpretation of the Nonthreshold Concept. The toxicological function shown in Fig. 1 fosters the illusion that even very small doses of radiation can result in a cancer. However, as discussed above, if the dose–response curve is expressed instead in terms of the radioepidemiological relation between the absolute number of attributable cancers and the collective energy ε, cancer occurs only if this quantity exceeds a minimum value, ε_0. Therefore we conclude that the nonthreshold aspect of the linear hypothesis is seriously misleading and probably invalid since radiation-attributable cancers are very unlikely to appear at any given small value of D unless ε at that value exceeds the required minimum, ε_0.

This interpretation of the no-threshold thesis is supported by a basic fact, well known to radiobiologists working with cancer or other quantal responses in either animals or cells, that more subjects must be exposed at low values of absorbed dose in order to be able to observe an excess number of responders (although the procedure is frequently regarded

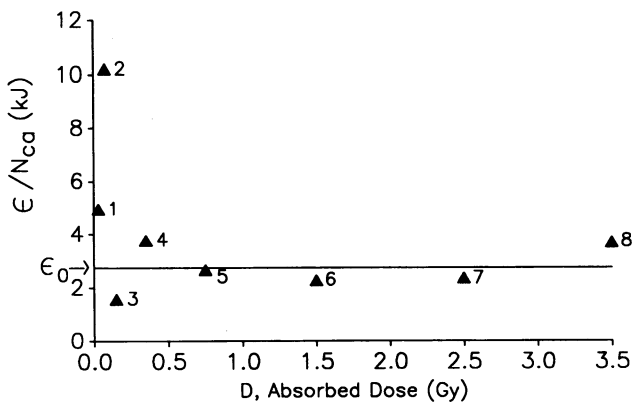

FIG. 4. Collective energy ε_0 (kJ) that must, on average, be absorbed in a population for one excess cancer to occur, as a function of absorbed dose (Gy). It is shown that ε_0 remains constant down to the lowest values of absorbed dose.

only as a means of improving the statistical quality of the data). Also, the fact that the very low-dose groups of people among the atomic bomb survivors were used as "in city" comparison populations indicates a tacit acceptance by those using the data that a level of dose exists below which, to a determinable level of confidence, no attributable cancers can be found. However, there appears to have been little or no overt recognition of the fact that acceptance of this need for more subjects at a low value of D is tantamount to acceptance of the requirement to increase the value of ε until it exceeds the value of ε_0.

Collateral Energy Deposition. The term collateral energy deposition is used here to denote the energy transferred by nondeterministic means to those biological structures and substances that are inert, in the sense that they cannot be causally related to an attributable cancer. The conclusion that there must be a minimal value of collateral energy deposition for one cancer to appear can be appreciated only by use of the concept of collective energy, ε. The reason is that, in terms of absorbed dose alone, the dose to a small target is numerically the same as the dose to one that is very much larger—e.g., a person.

To appreciate the magnitude of the factor that separates collateral and deterministic energy deposition, it is instructive to compare the total amount of radiation energy associated with the linear hypothesis (Fig. 2) with the amount of energy sufficient to initiate the transformation of a single cell. Were it possible to deliver this energy only to the cellular target in a nondestructive but precisely directed way—which is beyond the realm of reality—then this smallest amount might be the energy equivalent of perhaps one to three ionizations delivered to a single gene. This amount would be 1–3 times the mean amount of energy required for one ionization ($\approx$34 eV) or $\approx 5 \times 10^{-18}$ J. This value is smaller by a factor of $\approx 10^{21}$ than the calculated value of $\approx$3 kJ required for cancer induction, as we have determined radioepidemiologically. The result indicates that the large value for ε_0 is due to the collateral energy deposition that is inseparably tied to many, if not most, random processes.

The aim of this paper is not to prove that the probability of attributable cancer is zero at low values of D. Rather, it is to emphasize the repeatedly confirmed radiobiological fact that attributable cancers and other cell-associated quantal responses will be observed at low values of D only if the irradiated mass and thus the resulting ε are relatively large. This means that, in the region in which extrapolation to low doses is practiced using Fig. 1, no attributable cancers will be observed.

DISCUSSION

The Concept of Dose. The basic phenomenon that underlies our principal arguments is a fundamental difference that necessarily exists between the dosimetric practices traditionally used with medications and those developed for the energy deposited by ionizing radiation. In the former case, the dose frequently is given in terms of D. To obtain ε accurately, each subject must be weighed, and, based on this mass, a measured amount of the chemical must be calculated separately for administration to each. In doing this, one is repeatedly reminded that a quantity ε exists and that the severity of effect on the subject depends on its value. However, in radiation dosimetry quite the reverse is true. Although the dose is always given in terms of D, there is no requirement to weigh any subject, and the quantity ε is seldom either defined or used. Thus, there is usually no reason to be aware that such a radiotherapeutically and otherwise useful quantity exists, let alone to conclude that the severity of an effect on an exposed population studied radioepidemiologically should depend on its value. Awareness of the existence and importance of ε would be enhanced were the quantity collective energy to be added to those defined by the International Commission on Radiation Units and Measurements.

Is There a Threshold? We have not called the minimal energy requirement a threshold, partly because ε_0 is not a threshold in the classical sense, but also to avoid implying that the value we estimated might be some universally applicable threshold energy requirement for cancer. The value of $\approx$3 kJ applies only to the data used and the confidence limits that apply to these data and would be different if, for instance, the "cancers other than leukemia" group used were expanded to include leukemia, if the population had been exposed to radiations of higher LET (linear energy transfer), or if the dose rates had been lower. Furthermore, an increase in the confidence level would lead to an even larger value of ε. On the other hand, it is possible to decide on a single value of ε_0, for radiation protection purposes. Finally, the development of the ε–response curve in Fig. 2 is not meant to imply that the use of this function represents the only approach to determining the excess attributable cancers in an exposed population.

Public Health or Medicine? We can now address the questions posed in the Introduction. A most important conclusion that we reached in this work is that a strong need exists for a fuller recognition of the fact that the "low-level" exposure associated with radiation protection is solely a public health and epidemiological problem and should be so analyzed (it is only the high-level exposure associated with radiotherapy and accidental overexposure that constitutes individual-oriented medical problems). It is unfortunate that an accident of history, which caused the toxicological model to be applied to epidemiological problems, led to the present efforts to determine, with great accuracy, the dose and thus the presumed risk to each individual. This practice conveys the impression that "risk" can be treated as if it were a measurable property of the individual, when, in fact, it can only be measured as a property of an exposed population.

Medicine cannot be made to do the job of public health including epidemiology by extrapolating the response of an individual to a population. Conversely, epidemiology cannot be made to do the job of medicine by extrapolation of a population response to the individual by using concepts of risk or probability. In the annual publication *Accident Facts* (7), neither risk nor probability is mentioned. Perhaps the emphasis in radiation protection and the radioepidemiology on which it depends should therefore shift decisively away from attempting to determine with ever-increasing accuracy the risk to each individual, with the implication that the aim is to limit the amount of this abstruse quantity to the individual, and emphasize instead the estimation of the actual number of attributable cancers (or other effects) expected to occur in unidentified and unidentifiable persons in a particular exposed population.

Limits of Reciprocity. The fact that $\approx$3 kJ of collective energy required for one cancer to occur in a population would certainly be acutely lethal if delivered to one person demonstrates that the reciprocity between m and D in Eq. 1 breaks down at large values of absorbed dose to one or a few persons. Furthermore, if it is assumed that no one will die of acute radiation injury at doses of 2 Gy or less, then reciprocity for this effect would break down when $\approx$25 persons have received this dose. At the lower-dose end, no protective mechanisms have as yet been shown definitely to exist. Possible mechanisms include adaptive or hormetic processes and the presence in the body of killer cells or other agents that may be able to seek and destroy carcinogenically transformed cells.

The futility of concern for the single individual exposed to low-level radiation is suggested by the fact that an individual

receiving 0.1 cGy is below the average energy requirement for a cancer by a factor of some 50,000. The findings reported here also demonstrate the inherent futility of epidemiological studies on populations for which the value of collective energy is less than ≈3 kJ in attempting to settle the issue of a possible excess incidence at such low levels of exposure.

The definition of low-level exposure to radiation as a low dose to the exposed individual(s) might better be extended to include the condition of less than ε_0 kJ to the exposed population.

ε in Radiobiology. In cellular radiobiology, no attempt appears to have been made to use or even to recognize the existence either of the cell analogue of collective dose—i.e., cell·Gy—or of collective energy. In almost all radiobiological experiments using populations of one cell type—e.g., in tissue cultures in which attributable quantal responses of various types (e.g., lethality, mutagenesis, malignant transformation, or chromosome aberrations) are observed—it is, in fact, a kind of cellular epidemiology that is being practiced (8, 9). To make such studies useful as the cellular analogs of human radioepidemiological studies, it is necessary to simulate a situation similar to that which existed with the atomic bombings—i.e., one that has resulted in some (very large) number of dosed cells distributed over a range of dose intervals. The validity of the cell analog of the epidemiological form of dose–response curve (Fig. 2) and the constancy of ε_0 as a function of D (Fig. 4) could thus be tested.

Chemical Carcinogenesis. The concept of collateral agent deposition appears to be a general one. It may well apply to chemical carcinogenesis in which, especially in low-dose exposures, large amounts of agent must be distributed over many persons to result in any significant probability that one genic target, capable of triggering the expression of a cancer, will absorb a sufficient amount of agent to be transformed. The collective amount of agent, and not its concentration, would appear to be the significant variable in the context of carcinogens.

Helpful comments on this paper were provided by Drs. M. A. Bender, L. Wielopolski, E. P. Cronkite, L. E. Feinendegen, R. G. Fairchild, and C. M. Meinhold. This work was supported by the Office of Health and Environmental Research of the U.S. Department of Energy under Contract DE-ACO2-76CH00016.

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