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The Risk Equivalent of an Exposure to-, Versus a Dose of Radiation

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Introduction

The subject matter of this talk is the long-term effects of radiation, with most emphasis placed on the potential carcinogenic effects of low-level exposure (LLE). The principal point to be made is that the so-called "linear, no-threshold dose-response" curve, a central pillar in radiation protection philosophy is not, with LLE, 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.

That the linear no-threshold, or proportional relationship is widely used is seen in the way in which the values for cancer risk coefficients are expressed--in terms of new cases, per million persons exposed, per year (or per lifetime), per unit exposure or dose. This implies that the underlying relationship is proportional, i.e., "linear, without threshold".

Now, why is such a relationship assumed? One reason derives from data such as that shown in Figure 1 (1), for breast cancer in the human female. These are actual observations made on women given small exposures approximately weekly, in the fluoroscopic monitoring of pneumothorax therapy for tuberculosis. Note that a proportional curve appears to fit the data. Nonetheless, such data do not in themselves justify adoption of this relationship, because the limits of error are so large that several other kinds of relationships could be drawn instead. Thus, this use of a proportional relationship does not in itself prove that it is correct or even most suitable for general use.

However, evidence of the above type is not the only reason why the linear, no-threshold relationship is assumed to apply generally. Good bases can be found in radiobiology, examples of which are now given.

Radiobiological Bases for Proportional Curves

In Figure 2 (2) are shown functions for the fractional number of cells with chromosomal aberrations, versus the absorbed dose. The coordinates are essentially the same as those used in Figure 1. The upper curves are all for high-LET radiations; the lower two curves are for low-LET radiations. Obviously, the upper curves are linear and without threshold. With the low-LET curves, however, the relationship is basically curvilinear, with increasing slope. However, 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, a fan-shaped set of curves, all proportional, is observed.

The same type of results can be seen in a number of other cellular systems, e.g., for a color mutation in the cells of the stamen hairs of the plant Tradescantia (3) for other cell mutations and for cell lethality. The same can also be seen for many types of animal tumors, as shown in Figure 4 (4). Thus there is little doubt that such curves for "single cell-originating endpoints", at least the initial low-exposure portions, do in fact represent linear no-threshold relationships.

The next question, however, is, what does this linearity mean? Figure 4 represents a plot taken from the literature, and a number of similar examples can be found. Plotted with the same labels on the two axes (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 linear, no-threshold curve is not. The presentation conveys the idea that the proportional curve represents the same phenomena dealt with routinely in pharmacology and toxicity, and that the proportional curve is simply an aberrant form of the threshold, curvilinear function. The implication is that those biological systems that follow a "linear, no-threshold" plot are much more sensitive than is a system that follows the threshold-type of relationship.

The above-stated implications and interpretations simply are not correct. It is important to show that these plots are for very different things—that they have nothing in common. As will be shown below, the threshold plot represents the amount of agent received (true dose, delivered in either a random or ordered mode, versus the fraction of equally dosed individuals that will respond quantally [i.e., undergo an all or nothing alteration such as death or lasting disability (persons), or death, chromosome changes, or transformation (cells)]. Since the fraction responding quantally (5) also represents the risk of a quantal response among only the few receiving the same dose of the agent in question, the curve can be said to represent the risk-equivalent of dose, as a function of increasing dose.

The linear, no-threshold plot, on the other hand, represents the amount of exposure of individuals to hazardous objects in the environment versus the fraction of those exposed who were hit, received randomly determined and thus unequal doses, and were consequently injured, some severely enough to show a quantal response. Since this fraction (proportion, incidence) responding also represents the risk of a quantal response, but among a usually-large

population of exposed individuals, only a small fraction of which may receive a dose with a still smaller fraction responding quantally, the curve can be said to represent the risk equivalent of exposure, as a function of increasing exposure.

In other words, injury received as a result of random processes, i.e., accidents, have two separate and independent components, 1) the probability, P_1, of of being hit and injured without regard to the severity of injury, and 2) the severity of injury, represented by the fraction of injured individuals who respond quantally (equal to the probability, P_2, of a quantal response). Either the probability (of receiving a dose) element of the total risk (P_1), or the total risk (the product of P_1 and P_2) is correctly represented by a linear, no-threshold relationship with exposure on the abscissa; only the severity element (P_2) of the total risk, with dose on the abscissa, is correctly represented by the threshold, curvilinear relationship.These two basically quite different functions should never be placed together on the same plot, and certainly not with the same axes.

The basis for the linear, no-threshold relationship is now examined further. Consider what happens when biological materials, particularly cells, are placed in a field of radiation (organs can, of course, be viewed simply as an "organized" population of functional cells). A radiation field is composed of charged particles moving rapidly. It is the interaction of these moving particles with cells or parts of the cell, with transfer of the potentially harmful agent kinetic energy, that leads to biological damage. It is important to emphasize that these interactions are stochastic in nature, i.e., brought about by random processes.

Now, in the high-level exposure (HLE) region, which the preceding speaker, Dr. Saenger, was discussing (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 not only once, but many times. Under these conditions, the cell dose derives from multiple hits of random size. This tends to even out the amount of energy received by the cells, and thus the severity of injury. Therefore, the average dose to the cells, and to the entire organ, i.e., the energy density or energy per unit mass, is the same for organ and cells alike. Accordingly, the response seen in the cell population (organ) increases only because the average cell (organ) dose increases. Under the circumstances, one is interested primarily in organ or cancer failure, due to direct and lethal damage to a large fraction of the equally dosed cells, and use of the average absorbed dose to the organ is thus appropriate. It was in this connection that radiation "dose-response" curves were (appropriately) developed. The difficulty arose when the use absorbed dose and RBE was extended down to the LLE region, and to "single cell", rather than organ effects and responses.

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, there is first one cell hit, then shortly a second, a third, and so forth. So, rather than every cell being hit many times, as is the situation with HLE and acute organ effects, we now have only a very small fraction of the cells within the organ hit at all. Further, in these interactions, there is a single, sudden transfer of energy, in discrete amounts that vary substantially from cell to cell.

The above-described situation is exactly analogous to that encountered in macro accidents familiar to everyone. That is to say, as a result of the stochastic transfer of the potentially harmful agent energy to the small fraction of exposed persons unfortunate enough to be involved in a collision

with an "agent carrier", damage is done to a small fraction of the exposed population (the vehicle carries the agent kinetic energy, some part of which is transferred in a collision), If this analogy is true, then 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.* Hence, macro accidents will be examined, with this analogy in mind, before returning to the "micro accidents" experienced with radiation exposure.

The Macro Accident Analogy

Before looking at macro accident relationships, it is mandatory to examine more carefully the differences among the concepts of being exposed to hazardous objects; being hit, dosed, and injured in an accident; and being killed if hit. Vehicle accidents serve as a good example for present purposes because they occur quite frequently (6), because of their general familiarity, and because the harmful agent is kinetic energy (as it is a radiation).

In Table I are shown the statistics for a typical year in the United States, during which approximately 200 million individuals are exposed to agent-carrying (moving) vehicles. However, the fact of being exposed obviously does not equate to being "dosed". Only those unfortunate enough to be in an accident become "dosed" from the transfer of energy, and thus injured to some degree. Therefore, only a small fraction of those exposed, some 5 million individuals per year are hit and dosed. Of those hit, dosed, and injured, only a small fraction, about 50,000 per year, will respond quantally (will be killed). As seen in Table I, the two (above discussed) independent probabilities, P_1 and P_2, are involved. The product of the two, equal to the total average yearly risk of dying from a vehicle accident, is (1/40 x 1/100), or 1/4000.

*HLE to radiation cannot be simulated with macro accidents simply because the casualty is immediately removed from the scene for treatment as may be required. Thus "multiple hit" accidents characteristic of HLE are virtually nonexistent.

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 in principle only as nameless individuals, or "statistics". The physician plays a very different role. The physician sees only those individuals who are hit, dosed, and injured, and these identified individuals are, of course, given the required medical attention. The physician has little or no interest in either the applicable fluence of vehicles, the risk of a patient having been dosed, or the magnitude of the dose. His or her interest is in the individual, and in evaluating the severity of the injury. This is done on the basis of a variety of medical and laboratory findings. With these findings, he or she is then able to make an assessment of the probability (P_2) that the individual may succumb to the vehicle-induced injury, i.e., experience a quantal response.

Note that the word "dose" has thus far not entered the picture definitively. Normally the physician evaluates the severity of injury, and on this basis alone estimates the probability that the individual will or will not die. Implied is a relationship, the probability of death as a function of the severity of injury. However, only rarely is such a relationship formalized.

Now let us examine several formal relationships, one involving dose, that can be developed for a more complete description of the events following automobile accidents, even though none are now used normally (the annual "Accident Facts" booklet (6) contains only tabular statistics, and does not mention functional relationships). The first type of function to be considered is shown in Figure 5, and is based directly on data taken from the Accident Facts booklet. Note first the lower flat curve A (i.e., the curve with a slope of zero), which represents the manner in which the statistics are presented in the booklet (as stated above, no linear, non-threshold curve is

implied or used). Note that the number killed per year is remarkably constant, despite the widely varying characteristics of drivers and of driving conditions. This is a differential curve (i.e., deaths per year). The same kind of (flat) curve could also have been presented for the number hit and injured per year.

Now note that a "linear, no-threshold" relationship (curve A^1) can be obtained from curve A simply by changing this differential form into the integral ("cumulative") form (curve A^1), shown in Figure 5. Thus one can see that "linear, no-threshold" curves can be "manufactured" easily from statistical data dealing with injury resulting from stochastic collisions with hazardous objects in motion.

Note that the abscissa for these proportional curves, unlike that shown for the similar curve in Figure 4, is not "absorbed dose" or a dose of any kind. The correct quantity is the "field-oriented quantity" exposure, expressed as fluence, the mean number of vehicles, per unit presenting area, per unit time, "seen" by the exposed individuals. However, the exposure (fluence) is the product of the mean fluence rate of vehicles and the exposure time. 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, in units of years, is used as the independent variable. Also, since the proportion (incidence) of hit and injured is proportional to the exposure expressed as fluence, this "object-oriented" quantity could also be used as the abscissa in Fig. 5.

Thus, linear, no-threshold relationships are inherent in the data obtained in the realm of Public Health and accident statistics. The reason why they are not seen normally is that the tabulated statistics on exposure, injury, and death are adequate for purposes of description and prediction, making functional relationships unnecessary. Also, functions with zero slope,

or cumulative "linear, no-threshold" relationships (Figure 5) are simply too trivial to warrant plotting (see discussion section for reasons why the cumulative curve actually is inappropriate).

Whatever the merits of the "linear, no-threshold" relationship may be, it alone is not adequate to describe completely the processes involved in the chain of events leading from exposure to accidental death. Missing is the formalism involving the "object-oriented" concept of dose, whereby the fraction of those injured, and who die as a result of their injuries, might be derived from the incidence of those dosed and thus injured. This approach, completely unnecessary with macro accidents other than for formal description and in research (but necessary with micro accidents), is now presented for illustrative purposes.

Rather than evaluate the probability of dying purely on the basis of severity of injury, one could in principle place transducers or other instruments on all, or some representative fraction of those exposed. The transducer, which could be read immediately after the accident occurs, would provide a quantitative estimate of the amount of energy transferred in the collision. By this maneuver, the unpredictable distribution of energy deposits becomes a known distribution, suitable for prediction of the fraction of injured that will respond quantally.

The amount of energy transferred is conceptually a dose and could be so referred to. However, because a number of operational differences exist between injury delivered stochastically versus that delivered in an ordered fashion such as may be done in pharmacology, toxicology, or medicine, the amount of energy transferred stochastically will be referred to here as "hit size".

One could then develop a function for the probability of death, as a function of increasing hit size, to produce a threshold, curvilinear function similar to curve a in Figure 4. Such curves, actually obtained with animals allowed to impinge on hard surfaces at different velocities, are shown in Figure 6. The linear curves shown on the probit plot would become curvilinear as is curve a in Figure 4, were the ordinate an arithmetic scale instead of a probit transformation (5).

Note the remarkable similarity between this plot, and the dose-response relationships so familiar to every pharmacologist, toxicologist, and physician. In fact, the "hit-size"-response curve, termed a "hit-size effectiveness function", or an HSEF (7-11), is in principle identical to the similar pharmacologic-toxicologic curve. The reason for this is that, everything else being equal, the organ or organism has no physiological means of detecting whether a given amount of injury was inflicted by accident, or by intent. The prizefighter's body has no means of distinguishing the injury to any organ from blows delivered intentionally in the course of a fight, from the identical injury that could be delivered quite accidentally and completely without intent.

Then how would the HSEF be used? The procedure is in principle quite simple, for any given individual. P_1 is, as stated, the number hit and injured, per person exposed. The HSEF, for a given determined value of hit size, yields P_2, the fraction of those hit and injured who will die. The total risk for the given exposure is then simply $P_1 \times P_2$.

If one is dealing with a population of exposed individuals, then a similar but somewhat more complicated approach, depicted in Figure 7, must be followed. Note in the Figure that one has a wide distribution of hit sizes

for a group of accidents, and that the distribution is skewed to the left because relatively few accidents have life-threatening consequences. Note that the hit sizes, randomly distributed in time, have been rearranged here in order of increasing hit size. Also shown in the Figure as curve B is an HSEF. One must then multiply every point on the distribution A, by the corresponding point on the HSEF B, to determine, at every hit size, the fraction of individuals injured that will die. The result is the shaded distribution, marked "area equal I_q". The area under this distribution represents the expected excess incidence of deaths for the given exposure. Given in more concrete terms, consider the 200 million exposed each year in the U.S.A. The area under the distribution A represents the total fraction of that 200 million, namely, 5 million, who would be expected to be hit and injured in the vehicle collision. The shaded area, marked I_q, obtained by multiplying the distribution A by the hit-size function B, yields the area I_q, equal to the 50,000 expected to die from the one-year exposure. The total average risk is then $(5 \times 10^6/200 \times 10^6)$ $(5 \times 10^4/5 \times 10^6 = (1/40 \cdot 1/100) =$ 1/4,000.

Now something must be said about the concept of linear energy transfer (LET) or radiation quality, and what this concept means in the vehicle accidents analogy. It means, in principle, that the moving vehicles comprising one vehicle "field" are capable of transferring more energy in an average accident, than are those in another. Two factors enter, the mass of the vehicle, and its velocity. If the average speed is kept essentially constant, then, in an accident, a bus or a large truck can transfer much more energy than can, for instance, a small Volkswagen, so that the accident and the injury is likely to be more severe. Another way of accomplishing the same thing is to keep the mix of vehicle types the same, but change the average

speed (e.g., by changing the speed limit). Then faster moving vehicles of any given type will transfer more energy and cause more damage (injury), than will the slower moving vehicles of the same type. This collective agent transfer capability is known broadly as the "quality" of the mix of vehicles ("particles") and their velocities, and it is obvious that the higher the LET of the vehicles, the larger the mean hit size from a collision can be.

The importance of this is that if, for instance, the distribution shown as curve A in Figure 7 is for "low-LET" vehicles, then a distribution for "high-LET" vehicles would be shifted to the right, so that mean LET would obviously become larger. The differences in effectiveness between high and low-LET vehicles is the analogue of the "relative biological effectiveness" (RBE) concept for radiation. The higher-LET vehicles obviously have a larger RBE. Thus, with any given distribution of vehicle sizes or velocities, this would show up in the shape and location of the distribution of hit sizes. However, these distributions overlap substantially, suggesting that the RBE is due in large part simply to the fact that any larger hit size, essentially independent of the vehicle type from which it was derived, is more effective than is a smaller hit size. This suggests replacement of RBE with a single continuous function, the HSEF, which covers all hit sizes from the minimum to the maximum. Thus the entire concept of RBE can be replaced by the HSEF. Multiplying any distribution of hit sizes from any mix of vehicles, by the HSEF, yields another smaller distribution, the area under which represents the expected excess number of persons expected to die if exposed to that particular mix of vehicles.

For a given exposure, this expected excess incidence of deaths in a population, and the risk of dying, for the average individual in that

population are numerically equal. Thus in general, a given probability or risk value is nothing more than the equivalent of, or a synonym for, the expected excess incidence of injured (or lethally injured) individuals in the exposed population.

The Micro Accident Analogy

Micro accidents (charged particle-cell interactions), which represent the only means by which the agent energy is transferred from the radiation field to a biological entity or "individual", are now discussed. First, however, the question must be asked, why is the term (absorbed) "dose" now used as the abscissa for the initial linear, no-threshold part of a so-called dose response curve, if the correct parameter is not dose at all?

The principal 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 in an earlier era when radiotherapy and other forms of HLE were of principal interest. When the late "single-cell" effects became of concern with LLE, there was no obvious reason why the same quantities should not be applied to the single cell endpoints of importance with LLE.

The principal single cell endpoints of concern are mutagenesis and carcinogenesis. Disease in offspring due to mutations are obviously single cell in origin. However, a large amount of work has been done to show that many cancers, whatever their origin may have been, are monoclonal in nature. This is essentially tantamount to saying that the "initiation" of the cancer is also single cell in origin. That is to say, it is initiated by a maglignant transformation, a quantal response in a single cell.

The importance of this finding is that, for low-level radiation, the biological "individual" of interest, is neither the organ nor the organism, but the single cell. Thus the "dose" (hit size) we are interested in, and

which may be responsible for the transformation of a cell, is that to the cell(s) and not that to any organ or the entire individual. It is thus appropriate to see what absorbed dose means in terms of energy absorption in the individual cells of interest, in a population of cells (an organ) experiencing LLE to radiation.

The calculation of "absorbed dose" to the cell population is shown in Figure 8 (see Fig. legend). Note that the absorbed dose to cells reduces simply to the product of the fraction of exposed cells that are hit, and the mean hit size, i.e., it becomes $(\bar{H} \frac{N_H}{N_E})$. It is thus a composite quantity that incorporates, and thus confounds, one variable related to P_1, and another related to P_2. Because the expectation value of the mean hit size becomes constant with LLE* (Fig. 8), the mean absorbed dose to the cell population (organ) is then simply proportional to the fraction of exposed cells hit (i.e., it continues to decrease only because unhit or "zero-dosed" cells are increasingly included in the averaging process, as the absorbed dose decreases). In other words, it ceases, in effect, to be a dose at all. Rather, it becomes, as with vehicle accidents, either the (fractional) number of exposed cells hit (an object-oriented quantity), or its (proportional) alternative, the field-oriented quantity, particle fluence. Thus the initial proportionality is explained in the same terms as the proportional cumulative curve for vehicles (Fig. 5). Also, the ordinate is quite different from a pharmacologic dose-response curve or an HSEF, in which the fraction of cells responding is of a group of <u>equally</u> dosed cells. The ordinate with the linear, no-threshold curve, however, is the fraction of <u>unequally</u> dosed cells,

*This is because the small fraction of exposed cells that are hit have received only one hit of randomly determined size, with consequent wide dispersion of individual hit sizes around the expectation value of the mean.

with a wide distribution of hit sizes, responding in an exposed population (i.,e., as with vehicle accidents).

Thus, the proportional curve and the threshold non-linear curves for radiation exposure are completely different. None of the proportional curves can be interpreted as "any amount (dose) of radiation, no matter how small, can be harmful or lethal", simply because cell dose does not appear as a variable in the function. If we note that one of several quantities appropriate for the abscissa is time, then the correct interpretation is that there is virtually no time interval too short for a micro accident to occur. However, small hit sizes ("doses") to the cell are markedly inefficient in causing a quantal response. In other words, an exposure at any fluence rate, or for any length of time, in principle, may or may not be associated with an accident. However, if an accident occurs, it is the large hit sizes ("doses") to cells that are largely responsible for a cell quantal response, such as death or malignant transformation.

In light of the above, micro accidents from LET radiation can be handled in a manner quite analogous to that described in detail above for macro accidents. With reference to Figure 7, panel A shows a distribution of hit sizes for similar cell populations exposed in a field of low-LET radiation. The hit sizes are lined up neatly in order of increasing magnitude. In panel B is shown an HSEF for cell transformation (rather than organ transformation or death, as discussed above). If the distribution in panel A is multiplied by the hit-size effectiveness function in panel B, then one gets the distribution in hit size of cells that will transform. The area under this distribution gives the total expected excess incidence of transformation, or total risk of transformation, for a given amount of exposure. In other words, for some given total number of exposed relevant cells, the area under the

distribution in panel A, gives the fraction that will be hit and injured. To get the total fraction that will transform, for the given exposure, one must then multiply the distributions by the HSEF, and sum over the resulting distributions shown in panel C. The procedure is entirely analogous to that applicable to macro accidents.

However, although with vehicles the use of hit size and an HSEF for organs was essentially of academic interest only, the process certainly is not an idle exercise for cells. The reason is, obviously, that no physician (or anyone else) can observe cells in the living person that have been injured or transformed, and no such transformation, or any supposed "causative" agent can be linked definitely to any clinically observed cancer. Further, no cancer has a "marker" indicating what agent was causative. Nor can the population of interest for radiation protection be observed adequately epidemiologically, to determine the excess incidence, or risk. This is in part because of the long latent period between exposure and overt cancer expression, and also because the low limits of exposure and the relatively small population sizes do not permit adequate statistics to be obtained. Thus, in order to estimate, at the time of exposure, the expected excess cancer incidence, one must, in principle, use either the cell "dose" and HSEF approach, for which the conceptually much less appropriate absorbed dose-RBE method is a poor substitute.

Note again that the HSEF is a cumulative integral curve, analogous to the dose-reponse curves in pharmacology and toxicology. The derivative of this curve yields an estimate of the distribution of sensitivities of different individuals. This is true of either the HSEF, or the analogous dose-response function in pharmacology and toxicology.

Now consider what is called a "dose-response" relationship in radiation, i.e., the linear, no-threshold curve A in Figure 4. If the derivative of this

curve is taken, the result is a flat (zero slope) curve, indicating that all individuals are of the same sensitivity. This is, of course, nonsense. It further indicates that the abscissa for the linear, no-threshold relationship cannot be dose in any form, but rather the exposure, expressed either as the fluence, or in terms of several possible surrogates, e.g., the incidence of hit and injured (I_H), or time if the mean fluence rate is constant.

It is now necessary to describe briefly how an HSEF for cells can be estimated. Just as one rarely if ever can measure directly the amount of energy absorbed in living tissues, so that a phantom is often used, so an instrumented phantom cell must be used to determine, for a given exposure, the fraction of cells hit, and the distribution of energies in those cells. A suitable cell phantom, devised by Rossi (12), consists of a spherical proportional counter filled with tissue-equivalent gas. If the pressure is reduced appreciably in the chamber, then the much larger cell phantom will simulate, in terms of responses per hit by a charged particle, the amount of energy transferred to a cell. As soon as a cell simulator registers a hit, it returns to its pristine state. Thus the number of hits on a "single" pristine phantom (i.e., per exposed "cell") can be collected, and the distribution of hit sizes can be recorded. Thus the area under the distribution in panel A of Figure 7 registers, with application of a suitable "scaling factor" which may be as large as one million, the (fractional) number of hit cells per exposed cell, i.e., the expected excess incidence of hit cells (i.e., P_1).

In order to obtain an HSEF a large amount of qualitative biological and microdosimetric data, obtained with radiation covering a wide span of LETs, is required. Having the overlying hit-size distributions, and the relative effectiveness of the different distributions in producing quantal responses, a

computer-assisted iterative procedure permits estimation of an HSEF that best represents the entire set of data (7-10). An illustrative HSEF for chromosome abnormalities is shown in Figure 9. Similar curves (not shown) have been developed for different mutations detectable in the individual cell, for cell lethality, and for other endpoints.

Of particular interest are HSEF's for cancer induction in the mammal. Also of special interest is an HSEF for some forms of chromosome translocations, since it is chromosomal aberrations such as this that have been implicated as playing a key role in the development of "normally occurring" cancers. Thus there is some reason to expect that the shape of this HSEF, obtained on human cells, would represent rather closely that for induction of human cancer.

Summary and Conclusions.

First a caveat, namely, what has been presented on low-level radiation, although conceptually correct, is in the research and developmental stage and not at present suitable for application. However, if and when it is adequately developed, it could in principle replace, for LLE, current concepts of RBE and of the quality factor, Q. It therefore could also, in principle, replace absorbed dose, the standard radiation, dose-equivalent and rem. However, even the adoption of the "HSEF approach" would not do away with absorbed dose, or even RBE, for HLE and the associated acute effects on organs or tumors.

However, it is suggested that HLE such as is used in cancer therapy and in connection with radiation accidents has so little in common with LLE and the late effects, carcinogenesis and mutagenesis, that the two might well be separated completely. This for the same reason that diagnostic and therapeutic radiology have been separated--the two disciplines have practically nothing in common. So with HLE versus LLE. HLE is closely allied

to pharmacology and toxicology, and requires only one function, the object-oriented quantity dose versus organ (or cancer) response, for a full evaluation of the probability of a quantal response as a function of absorbed dose to the organ (i.e., only P_2 is needed because P_1 is unity). LLE, on the other hand, is not at all analogous to pharmacology and toxicology. Rather, it represents a public health problem in which the group of "individuals" exposed to hazardous objects happens to be cells, rather than organs or organisms. Thus, the concepts, quantities, and terminology to be applied to low-level radiation should be reexamined, to make it conform to that of public health and accident statistics, i.e., in which both P_1 and P_2 must be estimated. LLE to radiation should be much more widely recognized as a public health discipline in which the health of the population is the focus of attention, because it does not belong to the "private health" disciplines in which the health of a specific, identified individual is the focus.

It is often stated that low-level irradiation is "cumulative", a term that is particularlty frightening to most people. This is because it is interpreted that, if one is exposed in a low-level radiation field such as that used in diagnostic radiology, or which exists because of background radiation or around reactors, that actually there is some small effect produced in the cells of interest. It is also believed that these small "effects" can "add up" (i.e., be cumulative), ultimately to produce a cancer.

The above is not at all true. It is true that, with LLE, injury to the cell does occur in the small fraction of cells hit. However, since only "single hits" are experienced with LLE, a cell transformation can result only from a single large hit. If a hit has not been large enough to cause a transformation, then the evidence is overwhelming that full recovery ensues rapidly, (i.e., there is no lasting relevant subcellular injury to be cumulative).

The misconception of cumulative effects of LLE of the cell undoubtedly arises from the "linear, no-threshold" curves frequently plotted, e.g., curve b in Figure 4. Because "dose" is on the abscissa, and the threshold curve is shown simultaneously, this is frequently taken to mean that injury must be cumulative in an individual. However, cell transformation and a resulting cancer is quite rare--so rare that only an extremely small fraction of cells hit, and therefore of individuals, develop cancer as a result of even reasonably high-level exposure to radiation. Thus what is "cumulative" is the number of transformed cells in a large population composed of the combined cell populations of many individuals. A cumulative curve for already transformed cells in a population of individuals obviously cannot be interpreted as multiple incremental "effects" that could be "cumulative" in the individual.

In addition to being misleading, the cumulative linear curve is unnecessary and inappropriate in a Public Health context. As stated above and shown in Figure 5, Public Health and Accident statistics are given on a per year basis. This is largely because shorter times would result in poorer statistics, while appreciably longer times would cease to represent a period of reasonable stability in a population in a quasi-equilibrium condition. Thus, since radiation exposure is a Public Health problem, the use of cumulative curves over exposure times longer than one year should be discouraged for other than investigative purposes.

The basic confusion between proportional and threshold curvilinear functions with LLE to radiation appears to lie in the fact that, with LLE, absorbed dose becomes a composite quantity. The two elements must be decoupled. If this is done, then it becomes obvious that one needs to

evaluate both P_1, the probability of a hit with injury, and P_2, the risk equivalent of the object-oriented quantity dose, as a function of increasing dose. The product of P_1 and P_2, for any given exposure, yields the risk equivalent of the field-oriented quantity exposure, the final product needed for Radiation Protection purposes. It is the failure to distinguish clearly between the risk equivalent of exposure versus that of dose, that is largely responsible for the confusion, apprehension, and outright fear that has surrounded LLE and "linear, no-threshold" relationships.

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References

1. Boice, J. D., Jr. and Manson, R. R. Breast cancer in women after repeated fluoroscopic examinations of the chest. J. Natl. Cancer Inst. 59, 823-832, 1977.

2. Skarsgard, L. D., Kihlman, B. A., Parker, L., Pujara, C. M., and Richardson, S. Survival, chromosome abnormalities, and recovery in heavy-ion-and x-irradiated mammalian cells. Radiat. Res., Suppl. 7, 28-221, 1967.

3. Bond, V. P. Quantitative risk in radiation protection standards. Radiat. Environ. Biophys. 17: 1-20, 1979.

4. Fry, R. J. M., Powers-Risius, P., Alpen, E. L., and Ainsworth, E. J. High LET radiation carcinogenesis. Radiat. Res. 104, S188-192, 1983.

5. Finney, D. J. Probit Analysis, 3rd ed., University Press, Cambridge, 1971.

6. Accident Facts. U.S. National Safety Council, Annual Report.

7. Bond, V. P. The conceptual basis for evaluating risk from low level radiation exposure. Critical Issues in Setting Radiation Protection Dose Limits. National Council on Radiation Protection and Measurements, Washington, DC 1982.

8. Bond, V. P. and Varma, M. N. Low level radiation response explained in terms of fluence and cell critical volume dose. Eighth Symposium on Microdosimetry, Julich, West Germany, pp. 423-439, Commission of the European Communities, Harwood, London, 1983.

9. Varma, M.N. and Bond, V. P. Empirical evaluation of a cell critical volume dose vs. cell response function for pink mutations in Tradescantia. Eighth Symposium on Microdosimetry, Julich, West Germany, pp. 430-450, Commission of the European Communities, Harwood, London, 1983.

10. Varma, M. N., Bond, V. P., Marshall, I. R., Robinson, C. V., and Schairer, L. A. Comparison of observed pink mutations in Tradescantia due to californium neutrons with calculated values using hit-size weighting theory. Proceedings of the Seventh International Congress of Radiation Research (J. J. Broerse, G. W. Barendsen, H. B. Kal, and A. J. van der Kogel, Eds.), B4-B42. Martinus Nijhoff, Amsterdam, 1983.

11. Bond, V. P., Varma, M. N., Sondhaus, C. A., and Feinendegen, L. E. An alternative to absorbed dose, quality, and RBE at low exposures. Radiat. Res. 104, 552-557, 1985.

12. Rossi, H. H. Spatial distribution of energy deposition by ionizing radiation. Radiat. Res. 12, 290 (1960).

Figure Legends

Fig. 1 Cancer incidence in women receiving small weekly exposures to x-radiation, for monitoring of pneumothorax treatment of tuberculosis. From Boice et al., Ref. 1.

Fig. 2 Chromatid exchanges as a function of dose, in cells exposed to strongly accelerated heavy ions, and to and x rays. From Skarsgard et al., Ref. 2.

Fig. 3 Harderian gland tumors in mice exposed to strongly accelerated heavy ions, and to x rays. From Fry et al., Ref. 4.

Fig. 4 A figure selected from the literature, in which a "linear, no threshold", and a threshold, curvilinear function are plotted on the same graph. This gives the incorrect impression that these completely different functions are simply variations of the same function.

Fig. 5 Statistics on vehicle accidents (Ref. 6) plotted as the zero-slope derivative function represented by the data (curve A), and made into an integral (cumulative) function (curve A^1). The abscissa clearly is not dose, so that the "no-threshold" cannot be interpreted as due to unusual sensitivity.

Fig. 6 The LD_{50} values for animals caused to impinge at high velocities on a hard surface. The LD_{50} for man, about 25 ft/sec (approximately 17 MPH), is an estimated value.

Fig. 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.

Fig. 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". It is clear that D is a composite quantity, with very different meanings with HLE vs LLE.

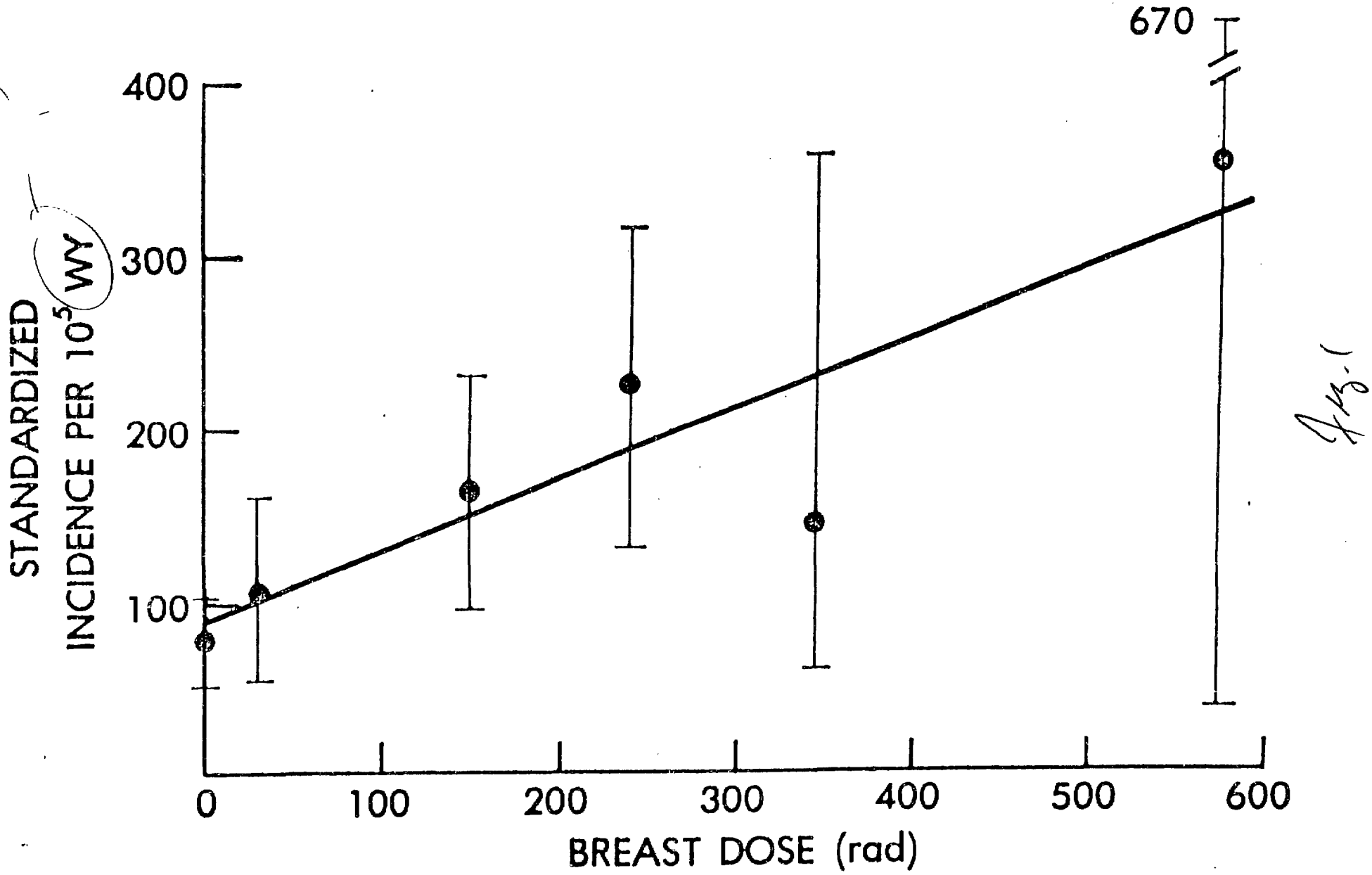
Fig. 9 A representative HSEF, for the same set of data shown in Figure 2. The abscissa is given in terms of the microdosimetric quantity y, expressed in $keV/\mu m^{-1}$, so that ready accommodation to different target diameters is possible. This can easily be converted to energy per unitmass, or "cell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

Table I

The Risk of Exposure to Moving Vehicles
U.S.A. Statistics for One Year

Persons exposed	200,000,000	
Those exposed 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 exposure, injury and death -- 1/40 x 1/100 = 1/4,000



BOND
11-671-71

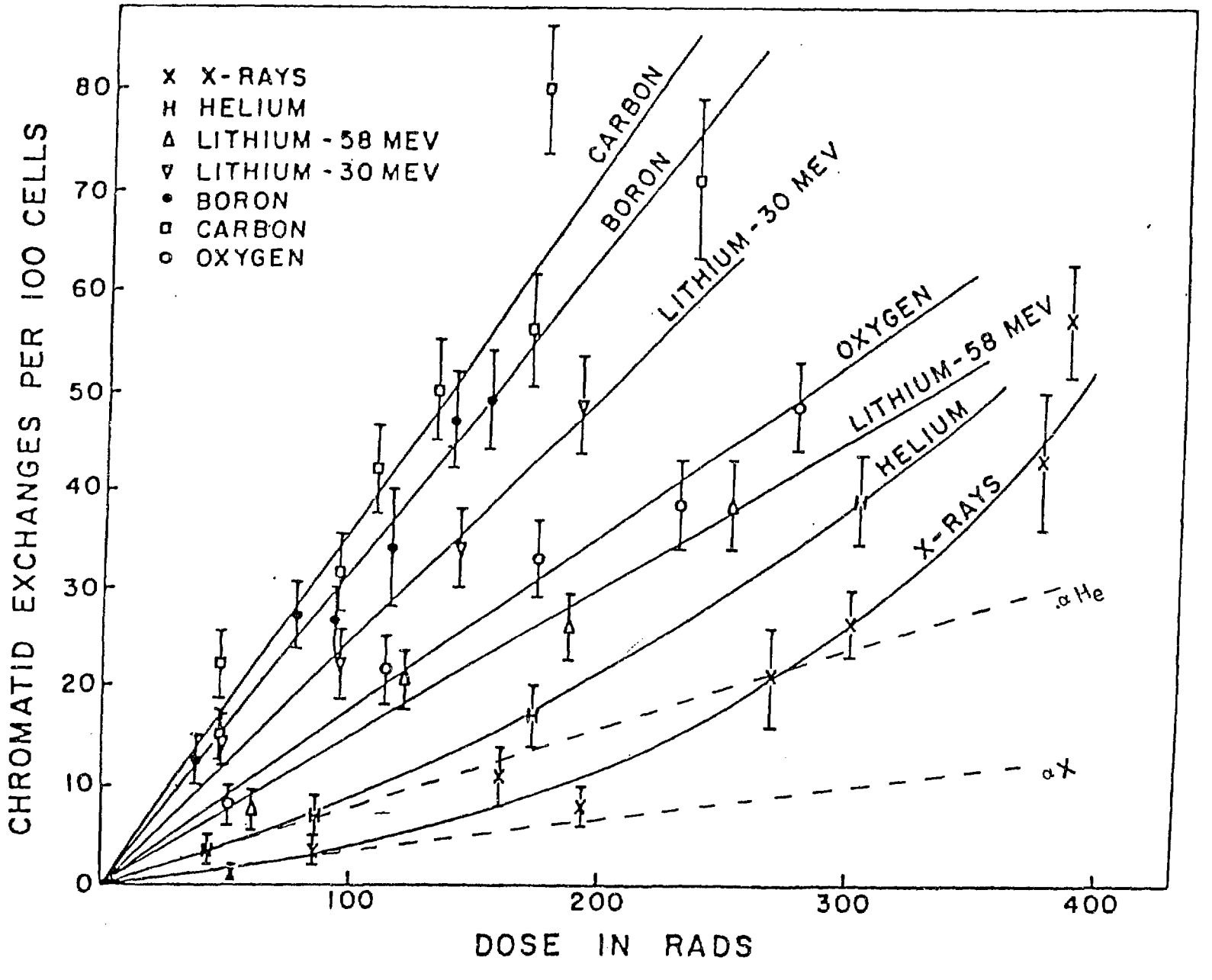


fig 2

BOND
8-31-81

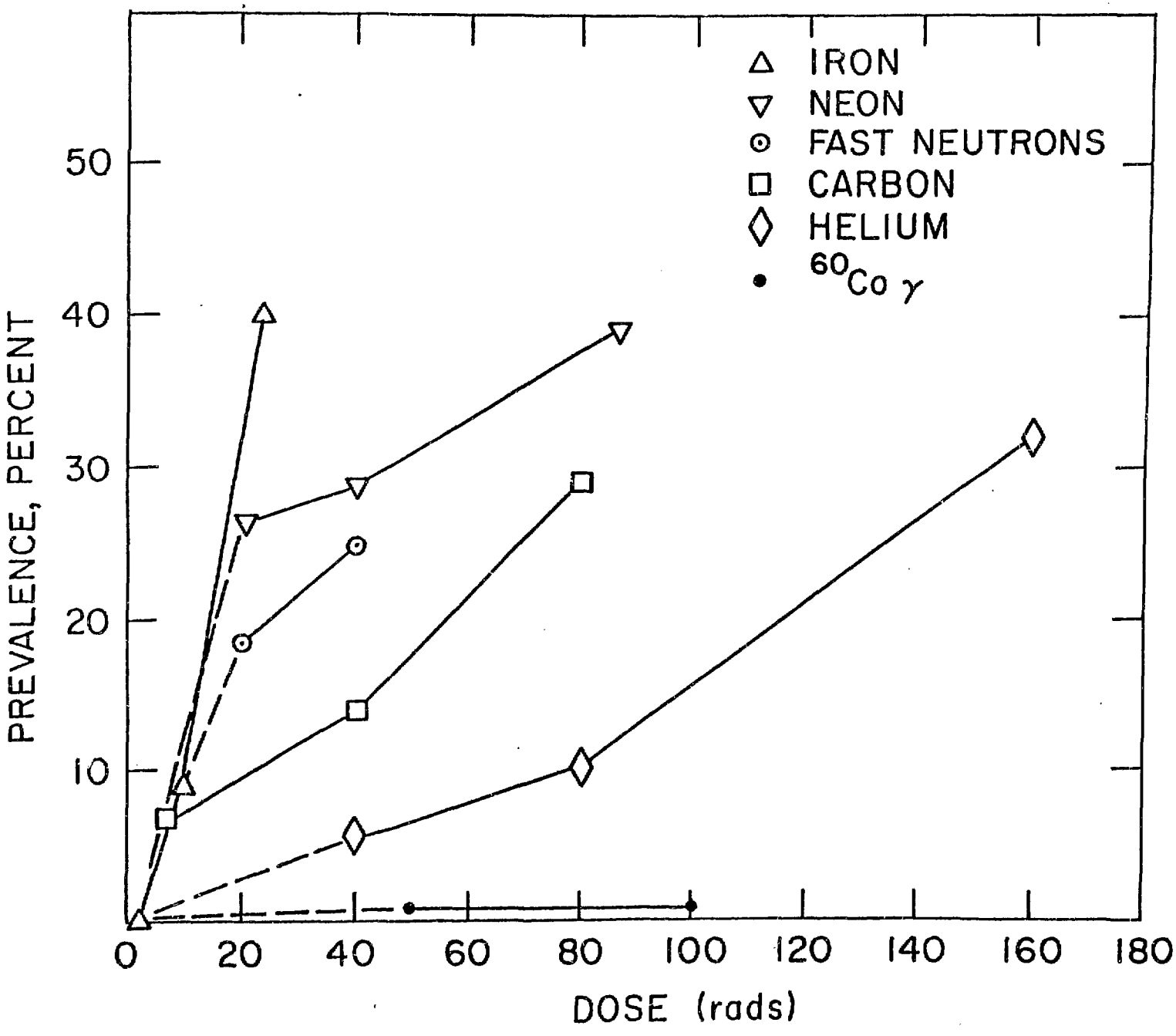


Fig 3

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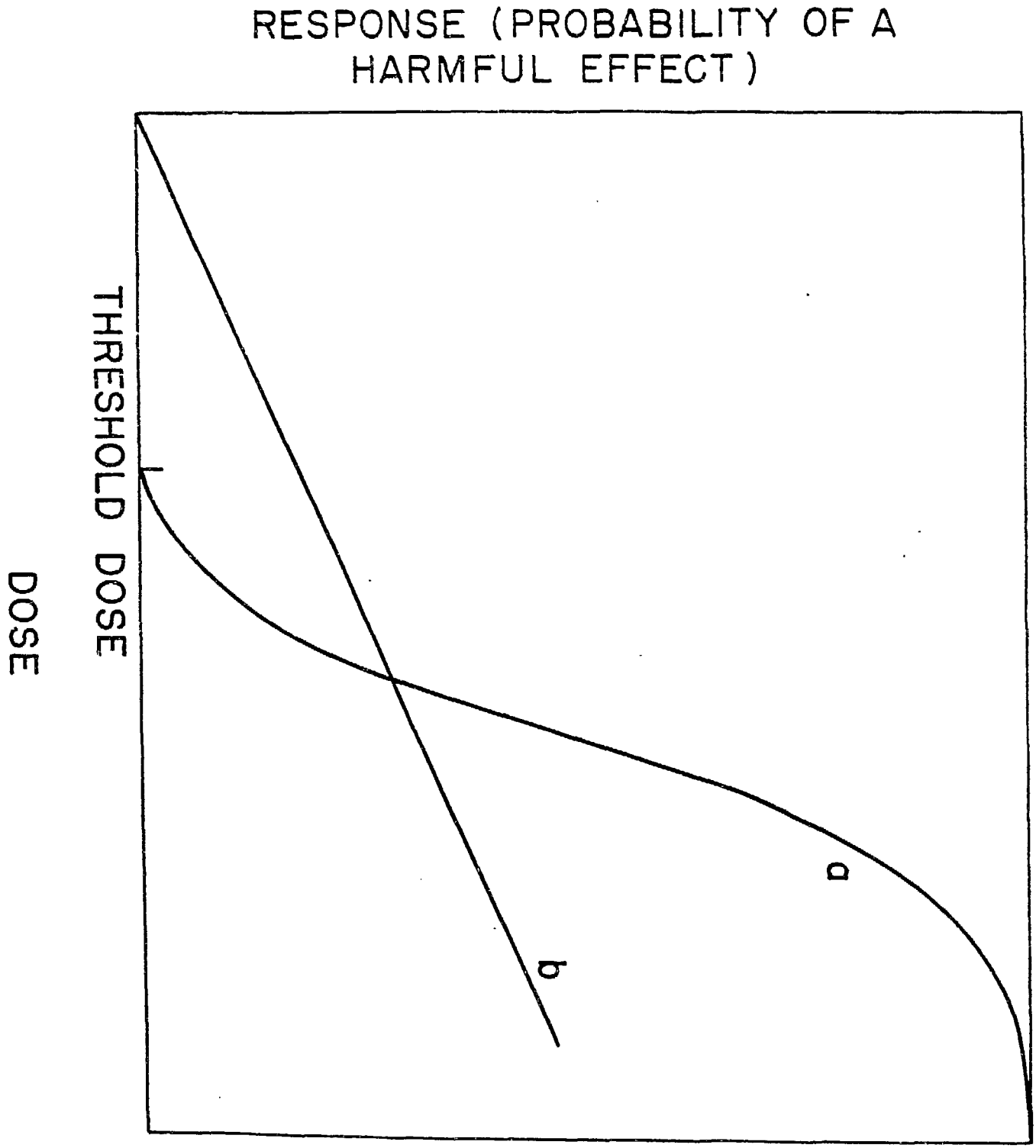
RESPONSE (PROBABILITY OF A HARMFUL EFFECT)
THRESHOLD DOSE
DOSE
a
b

Fig. 4

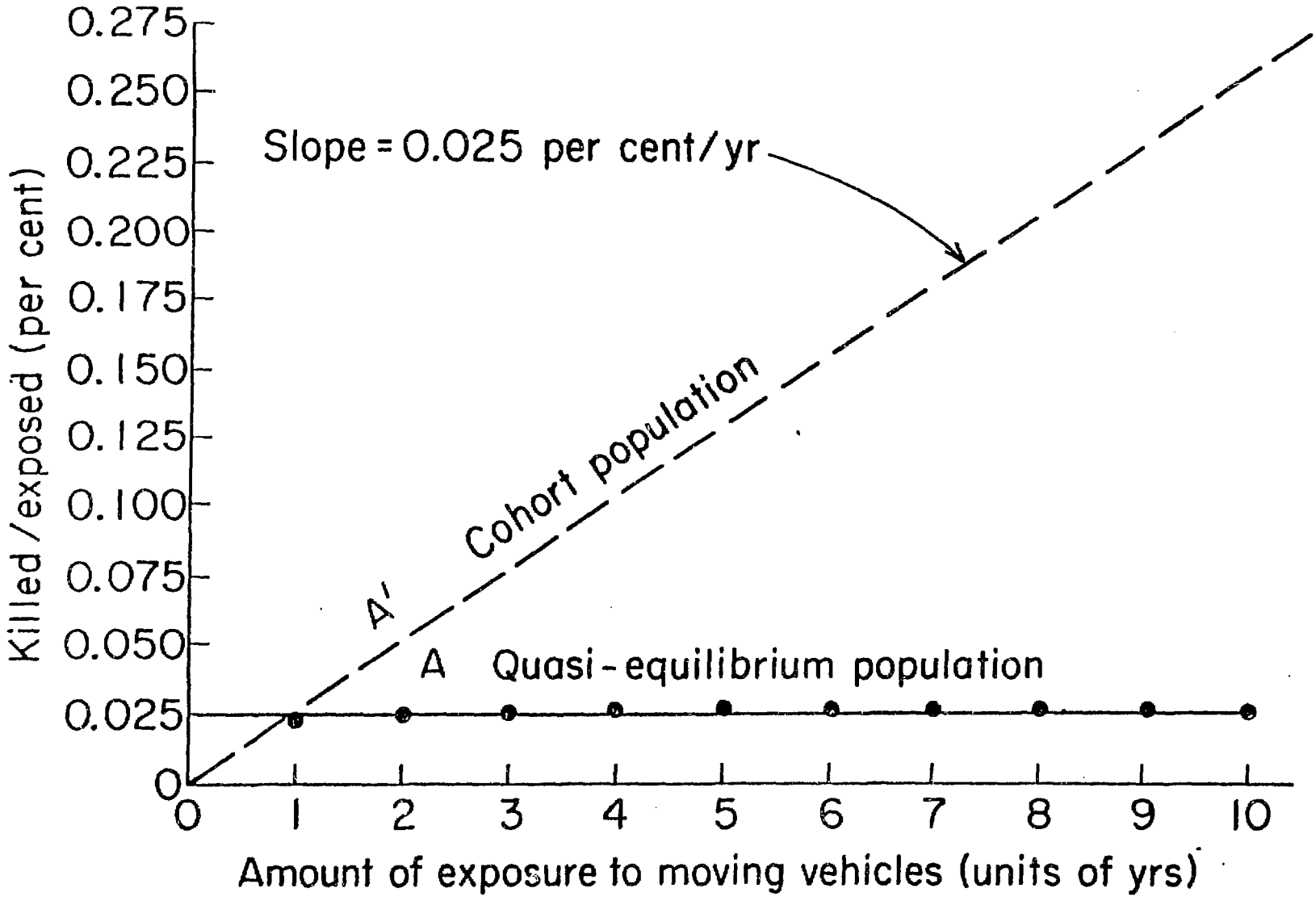

Fig. 5

BOND
1-885-83

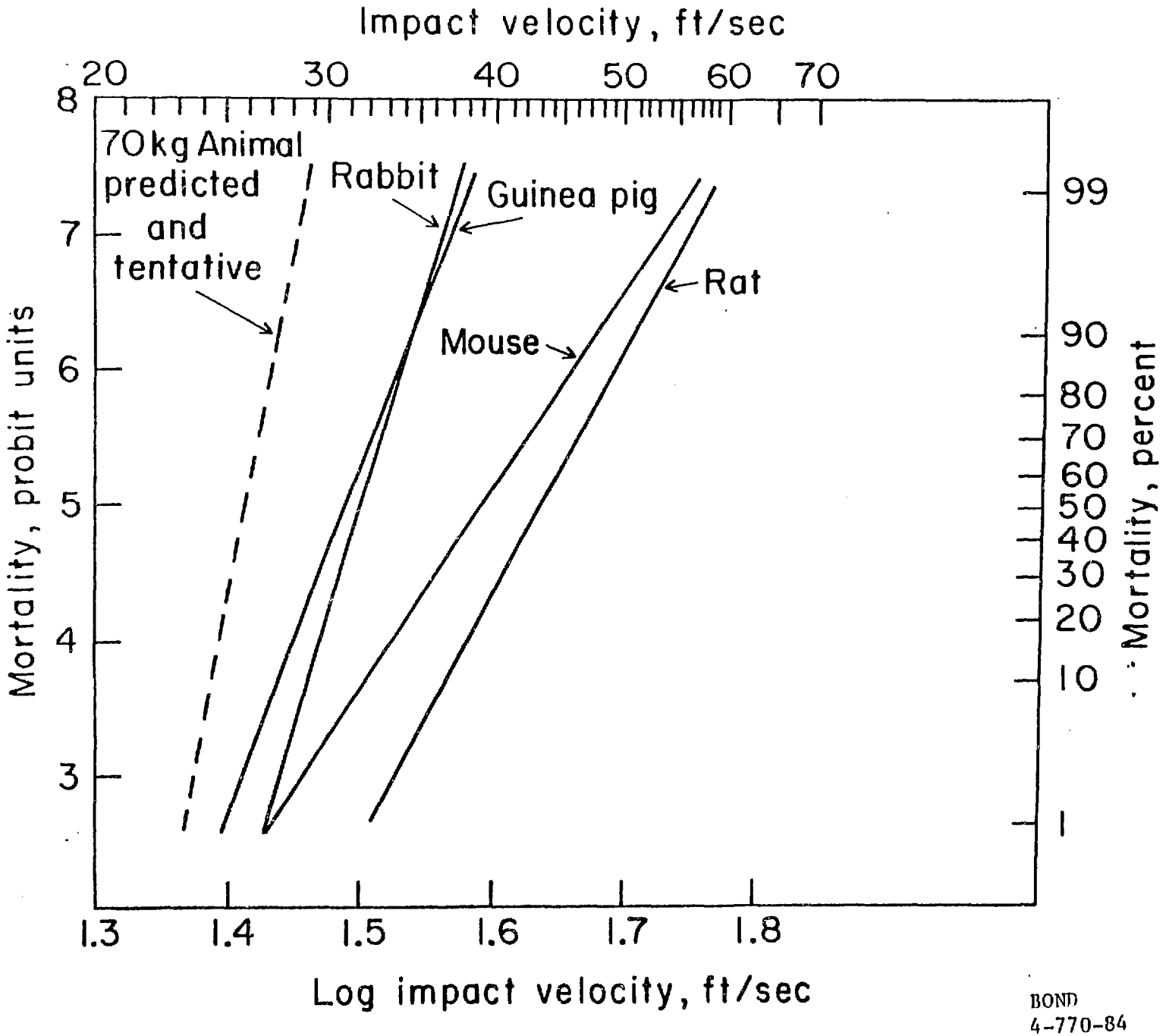
Impact velocity, ft/sec
20
30
40
50
60
70
70 kg Animal predicted and tentative
Rabbit
Guinea pig
Rat
Mouse
Mortality, probit units
8
7
6
5
4
3
99
90
80
70
60
50
40
30
20
10
1
Mortality, percent
1.3
1.4
1.5
1.6
1.7
1.8
Log impact velocity, ft/sec
BOND
4-770-84

Fig. 6

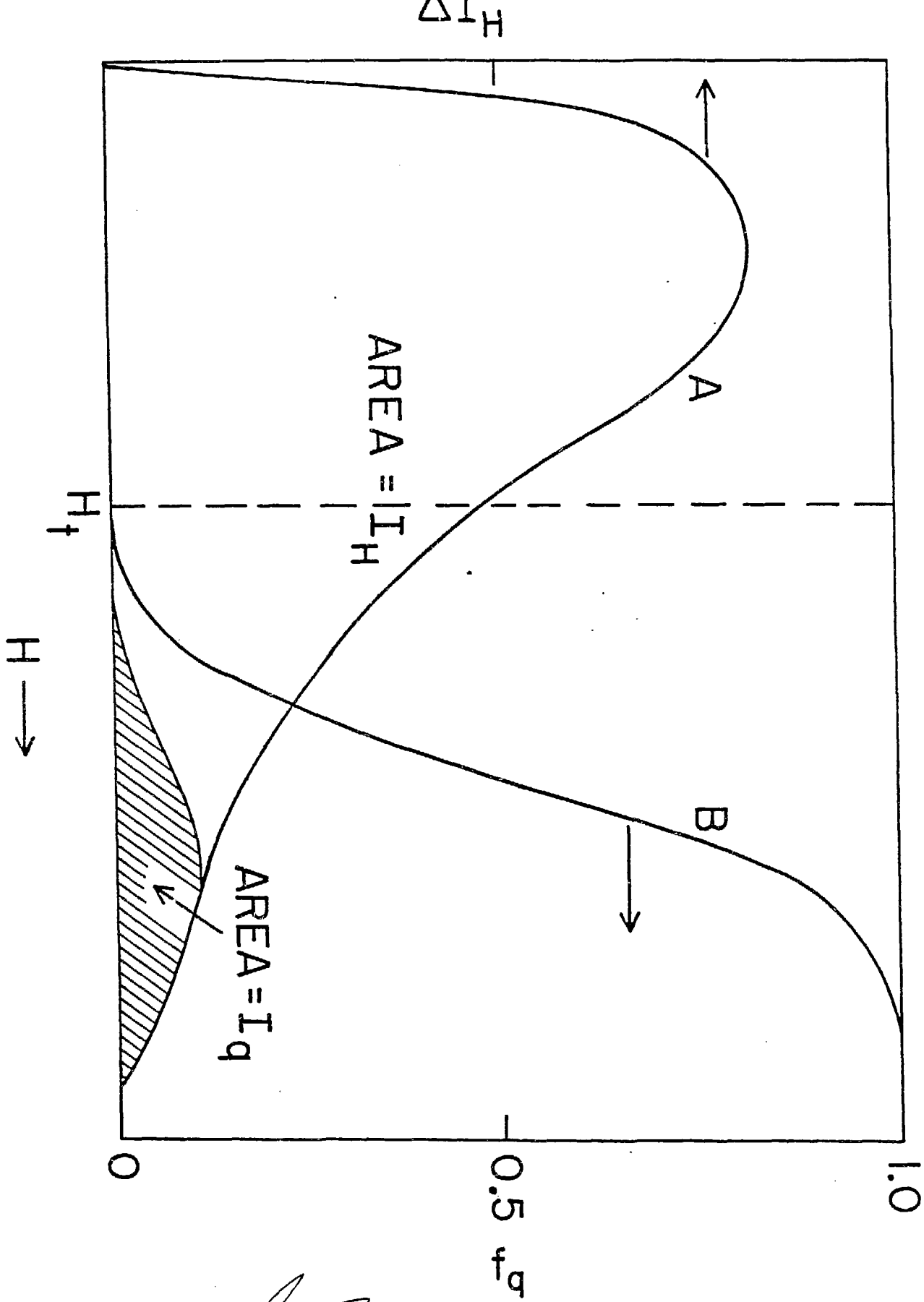

Fig 7

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

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

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

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

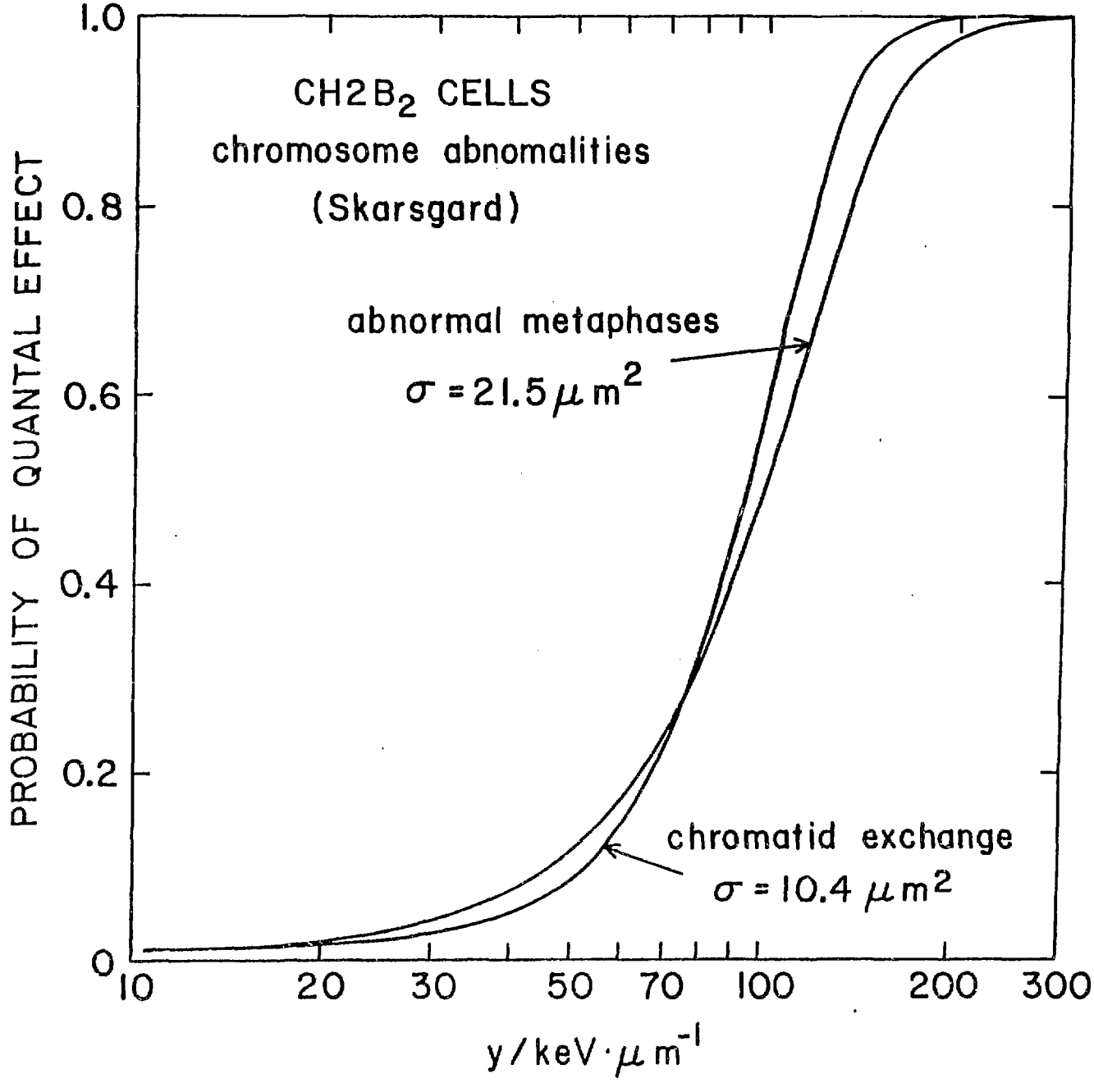
1.0
0.8
0.6
0.4
0.2
0
PROBABILITY OF QUANTAL EFFECT
CH2B2 CELLS
chromosome abnomalities
(Skarsgard)
abnormal metaphases
σ = 21.5 μm²
chromatid exchange
σ = 10.4 μm²
10
20
30
50
70
100
200
300
y / keV · μm⁻¹

Fig. 9