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RISK EQUIVALENT OF EXPOSURE VERSUS DOSE OF RADIATION

Victor P. Bond, M.D., Ph.D.

Radiation is perhaps unique among all agents of interest in the Health Sciences, in that it alone is both a therapeutic agent for the control of cancer, and an essentially ubiquitous environmental agent with a potential for increasing the cancer rate in human populations. Therapy is accomplished with high-level exposure (HLE) to radiation, i.e., large doses are delivered locally and in a controlled fashion in order to effect control or a cure. Thus it conforms to the concepts and approaches of pharmacology, toxicology, and therapeutic medicine. Only one function, that which relates the object-oriented and non-stochastic independent variable organ dose to its effect on a cancer or an organ is needed to estimate the probability, P_2, of a quantal response. Only P_2 is needed because P_1, that the cancer slated for such treatment will receive some amount of the agent and be affected to some degree is effectively unity.

The health problem involving low-level exposure (LLE) to radiation, in contrast, is not at all analogous to those of pharmacology, toxicology, and medicine. Rather, it presents a public health problem in that it is a population, albeit of cells, that is exposed in a radiation field composed of moving radiation particles, with some consequent low-order carcinogenic or mutagenic risk. During exposure, energy is transferred to cells stochastically (i.e., through random processes) with respect to which cell is hit and how much energy is transferred, rather than in the ordered fashion characteristic of HLE. Under these circumstances the use of dose as an independent variable is proscribed because the amount of stochastically transferred agent is beyond human control. Thus, the concepts, quantities,

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and terminology applied to low-level radiation must be modified from their present orientation toward pharmacology, toxicology, medicine and "dose" to conform to those of public health and accident statistics, in which both P_1 and P_2 for the exposed cells must be estimated. The unique opportunity afforded by radiation to develop quantitatively the relationships between public health and therapeutic medicine is taken advantage of. A principal point I shall make is that the so-called "linear, no-threshold dose-response" curve, characteristic of LLE and accident statistics only and a central pillar in radiation protection philosophy is not a "dose-response" curve in any sense that a physician, a pharmacologist, or a toxicologist would accept. Rather, neither the "dose", nor the "response" mean the same as do these terms as used in medicine.

The linear no-threshold, or proportional relationship is widely used, as is seen in the way in which the values for cancer risk coefficients are expressed--namely, in terms of new cases, per million persons exposed, per year (or per lifetime), per unit absorbed dose (rad) to the relevant organ. This implies that the underlying relationship is proportional, i.e., "linear, without threshold." Why is such a relationship assumed? One reason derives from data such as those shown in Figure 1[1] for breast cancer in the human female. These values are the observations made on women given exposures of the order of 3 rad approximately weekly, for the fluoroscopic monitoring of pneumothorax therapy for tuberculosis (the conceptually appropriate replacement for dose on the abscissa is introduced later). Here a linear rise in excess cases of cancer appears to fit the data. Nonetheless, such data in themselves do not justify the adoption of a proportional relationship, because the limits of error are so large that several other kinds of relationships could be drawn. Other reasons for assuming linear, no-threshold, relationships apply generally in radiobiology, examples of which I discuss next.

RADIOBIOLOGICAL BASES FOR PROPORTIONAL CURVES

Figure 2[2] shows the percentage of cells with chromosomal aberrations versus the absorbed dose. The coordinates are the same as those used in Figure 1. The upper curves are for high-linear energy transfer (LET) radiations; the lower two curves are for low-LET radiations. The upper curves are linear and without threshold; on the other hand, the low-LET curves are curvilinear, although they may well have an initial linear segment. Moreover, if the higher doses for the low-LET radiations are given at lower and lower dose rates, the upper part of the curves descend toward the lower axis and eventually become linear, as shown by the dotted lines in the figure. The net result is that, with LLE to radiations of all qualities, we see a fan-shaped set of curves, all proportional.

The same type of results are obtained in a number of other cellular systems, e.g. for a color mutation in the cells of the stamen hairs of the plant Tradescantia, for other cell mutations and for cell lethality, and for many types of animal tumors, as illustrated in Figure 3. Thus, there is little doubt that such curves for "single cell-originating" endpoints, at least the initial low-exposure portions, do represent linear no-threshold relationships.

The next question is, what does this linearity mean? Figure 4 represents one of several similar curves which are found in the literature. Plotted with the same two coordinates (i.e., absorbed dose on the abscissa, and "effect" or "response" on the ordinate) are two "dose-response" curves for radiation that appear to be quite different. One is the threshold-type curve, familiar in

pharmacology, toxicology, and medicine. The accompanying curve has no threshold and is linear. The mode of presentation conveys the incorrect impression that these completely different relationships are simply variations of one function. The implication often made is that animals whose responses follow a "linear, no-threshold" plot are much more sensitive at low doses than are those whose responses show a threshold-type of relationship. Such implications simply are not correct. The two curves are very different and have little or nothing in common.

The genesis of biological damage of any kind from radiation lies in the interactions that take place when cells are exposed to a field of radiation. Organs can be viewed simply as an "organized" population of functional cells. A radiation field is composed of charged particles moving rapidly. The interaction of these moving particles with cells, with the sudden, rapid transfer of discrete amounts of kinetic energy, this potentially harmful agent produces biological damage. It is important to emphasize that these interactions are stochastic in nature. In other words, the primary damage is the result of "micro accidents" involving a cell and a moving particle. Here the relevant part of the cell, the target-containing volume (TCV), is taken to be the nucleus which contains DNA.

In the high-level exposure (HLE) region, that is, the large organ absorbed dose familiar in radiation therapy and with large whole-body exposures to radiation, every cell in the radiation field, in an organ or in a cancer, is hit many times (i.e., the number of interacting particles exceeds substantially the number of exposed cells). Under these conditions, the dose to the cell derives from multiple hits of random size. This tends to even out the amount of energy per unit mass received by the cells and by the organ, and

severity of injury to both. Therefore, the average dose to the cells is practically the same as the dose to the entire organ, i.e., the energy density or energy per unit mass. Accordingly, the fraction of organs that respond quantally, i.e., show an all-or-nothing change, such as from a functional to a non-functional state, increases only because the average organ (and cell) dose increases. The resulting function, as often seen in medicine and toxicology, is curvilinear and threshold. Thus, in Figure 4, the coordinates are correct only for curve a.

With HLE, one is interested primarily in acute or chronic organ failure or in controlling the growth of a cancer. Both of these result from direct and lethal damage to a large fraction of the cells that nominally received equal doses. Thus the "target" structure of interest is the organ, so that use of the average absorbed dose to the organ is appropriate. It was in this context that radiation "dose-response" curves were developed (e.g., curve a, Figure 4). The difficulty arose when the use of absorbed dose and relative biological effectiveness (RBE) was extended down to the LLE region.

A very different situation pertains in the LLE region. Here, the number of moving particles is relatively small compared to the number of exposed cells. Consequently, with increasing exposure of the organ, first one cell is hit, then a second, a third, and so forth. So, rather than every cell being hit many times, as with HLE and acute organ effects, with LLE only a small fraction of the cells within the organ is hit. Thus the absorbed dose to the organ increases with exposure only because the energy per unit mass of tissue goes up as a result of the number of cells hit increasing, and not because the mean energy per hit cell is changing. Further, in these interactions, there is a sudden, single transfer of energy in discrete amounts that vary substantially from cell to cell. However, only a few damaged or

killed cells cannot cause the severe early effects on organs that have been described for HLE. Therefore, the biological target of interest becomes the cell, and the endpoint of interest is the "single cell"-originating effects, e.g., carcinogenesis and mutagenesis. By abnormal proliferation and invasion and displacement of organs, such damaged cells can cause functional failure of an organ and therefore, of the organism. Therefore, it is the distribution of cell hit sizes from a given exposure that becomes the focus of interest. The hit size to the cell (eukaryotic for present purposes) is the key. The cell is the elemental unit of life, being the smallest unit capable of quasi-independent existence and of reproduction.

Injury that may be sustained by cells as a result of these random doses from micro accidents depends on two separate and independent factors: 1) the probability, P_1, of being physically hit, without regard to the severity of the biological consequences; and (2) the probability of biological injury severe enough to induce a quantal response[3] e.g., malignant or genetic transformation.[3] The total risk to a cell is the product of P_1 and P_2. Both the probability of being hit (P_1), and the total risk (the product of P_1 and P_2) are correctly represented by a linear, no-threshold relationship with exposure on the abscissa. However, P_2 alone is not (see below).

THE MACRO ACCIDENT ANALOGY

The situation I described for cells exposed to LLE is analogous to that encountered in motor vehicle accidents familiar to everyone. Indeed, vehicle accidents serve as a good model because they occur quite frequently (Accident Facts),[6] because they are familiar, and because the harmful agent is kinetic energy (as it is for radiation). In traffic accidents, some fraction of the kinetic energy is transferred to an organ or organs. The small fraction of

the exposed individuals unfortunate enough to be involved in the collisions are damaged to a degree that depends on the amount of energy stochastically transferred. With this analogy, we should be able to examine, in perhaps more readily understandable terms, the basis for the linear, no-threshold relationship used in LLE to radiation.

Low-level exposure to radiation resembles macro accidents, essentially because all casualties are hit only once during a given exposure. Thus, the "multiplicity of hits" on all targets, characteristic of HLE to radiation, is virtually nonexistent. Thus, what is simulated by macro accidents is the single hits on the cell that can lead to late, single cell-originating effects, and not the multiplicity of hits per cell and the multicell effects that produce acute organ failure and death.

The table gives statistics for a typical year in the United States, during which approximately 200 million individuals are exposed to moving vehicles. The fact of being exposed does not equate to receiving a dose. Only 5 million people per year (1/40th) unfortunate enough to be in an accident become "dosed" with a transfer of energy, and thus injured to some degree. Of those hit, dosed, and injured, only about 1 in 100, about 50,000 per year will respond quantally, i.e., be killed. The two independent probabilities, P_1 and P_2, discussed above, are involved (but now for the organ, and not the cell). The product of the two probabilities, equal to the total average yearly risk of dying from a vehicular accident, is (1/40 x 1/100), or 1/4000. Thus, three distinctly different concepts are involved: being exposed to hazardous objects; being hit, dosed and injured in an accident; and being killed.

Those exposed and the number hit and killed per year are of interest to the Public Health Officer or others who deal with accident statistics, but only as nameless individuals, or "statistics". The physician plays a very

different role, seeing those individuals who are hit, dosed, and injured, and these identified individuals are given medical attention. The physician may have little or no interest in either the number of vehicles on the road at the time of the accident, the risk of a patient having been hit and dosed, or the magnitude of the dose, if it has been determined. The physician evaluates the severity of the injury directly in the affected individual, based on a variety of medical and laboratory findings. These findings allow an assessment of the probability that the individual may succumb to the injuries caused in the accident, i.e. experience a lethal quantal response. Implied are functions for the severity of effect on an organ, against the probability of a quantal response, which can be constructed. Only rarely is such a relationship formalized.

The annual "Accident Facts" booklet[6] contains only tabular statistics, and mentions neither functional relationships nor "dose". However, several formal relationships may be developed directly from these data. The first to be considered is shown in Figure 5. The lower flat curve A, with a slope of zero, represents the manner in which the statistics are presented in the booklet. This curve gives the number of people killed per year, which remains remarkably constant despite the widely varying characteristics of drivers and of driving conditions. The same type of curve also could be presented for the number of persons hit and injured per year.

A "linear, no-threshold" relationship can be obtained from curve A simply by changing it into the integral or"cumulative" form, shown as curve A' in Figure 5. Thus "linear, no-threshold" summation curves can be constructed easily from statistical data showing the number or fraction "dosed", injured, or killed per unit time, as a result of stochastic collisions with moving objects.

The abscissa for these proportional curves, unlike that shown for the similar curve in Figure 4, is not "absorbed dose" nor a dose of any kind. The correct quantity is the "field-oriented quantity" exposure, expressed in units of time, e.g., years. The strength of the exposure "field" is important, which is given by the mean number of vehicles per unit presenting area "seen" by the exposed individuals per unit exposure, or the "fluence rate", $\dot{\Phi}/t$. However, since the mean fluence rate of vehicles does not usually vary greatly from year to year, this can be regarded as constant. Thus the exposure time, e.g., in units of years, which is used as the independent variable in tables of accident statistics, is also the fundamental independent variable (abscissa) in Figure 5. If the field strength $\dot{\Phi}/t$ varies, then the product of the field strength and the exposure, $(\dot{\Phi}/t)t = \Phi$ can be used instead.

The linear, no-threshold relationships inherent in such data are not dose-response curves. Rather, they are exposure-response functions. Such curves are not seen normally, because the statistics on exposure, injury, and death are adequate for purposes of description and prediction, making functional relationships between the tabulated data unnecessary. Also, functions with zero slope, or cumulative "linear, no-threshold" relationships (Figure 5) are too trivial to warrant plotting.

However, the "linear, no-threshold" relationship, alone, is not adequate to describe the chain of events leading from exposure to accidental death. Missing is the concept of the amount of agent transfer and of the consequent severity of injury, which must be invoked whenever exposure with a non-zero probability of an interaction occurs. Only by this additional consideration may the fraction who die because of their injuries be derived analytically from the fraction of those hit, physically insulted, and affected. This nonempirical approach is of little or no value in handling macro accidents other than for formal description and in research, because the "latent period"

between an accident and decisive evaluation of the final outcome is usually short (days to at most weeks). However, I discussed it because it is necessary to predict accurately the number of casualties from micro accidents involving energy transfer to cells and the potentially consequent mutagenic and carcinogenic effects. The small incidence and long latent period (years) between mutagenic or carcinogenic transformation and the expression as cancer precludes using early observations of any type for prediction of the outcome. Thus indirect means, described later, must be employed.

In addition to evaluating the probability of dying from a vehicular accident solely on the basis of a clinical evaluation of the severity of injury, in principle, one could place transducers in various locations on all, or some representative fraction, of those exposed. The transducers, which could be read immediately after the accident would show the amount of energy transferred in the collision. Thus, the unpredictable distribution of energy deposited in the individual hit becomes a known distribution, suitable for prediction of the fraction of injured that will die, i.e., respond quantally.

We could then develop a function for the probability of death as a function of increasing hit size, termed a "hit size effectiveness function" (HSEF), [7-11] to produce threshold functions similar to those shown in Figures 4 and 6 (the abscissa given as impact velocity can readily be transformed into energy absorbed per unit mass, the hit size). The linear curves shown on the probit plot in Figure 6 would become curvilinear, as curve a in Figure 4, if the ordinate were an arithmetic scale instead of a probability (probit[5]) transformation. The curves shown in Figure 6 were obtained during research on accidents with animals.

We must now discuss further the conceptually appropriate name for the amount of agent transferred stochastically. It is true that only the amount of agent transferred is important in determining the fate of the individual

organism, and not whether it was delivered in a stochastic or orderly fashion. The prizefighter's body cannot distinguish an injury to an organ from blows delivered intentionally during a fight from an identical but accidental injury. Further, the amount of energy transferred is conceptually an "object-oriented" quantity, and can have the dimensions of absorbed dose, energy per unit mass. There is a remarkable similarity between the HSEFs in Figure 6 and the dose-response relationships familiar to pharmacologists, toxicologists, and physicians. In fact, the macro hit size-response curve for an organ, in principle can be identical in shape to the curves for the planned effects of drugs in pharmacology and toxicology. Thus the arguments for referring to the amount of agent transformed as a dose may be considered compelling.

Nonetheless, the term dose, in the macro world, has long been usurped for situations in which the agent is given in an ordered fashion, as is done in pharmacology, toxicology, or medicine. This translates into the key and inalienable criterion of dose--it must be usable as an independent or controllable variable, through which the physician can be assured that the desired severity of effect will not be exceeded. An amount of agent transferred stochastically does not meet this criterion. Thus, the amount of energy transferred accidentally and stochastically in a macro accident will not be referred to as "dose". Rather, it will be referred to here, as it is with cells and microaccidents, either as the amount of agent transfer, the hit size, or sometimes the amount of physical or biological insult*.

The HSEF can be used quite simply for any given individual exposed in a field of moving vehicles. P_1 is the fraction of individuals hit per exposure, i.e., the probability of a hit per person exposed. The HSEF then gives the

*Energy cannot be measured directly but only in terms of the severity of effect, in this instance number of ionizations per TCV. If a "tissue equivalent" phantom chamber is used for such a measurement, the reading can be regarded equally well as a measure of the severity of the initial physical or biological insult (effect).

probability of a quantal response, i.e., death, for a given determined value of hit size, and thus is P_2. The total risk for the given exposure is then simply $P_1 \times P_2$.*

This approach must be altered somewhat if the amount of serious damage to an entire subpopulation of exposed and hit individuals, with a wide distribution of hit sizes as depicted in Fig. 7, is to be evaluated. For a typical group of accidents, the distribution of hit size is skewed to the left because most accidents are minor[12]. Also shown in the Figure as curve B is an HSEF. Multiplying every point on the hit-size distribution A, by the corresponding point on the HSEF B determines, at every hit size, the fraction of individuals hit that will die. The result is the shaded distribution, marked "area equal I_q". The area under this distribution represents the expected incidence of deaths among those who have been hit, under the given exposure conditions.

In more concrete terms and with reference to Table I and Figure 7, the area under the distribution A represents the total fraction of the 200 million exposed, namely, 5 million, who would be expected to be hit and injured in vehicular collisions. Multiplying the distribution A by the HSEF B yields the shaded area, marked I_q, equal to the 50,000 expected to die, out of 5 million injured per one-year exposure. The total average risk is then $(5\times10^6)/(200\times10^6) \times (5\times10^4)/(5\times10^6) = (1/40\times1/100) = 1/4{,}000$.

Alternatively, the area I_H (Figure 7) could be normalized to unity, to obtain the fraction I_q/I_H, which would not vary under a constant set of driving conditions. Then for any given exposure, I_H need only be multiplied by this fraction in order to obtain I_q.

*In pharmacology or toxicology in which an agent is transferred to induce a desired biological response, P_1 is unity. This obviates a need to consider exposure to external hazardous objects, so that only P_2, the risk from a dose, must be evaluated.

The concept of linear energy transfer (LET)* or radiation quality, may be illustrated in the context of vehicular accidents. In principle, it means that moving vehicles in a given "field" may be capable of transferring a different average amount energy than are those vehicles comprising another field. Two principal factors enter: the average mass of the vehicles, and their average speed. If the average speed remains essentially constant, then, because a large vehicle can transfer much more energy than a compact car, the average severity of the accident and the injury is likely to be greater. Another way of accomplishing the same thing is to keep the mix of types of vehicles the same, but change their average speed. Then faster vehicles will transfer more energy and cause more injury than will slower vehicles of the same type. This collective agent transfer capability can be termed the "quality" of the mix of vehicles, and their velocities; the higher the LET of the vehicles, the larger can be the mean hit size from collisions.

The importance is that a given amount of exposure results in a hit-size distribution, shown as curve A in Figure 7. A distribution for "high-LET" vehicles would lie to the right of one for "low-LET" vehicles, so that the mean LET would become larger. If low-LET vehicles were taken as a "standard" LET mix, then the "relative biological effectiveness" (RBE) of higher-LET mixes could be related simply by a dimensionless number, e.g., a higher-LET mix could be two, three or more times as effective in causing deaths, as would be the standard. These differences in effectiveness between high and low-LET vehicles are basic to the understanding of the "relative biological effectiveness" (RBE) concept for radiation, and also of its relationship to the HSEF. The different LET distributions overlap substantially, suggesting that the RBE in large part is due to the fact that any larger hit size, with

*A more accurate designation would be energy transfer capability (ETC).

minimal dependence on the type of vehicle from which it was derived, is more effective than is a smaller hit size. However, if the overlapping distributions (Figure 7) are viewed simply as individual hits rearranged in order of increasing hit sizes, with some of a given size coming from vehicles of different mean LET, then one sees the basis for constructing an HSEF, such as shown in curve B in Figure 7.

Thus the RBE is conceptually a measure of the effectiveness of accidents resulting from exposure to different, more or less well-defined types of vehicles under stated conditions, or of different defined types of radiation particles in micro accidents. Yet in either exposure, the distributions of energy transfers from the moving object are broad and overlapping. However, if these distributions are multipled by the HSEF as shown above, we can predict the expected number of quantal responses from the population having been subjected to a given exposure. Thus, the HSEF can obviate the need for the RBE concept.

This discussion and Figure 6 are oversimplified in that usually an HSEF for only a single organ is considered. However, the various organs and regions of the body vary in sensitivity. Further, the severity of damage for a given amount of energy transfer will depend on the shape of the physical surface struck (flat, jagged, or pointed). For a more complete evaluation, several HSEFs would have to be invoked, one for each of the several principal conditions. Nonetheless, even with myriad different driving conditions and geometries of collision, the yearly mortality rate remains remarkably constant unless there is some marked generalized change, including a revision of the speed limit, use of seat belts, and gas shortages. The very large numbers of accidents and victims involved tend to smooth out and average these differences so that deaths per unit exposure can remain essentially constant.

For a given exposure, this expected excess incidence of deaths in a population, and the risk of dying for the average individual, are numerically equal (i.e., the risk is simply the value of the excess incidence, or the expected incidence, normalized to a "population" of one person). Generally, a given probability or risk value for a given health detriment in an individual is nothing more than the equivalent of, or a synonym for, the expected excess incidence of that detriment in the exposed population.

THE MICRO ACCIDENT ANALOGY

Micro accidents are charged particle-cell interactions in biological systems which represent the only means by which energy is transferred from the radiation field to a cell TCV (the nucleus). However, we must ask why is the term absorbed "dose" to the organ now used as the abscissa for the initial, assumed linear, non-threshold part of a dose-response curve, if the correct parameter is not cell hit size, or dose.

The answer is that the idea of absorbed dose to the organ, the total energy absorbed divided by the mass of the organ, or the average energy density, was developed earlier when radiotherapy and other forms of HLE were the main interest. When the late "single-cell"-originating effects became of concern with LLE, at first it was not recognized why the same quantities should not be applied. Yet, as discussed, the concept of dose to the organ, in LLE, is misleading if the organ is recognized as an organized population of vital cells.

The principal single-cell endpoints of concern are carcinogenesis and mutagenesis. Disease in offspring due to mutations undoubtedly originate in a single cell. Moreover, much work has shown that many cancers, whatever their origin, are monoclonal in nature. This is essentially tantamount to saying that the development and overt expression of a cancer depends for its origin in a malignant transformation in a single cell.

The importance of this finding is that, for LLE, the biological "individual" of interest, is neither the organ nor the organism, but the single cell. Thus the hit size to the cell, and not to the organ as a whole nor to an entire individual, is the applicable independent variable.

It is appropriate to see what the conventional absorbed dose to an organ means, in terms of energy absorption in the individual cells in an organized population of cells exposed to radiation. The approach is shown in Figure 8, in which the absorbed dose to the cell population reduces simply to the product of the fraction of exposed cells that are hit, the mean hit size, and number of hits per cell. Thus it is a composite quantity that incorporates, and thus confounds, the variables related to P_1 and to P_2. Because the expectation value of the mean hit size becomes constant with LLE* (Figure 8), the mean absorbed dose to the cell population is then proportional to the fraction of exposed cells hit. This fraction decreases as the absorbed dose decreases, but only because unhit or "zero-dosed" cells are increasingly included in the averaging process. Further, with respect to the last equation in Figure 8, the risk ratio I_H is well known to be proportional to the product of the field strength ϕ/t and the exposure, t. Thus absorbed dose is proportional to, and in fact is a dependent variable of ϕ (or t, if ϕ/t is constant).

In other words, "absorbed dose" to the organ, which is frequently shown as the abscissa of a radiobiological "dose-response" curve for LLE, in effect, ceases to be a dose at all. Rather, as with vehicular accidents, it becomes either particle fluence, a field-oriented quantity, or its proportional

*This is because the small fraction of exposed cells that are hit have received only one hit of randomly determined size, so that the expectation value of the mean remains constant.

alternative, the (fractional) number of exposed cells that has been hit, an object-oriented quantity that reflects also the severity of organ damage. Also, the ordinate is quite different from a pharmacologic type of dose-response curve or an HSEF, in which the increasing fraction of cells responding with increasing, graded organ doses is in groups of cells with nominally equal doses. In contrast, the ordinate with the linear, non-threshold curve, quantally responding is the fraction of cells with unequal hit sizes encompassing a wide distribution, as was shown with motor vehicle accidents. Thus, the initial proportionality is explained on the same basis as is the proportional cumulative curve for vehicles (Figure 5).

Hence, the proportional curve and the threshold non-linear curves for radiation exposure express completely different situations. None of the proportional curves can be used to state "any amount (dose) of radiation, no matter how small, can be harmful or lethal", simply because "dose" is not the independent variable. However, since one of the quantities appropriate for the abscissa is time, virtually no time interval is too short for a micro accident to occur during an exposure. An exposure at any fluence rate, or for any length of time, may or may not be associated with a cellular accident. However, if an accident occurs, it is the large hit sizes to cells that are responsible for a quantal response.

In light of this reasoning, micro accidents from LLE radiation can be handled in a manner quite analogous to that described for macro accidents. Referring to Figure 7, curve A becomes a distribution of hit sizes in a similar cell population exposed in a field of low-LET radiation. Curve B shows an HSEF for cell transformation. If the hit-size distribution in panel A is multiplied by the HSEF in panel B, the resulting distribution denotes those hit cells that have shown a quantal response. The area under this distribution gives the total expected excess incidence (risk) of quantal response, for a given amount of exposure.

Although with vehicles the use of hit size and an HSEF for individuals (and organs) was essentially of academic interest, the process in the radiation-hit cell analogue is not an idle exercise. The reason is that the causative agent that may have transformed a normal cell into a cancerous one cannot be established. No such transformation, nor any suspected "causative" agent can be linked definitely to any clinically observed cancer; cancers do not have a "marker" indicating what the causative agent was. Further, the human populations exposed to LLE, that need radiation protection, cannot in general be observed adequately epidemiologically. This is because of the long latent period between exposure and the expression of overt cancer, the small risk of cancer, low exposure limits, and the relatively small population sizes which do not permit adequate statistics to be obtained. To estimate the expected excess cancer incidence at the time of exposure, there is an advantage in using the cell hit-size and HSEF approach, for which the absorbed organ-dose-RBE method is a poor substitute and conceptually much less appropriate.

Figure 9 shows an HSEF, obtained for the same set of data given in Figure 2 (see below for derivation). As noted above for macro accidents, the HSEF for the cell is some ways analogous to the dose-reponse curves that are used commonly to describe the probability of a given effect in individuals following the controlled administration of a specific amount of agent in pharmacology and toxicology. In other words, the curve relates the probability of a quantal response to the cell hit size (often mistermed "dose"), received stochastically. The first derivative of this curve yields an indication of the distribution of sensitivities of different individuals. This is true of either the HSEF for cells, or the dose-response function in pharmacology and toxicology.

In contrast to that for the HSEF is the first derivative of the so-called "dose-response" relationship for LLE to radiation, i.e., the linear, no-threshold curve A in Figure 4. The first derivative of this curve is a flat, zero-slope curve, erroneously suggesting that all individuals have the same sensitivity. In fact, this derivative indicates no more than the probability of a cell being physically hit or injured with LLE per unit exposure--a constant. Further it indicates that the abscissa for the linear, no-threshold relationship cannot be dose, but rather the exposure, expressed either as exposure time, the particle fluence, or the incidence of hit and injured cells (I_H). Therefore, the essential difference between the familiar linear-no threshold curve and an HSEF is that the former represents the probability (P_1) of a physical event that deposits energy in the cell GSV, while the HSEF provides P_2, the probability that the deposited energy will cause a quantal biological response of the cell.

I shall describe briefly how an HSEF for cells can be estimated. Since the distribution of energy depositions leading to a cell dose cannot be measured directly in vivo, indirect means must be resorted to. A phantom cell can be used, which permits the determination of the fraction of cells hit, and the distribution of hit sizes in those cells. A suitable cell phantom, devised by Rossi[15], consists of a spherical proportional counter filled with tissue-equivalent gas. If the pressure is reduced appreciably in the chamber, then the cell phantom will simulate the amount of energy transferred to a cell, in terms of responses per hit by a charged particle. Thus the number of hits in this phantom, i.e., in this surrogate "cell", can be enumerated, and the distribution of hit sizes can be recorded. A scaling factor then converts

hits per phantom into hits per living cell. From this value, the area under the distribution in panel A of Figure 7 is obtained, yielding directly the (fractional) number of cells hit per exposed cell. This is the probability P_1.

The determination of an HSEF requires a large amount of quantitative biological and microdosimetric data from radiations covering a wide span of LETs. Having obtained the overlapping hit-size distributions and their relative effectiveness for radiations of different quality, a computer-assisted iterative procedure estimates an HSEF[7-10]. Thus the HSEF best represents the entire set of data shown in Figure 2[7-10]. HSEFs similar to that shown in Figure 9 have been developed in our laboratory for several different mutations detectable in the individual cell, for cell lethality, and for other endpoints (Morstin, K. personal communication).

The degree of severity of biological effect on the cell depends not only on the hit size, but also to some degree on the pattern of energy deposition ("track structure") within the sensitive target volume. A single alpha particle traversing a cell will leave a track composed of rather tightly clustered ions, while the number of ions from a low-LET radiation will be almost uniformly dispersed. With a low-level and low-LET exposure, however, a single hit usually deposits far less energy than transferred in the passage of an alpha particle. This means that the different hit sizes in fact do relate to different radiation qualities. For a given cell hit size, there may be contributions from radiations of several different qualities. The derived effectiveness at a given hit size thus may be the mean value of such contributions.

The empirical derivation of the HSEF, from observed cell responses insures that all assumptions as to physical or biological mechanisms are included, as well as the contributions from a very wide distribution of hit sizes. Thus it yields directly the same answers that the RBE can only approximate indirectly.

SUMMARY AND CONCLUSIONS

Although this material on low-level radiation is conceptually correct, the work is in the research stage and not yet developed for application. When it is adequately developed it might replace current concepts of RBE and of the quality factor, Q, for LLE. Similarly, it could replace absorbed dose, the standard radiation, dose-equivalent and rem.

I have suggested that the HLE encountered in cancer therapy and in radiation accidents has so little in common with LLE and its late effects, carcinogenesis and mutagenesis, that the two kinds of exposure should be separated completely. For purposes of radiation protection, the term exposure should completely replace the word dose.

As noted in the introductory paragraphs above, HLE is closely allied to pharmacology and toxicology, while LLE is not at all analogous to these disciplines. Rather, it represents a public health problem in that it is a population, albeit of cells, that is exposed to radiation particles. It should therefore be emphasized more that the concepts, quantities, and terminology to be applied to low-level radiation should be modified to conform to those of public health and accident statistics, in which the health of a population, whether of cells or humans, is the focus of attention.

It is often stated that low-level exposure to low-LET radiation is "cumulative", a term that is particularly frightening to most people. This follows from the erroneous interpretation that, if one is exposed in a low-level radiation field, such as natural background radiation and frequently in some diagnostic radiology procedures, there is some small amount of "radiation", or a small effect produced in cells which can "add up" (i.e., be cumulative), and ultimately produce a cancer.

We can best show that the above thesis is not true by again invoking the automobile analogy. Certainly all of us are exposed, day after day, to the risk of an auto accident. However, exposure alone causes no harm at all, so that nothing can accumulate. Even if one is in an accident of minor-to-moderate severity, there is nothing substantive to accumulate, i.e., the energy transferred is quickly dissipated. Also, healing is complete so that no damage accumulates that can change the risk of further exposure. However, what can and does accumulate over time is the number of casualties and deaths. Thus the "cumulative effect" is in the defined <u>population</u> and not in the exposed individual.

This is not to say that, with LLE, injury to some cells can occur in the small fraction of cells hit during a given exposure. However, an accumulation of damage does not occur if the mean time between successive hits in a cell is long enough for repair processes to be effective (a condition characteristic of LLE). If a hit was not large enough to cause a transformation (it must be understood that misrepair can cause cell transformation), the evidence is overwhelming that full recovery ensues rapidly, and no lasting subcellular injuries accumulate. Because of this fact, and as the findings from

epidemiological and experimental data show, cell transformation resulting in a cancer is quite rare, so that only an extremely small fraction of exposed individuals will develop cancer as a result of even a rather high-level exposure to radiation.

The confusion as to whether the linear-proportional or the threshold-curvilinear function (Figure 4) describes LLE to radiation appears to lie in large part in the fact that, with LLE, absorbed dose becomes a composite and therefore confounded quantity, the two constituents of which must be decoupled for a complete description of the risks involved. Only then does it become clear that one needs to evaluate both P_1, the probability of a cell being hit and injured during an exposure, and P_2, the probability of a cell quantal response from that hit. P_2 is the risk resulting from the amount of energy transferred to the cell, and not to the absorbed dose to the organ, from which neither P_1 nor P_2 for the cell are derivable. For any given exposure the product of P_1 and P_2 yields the risk of cell transformation due to the exposure, the product needed for purposes of radiation protection. The failure to distinguish clearly between the <u>risk equivalent of exposure</u>, i.e., that of the late single-cell manifestations of cancer and genetic effects stemming from the exposure and $(P_1 \cdot P_2)$ for cells, and the <u>risk equivalent of dose</u>,i.e., that of early organ failure and death stemming from a dose and P_2 for the organ only, is largely responsible for the confusion, apprehension, and outright fear that has surrounded LLE and "linear, no-threshold" relationships.

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FIGURE LEGENDS

Figure 1 Cancer incidence in women receiving weekly exposures of the order of 3 rad to x-radiation, for monitoring of pneumothorax treatment of tuberculosis. WY refers to women-years. From Boice and Manson[1].

Figure 2 Chromatid exchanges as a function of dose, in lymphocytes exposed in vitro to strongly accelerated heavy ions and to x rays. From Skarsgard et al[2].

Figure 3 Harderian gland tumors in mice exposed to strongly accelerated heavy ions, and to x-rays. From Fry et al.[4].

Figure 4 A figure redrawn from one appearing in Lindell, 1978, in which a "linear, no threshold", and a threshold, curvilinear function are plotted on the same graph. This mode of presentation gives the incorrect impression that these completely different relationships are simply variations of the same function.

Figure 5 Statistics on vehicular accidents[6] plotted as the zero-slope derivative function represented by the data (curve A), and made into an integral (cumulative) function (curve A'). The abscissa is not dose, so that the "no-threshold" cannot be interpreted as due to unusual sensitivity.

Figure 6 The LD_{50} values for animals impinging at high velocities on a hard surface. The LD_{50} for humans (the 70 kg animal in the figure) is an estimated value, of about 25 ft/sec (approximately 17 MPH).

Figure 7 A distribution of hit sizes for those hit stochastically in a large population (curve A), an HSEF (curve B), and those hit and injured who respond quantally (hatched area). See text for details.

Figure 8 Absorbed dose D, to the organ viewed as a population of cells. H is the hit size (dose) to the cell or cell genome; N_H and N_E are the hit and exposed cells, respectively; I_H is N_H/N_E ; and HLE and LLE are high-, and low-level exposure in a field of radiation, or of macro potentially hazardous "particles". This shows that D is a composite and thus confounded quantity, with very different meanings with regard to HLE vs LLE.

Figure 9 A representative HSEF, for the same set of data shown in Figure 2. The abscissa is given in terms of the microdosimetric quantity y, expressed in $keV/\mu m^{-1}$, so that ready accommodation to different target diameters is possible. This can easily be converted to energy per unit mass, or "cell dose". $\bar{c}$ is the assumed diameter of the TCV.

THE RISK OF EXPOSURE TO MOVING VEHICLES

U.S.A. STATISTICS FOR ONE YEAR

Persons exposed	200,000,000	
Those who are hit and injured	5,000,000	chances: 1/40
Those hit and injured who die	50,000	chances: 1/100

Total average risk of death -- 1/40 (P_1) x 1/100 (P_2) = 1/4,000

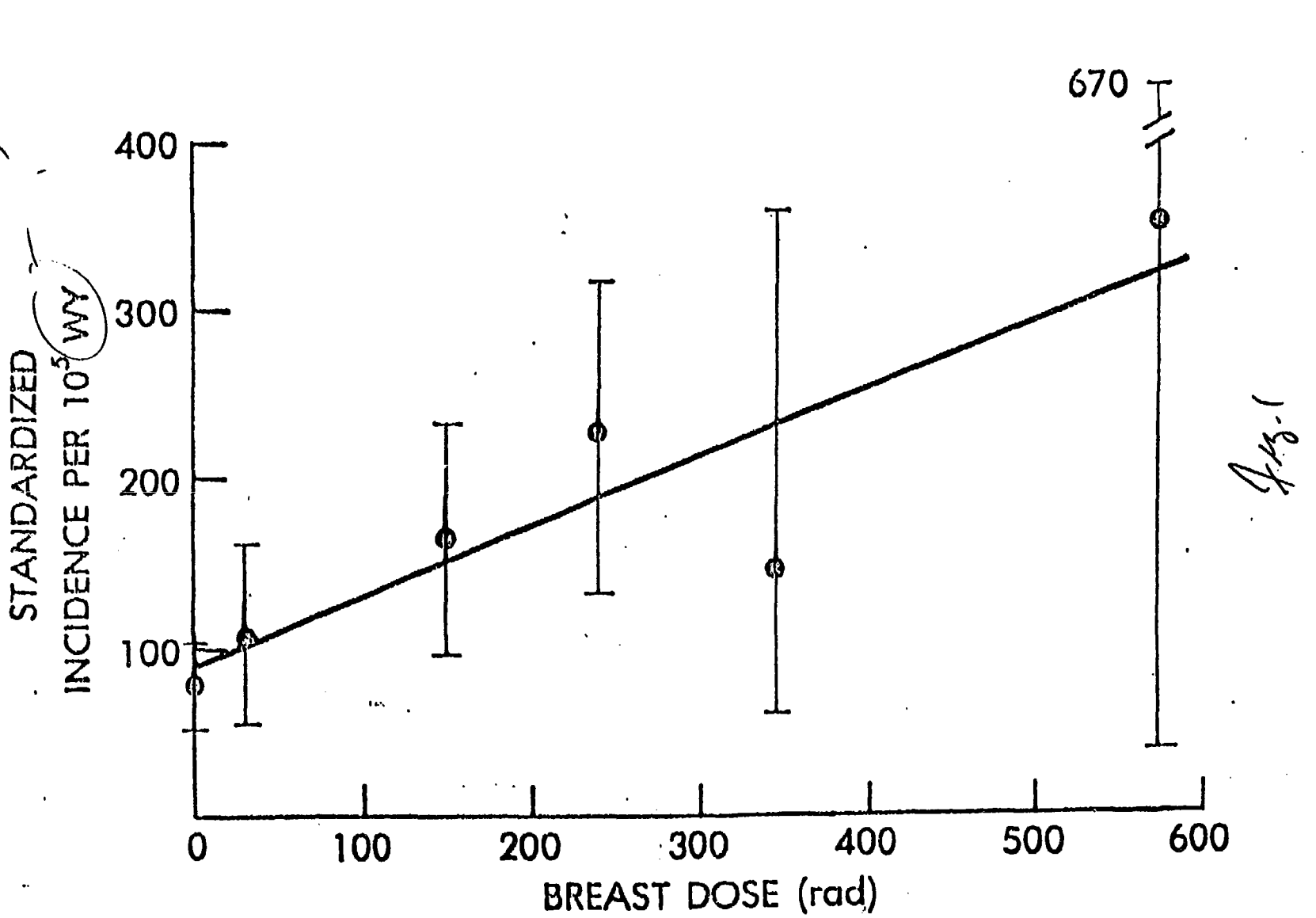


Fig-1

BOND
11-671-71

See replacement sheet VB

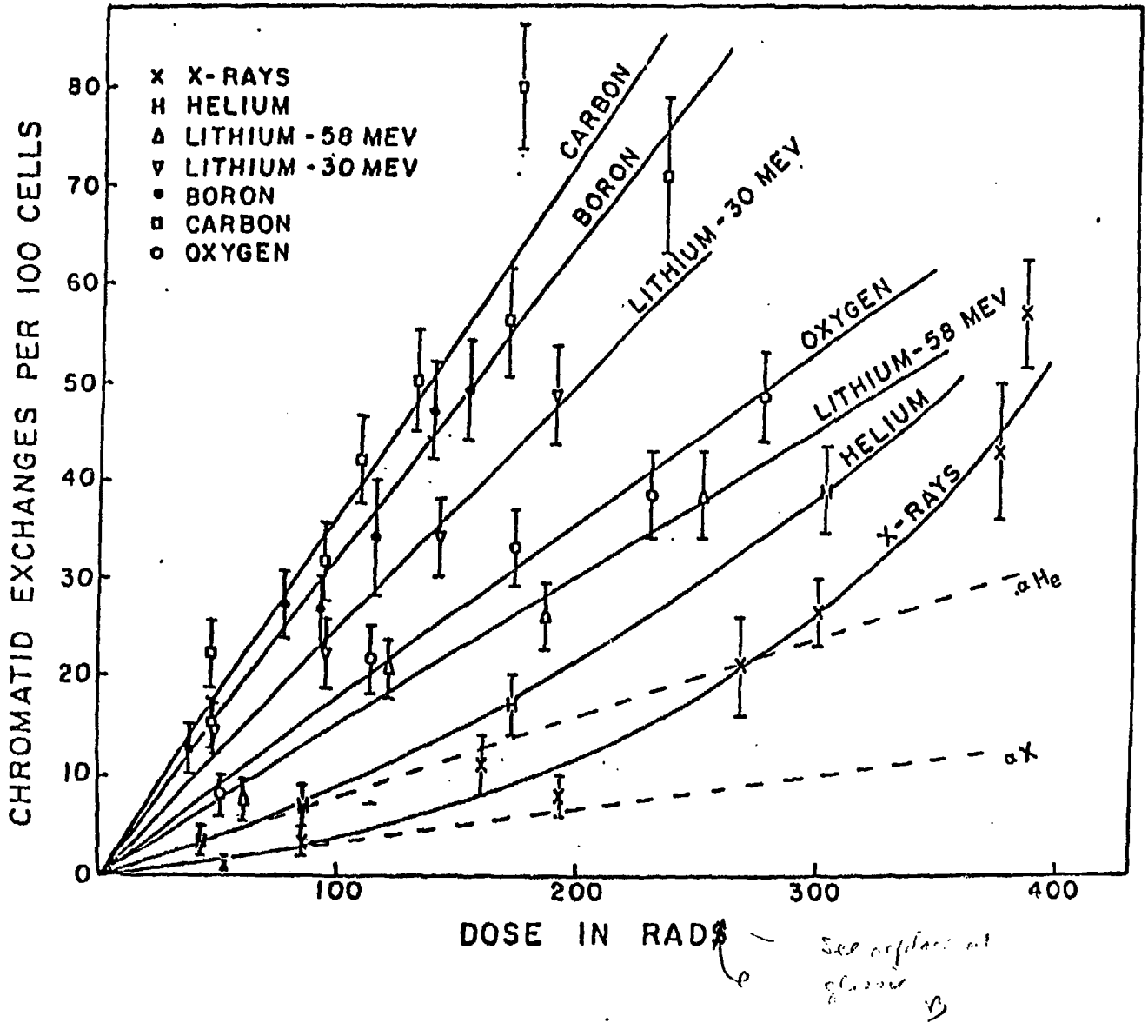
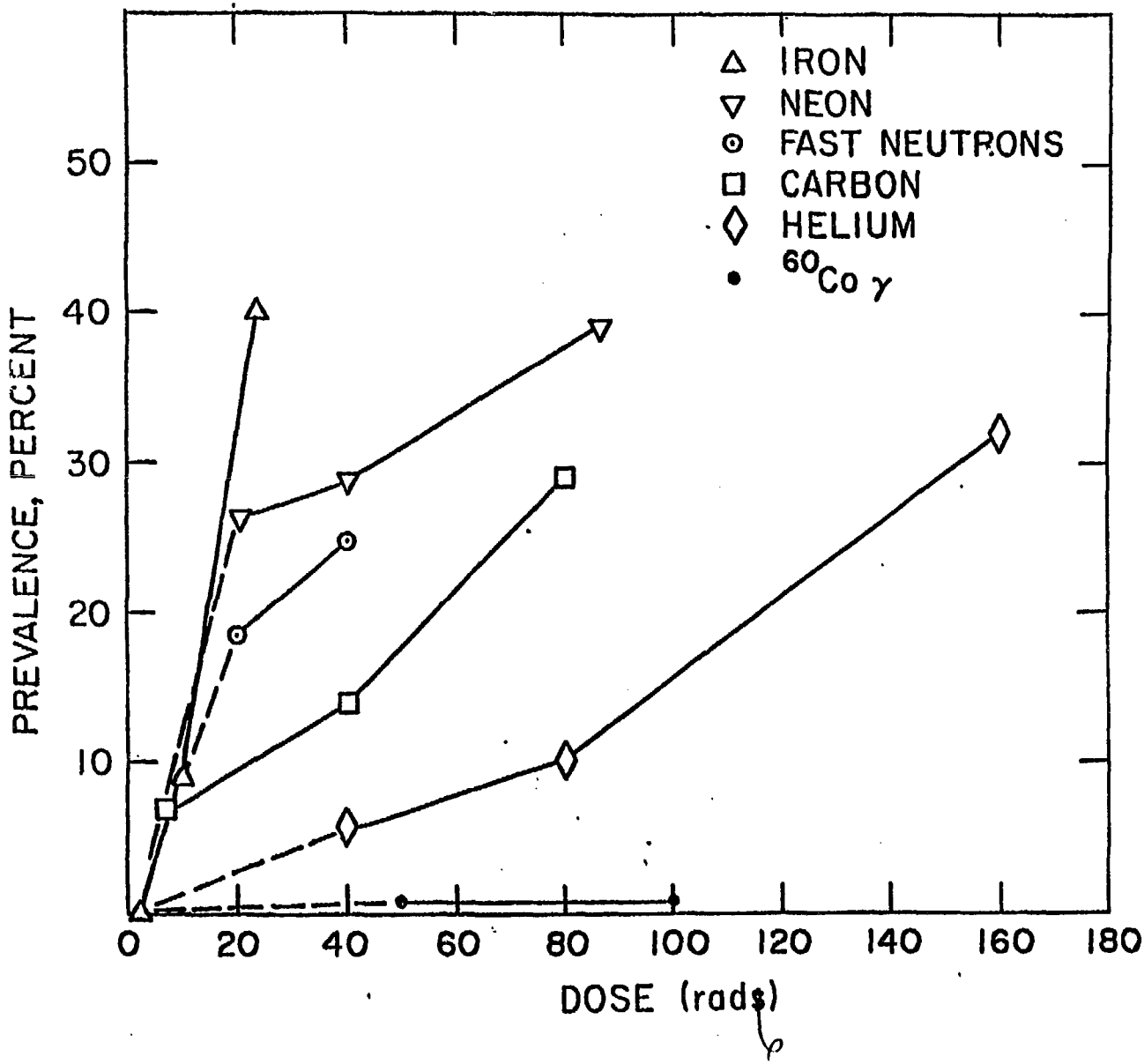


fig 2

BOND
8-31-81



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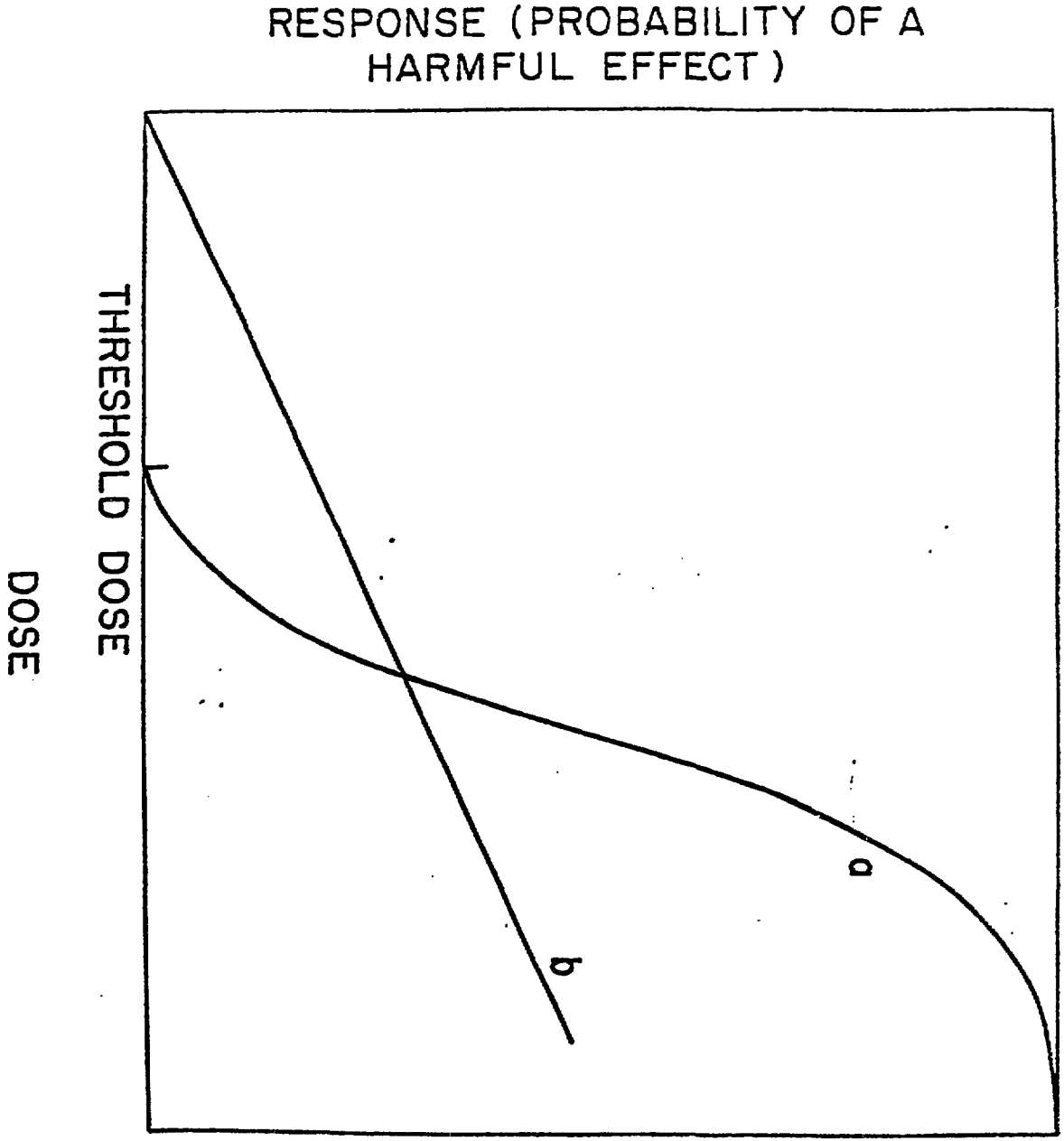
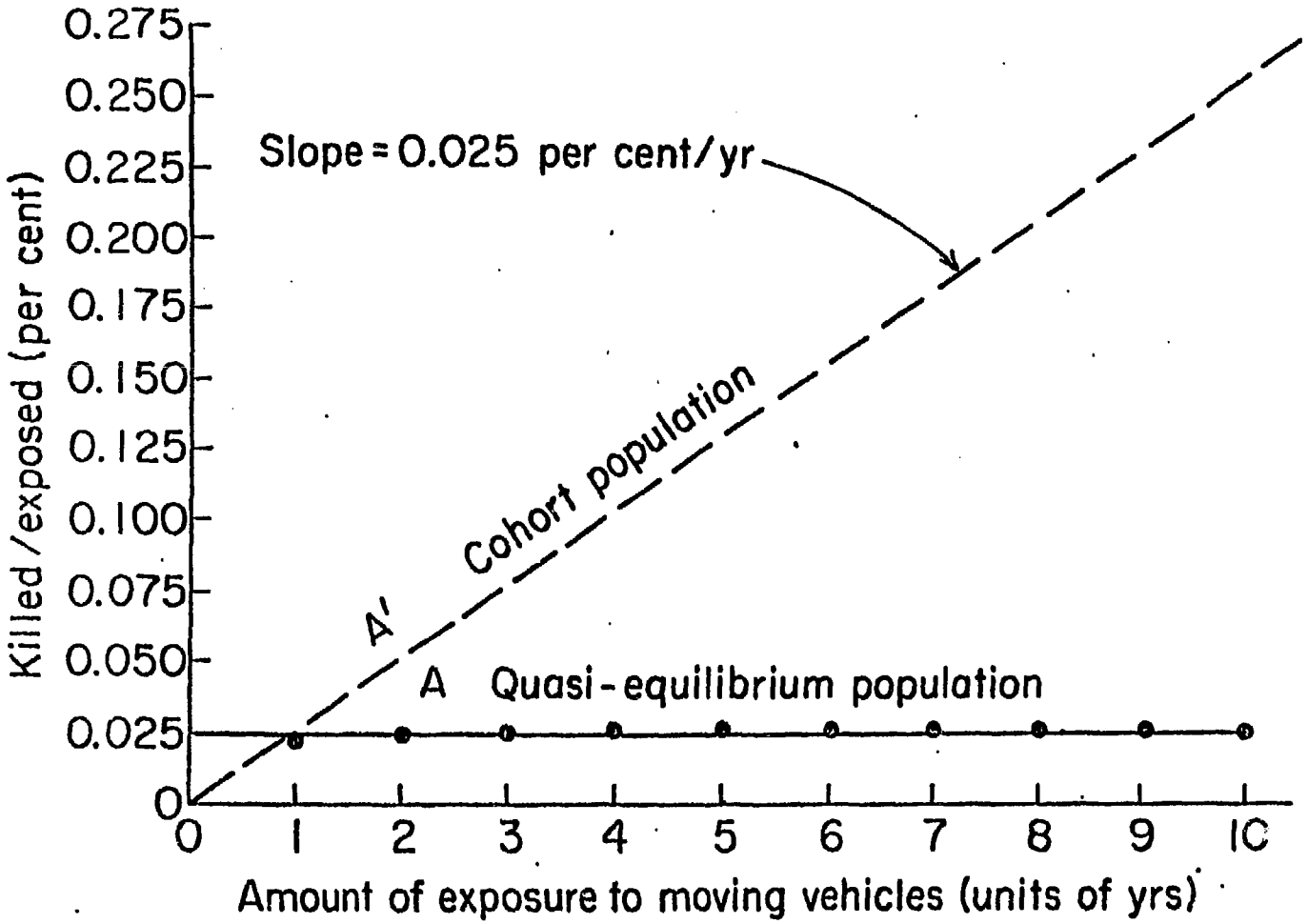

RESPONSE (PROBABILITY OF A HARMFUL EFFECT)
THRESHOLD DOSE
DOSE
a
b

Fig. 4


0.275
0.250
0.225
0.200
0.175
0.150
0.125
0.100
0.075
0.050
0.025
0
Killed/exposed (per cent)
Slope = 0.025 per cent/yr
Cohort population
A'
A
Quasi-equilibrium population
0
1
2
3
4
5
6
7
8
9
10
Amount of exposure to moving vehicles (units of yrs)

BOND

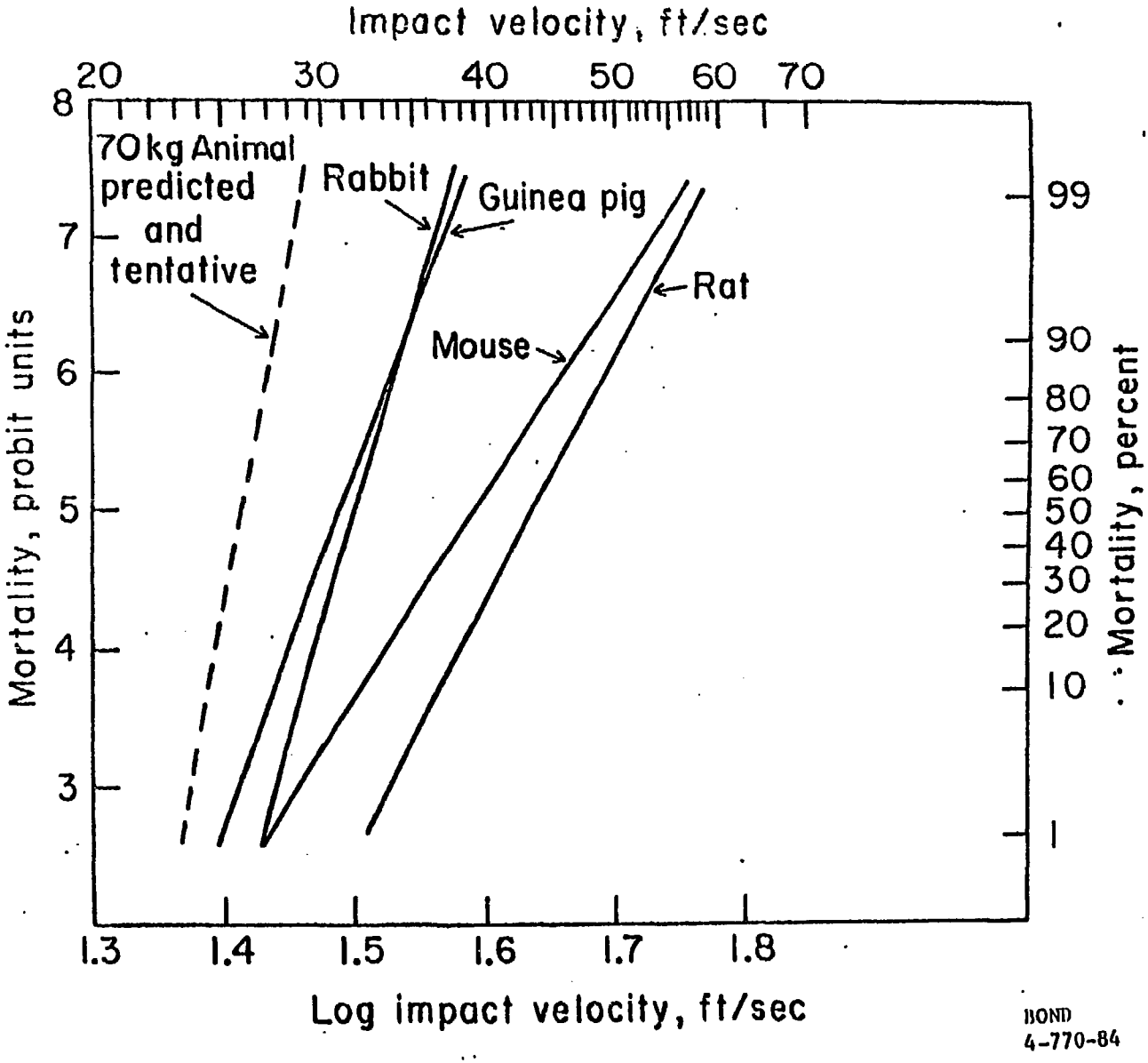

Impact velocity, ft/sec
20
30
40
50
60
70
70 kg Animal predicted and tentative
Rabbit
Guinea pig
Rat
Mouse
Mortality, probit units
8
7
6
5
4
3
99
90
80
70
60
50
40
30
20
10
1
Mortality, percent
1.3
1.4
1.5
1.6
1.7
1.8
Log impact velocity, ft/sec
BOND
4-770-84

Fig. 6

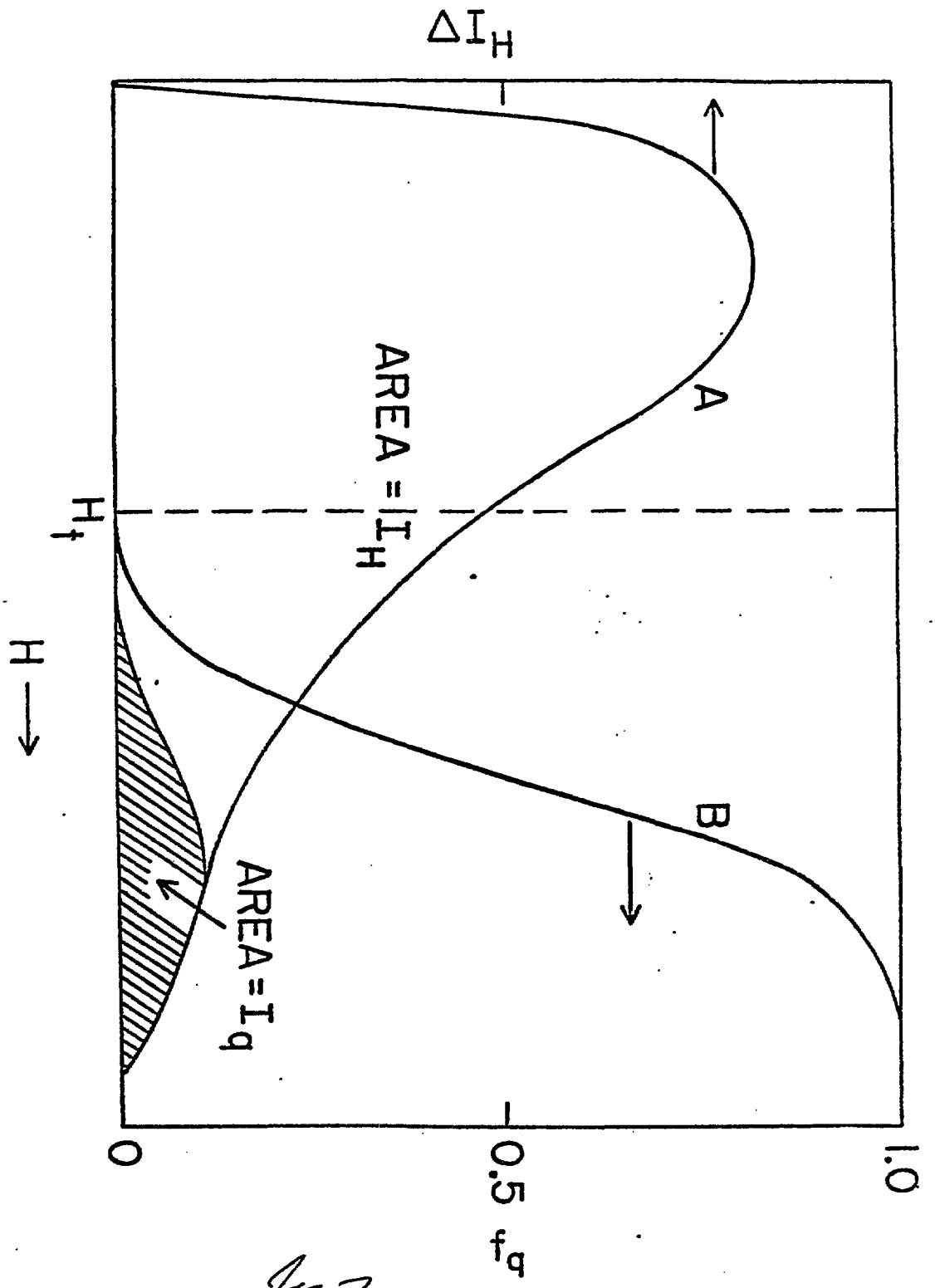


Fig 7

$$D = \frac{(H_1+H_2\text{---})}{N_E} = \frac{(H_1+H_2\text{---})}{N_H} \cdot \frac{N_H}{N_E}$$

$$D = \bar{H}\frac{N_H}{N_E} = \bar{H}I_H$$

HLE: $I_H \geqq 1.0$. Then $D \cong \bar{H}$

LLE: $\bar{H} = k$; $N_H \ll N_E$.
Then $D = kI_H$

1458

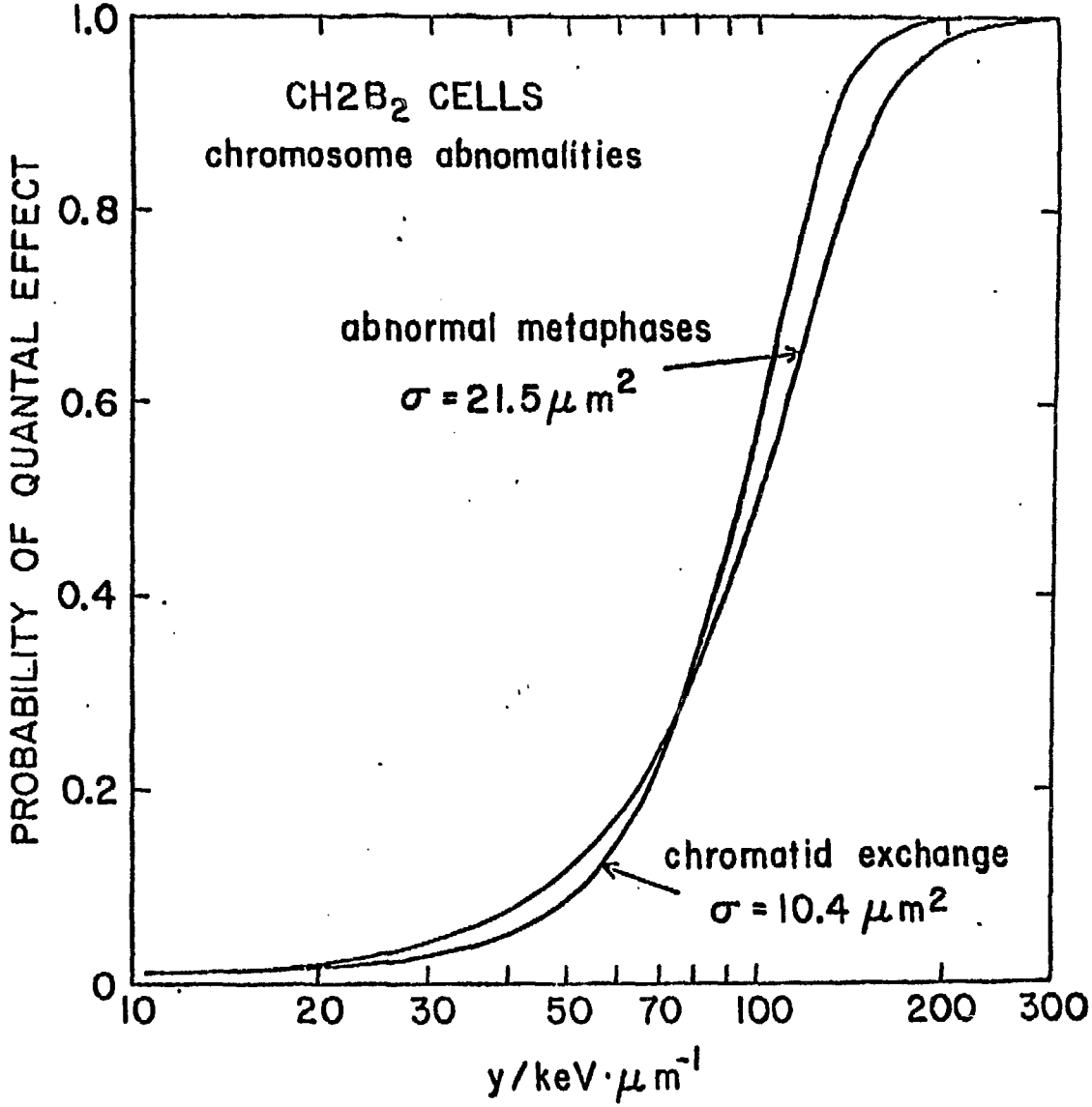
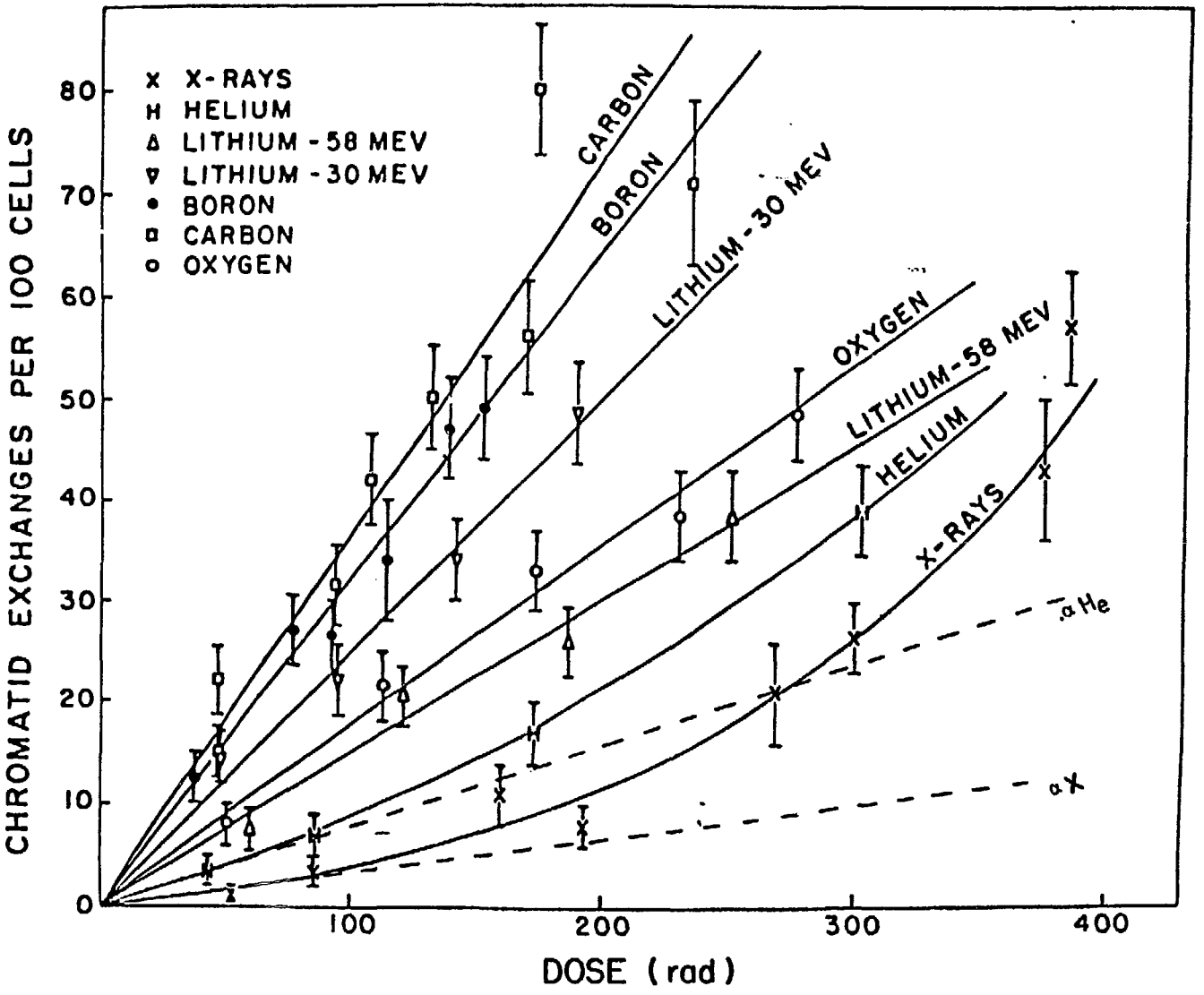
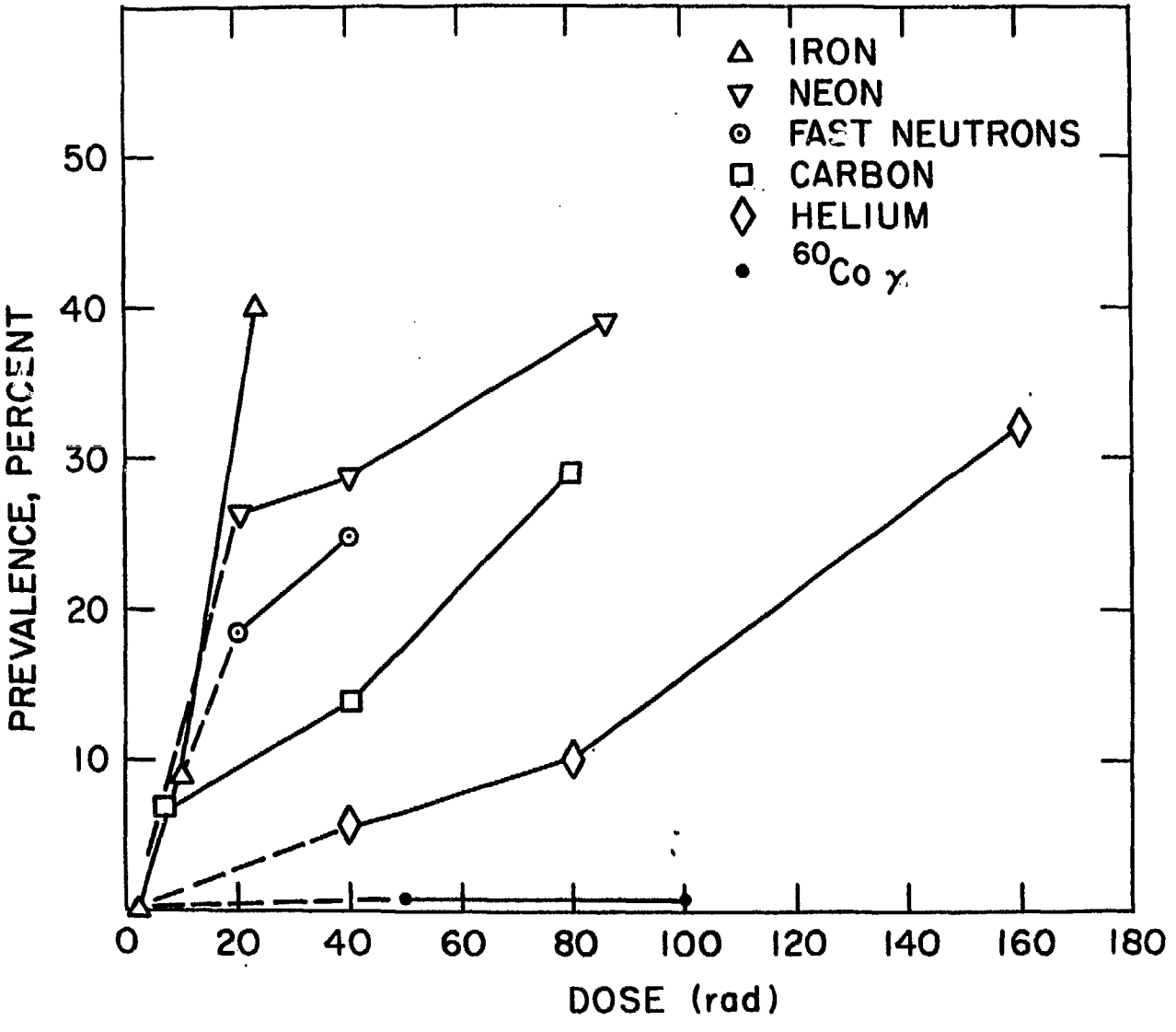

CH2B2 CELLS
chromosome abnomalities
abnormal metaphases
σ = 21.5 μm²
chromatid exchange
σ = 10.4 μm²
PROBABILITY OF QUANTAL EFFECT
1.0
0.8
0.6
0.4
0.2
0
10
20
30
50
70
100
200
300
y / keV · μm⁻¹

Fig. 9


X X-RAYS
H HELIUM
Δ LITHIUM - 58 MEV
▽ LITHIUM - 30 MEV
• BORON
□ CARBON
○ OXYGEN
CARBON
BORON
LITHIUM - 30 MEV
OXYGEN
LITHIUM - 58 MEV
HELIUM
X-RAYS
αHe
αX
CHROMATID EXCHANGES PER 100 CELLS
DOSE (rad)
0
10
20
30
40
50
60
70
80
100
200
300
400


IRON
NEON
FAST NEUTRONS
CARBON
HELIUM
60Co γ
PREVALENCE, PERCENT
50
40
30
20
10
0
20
40
60
80
100
120
140
160
180
DOSE (rad)