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Challenges to Low-Dose Linearity in Carcinogenesis from Interactions Among Mechanistic Components as Exemplified by the Concept of "Invaders"And"Defenders"

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ABSTRACT

The current practice in carcinogen risk assessment of using a linearized multistage model and assuming low-dose linearity is based on the false premise that the only relevant interaction between a chemical and the carcinogenic process is that the chemical may increase the number of attacks on DNA. This is an incomplete description of events because the chemical may affect more than one component of the carcinogenic process such as when a chemical reacts with other endogenous substances or activates a range of defense mechanisms. It has been found that there are potentially many cases in which linearity at low doses would not be expected based on the interaction between multiple components. The two-stage growth models, involving multiple mutations and cell birth and death rates, provide one means of exploring these interactions. In addition, if carcinogenesis is considered to be the imbalance between invading substances and defense mechanisms, it is relevant to develop and explore models which reflect the joint impact of such "invaders" and "defenders." In this case the probability of cancer would depend on whether the chemical increased or decreased the number of defenders or their efficiency as well as increasing or decreasing the number of invaders. A chemical's impact on multiple components of the carcinogenic process including a range of defenses, such as apoptosis, may produce a hormetic state.

INTRODUCTION

One of the current dogmas in cancer risk assessment is that, because it is possible for a single molecule of a

carcinogen to reach DNA, there cannot be a threshold for a carcinogenic effect. Furthermore, because increasing numbers of molecules are assumed to proportionately increase the chance of reaching DNA molecules and the dogma implicitly assumes that this increase in the number of molecules is the only dose-dependent event, linearity at low doses should be assumed. These assumptions have driven carcinogen risk assessment for nearly twenty years and are still accepted uncritically. Albert (1994) has recently described the casual way in which assumptions like these were first established. While it is possible for a single molecule to reach DNA, it is also possible to put a probability on such an event, based on the ratio of DNA to other reactive sites and the various defenses within the organism which may prevent the molecule from ever entering the nucleus. For a reactive chemical, the probability is so low that it can be discounted. Furthermore arguments concerning thresholds or non-thresholds are futile, because the debate should really be about the shape of the dose-response curve, including those regions where it may actually be hormetic. Carcinogen risk assessment should relate to practical considerations of public health and not to theoretical arguments of very dubious validity.

The classical models for characterizing the cancer dose-response relationship are based on very simplified representations of the mechanisms involved in the cancer process and are not detailed models reflecting the detail of the cancer process (Holland and Sielken, 1993). The earlier models such as the probit, logit, Weibull, and multihit models assume that there is a distribution of individual tolerances in the population and that cancer occurs whenever an individual's dose exceeds the tolerance. A second derivation of the multihit models assumes that a normal cell is transformed to a tumor cell after a certain number of hits. Multistage models assume that the transformation from a normal cell to a tumor cell occurs in an ordered sequence of irreversible stages. Moolgavkar and Knudson (1981) expanded the multistage model to include cell kinetics and parameters reflecting the birth and death of cells as well as transition rates from normal cells to initiated cells to malignant cells. We have extended this model (Sielken et al., 1994) to simulate the joint interactive effects of the cell birth, death, and mutation rates on the probability of a mutation occurring at the second stage within a given number of cell cycles, e.g., 20 or 50. It was found that the probability is very sensitive to the background mutation rates as well as the initiated cell death rate. Even a small initiated cell death rate greatly reduced the probability of a second mutation being found. The probability of a mutation occurring at the second stage was very low within the given number of cell cycles even though the initial mutation rate was in the range found in many mammalian cells.

Classical models of carcinogen dose-response relationships do not identify or reflect the biological processes

involved in a tolerance, hit, or stage. Thus, while the classical models may make reasonable assumptions about the general nature of the cancer process, they do not necessarily incorporate all the information that might be available concerning a specific chemical's biological properties. There are at least two possibilities for incorporating additional biological information into the classical models. One possibility is to make the functional form of the dose-dependence of any model parameter correspond as closely as possible to how the biological phenomena represented by that parameter changes with the dose. A second possibility is to incorporate as much biology as possible into the dose-metric itself. For example, the dose metric can incorporate whatever is known about the delivery process and target tissue dose corresponding to a particular exposure route and also incorporate whatever is known about what happens to that delivered dose once it reaches the target tissue. Of course, these two possibilities are not mutually exclusive.

Biological organisms are very complex systems and frequently utilize opposing forces to stabilize these systems within certain parameters. An example is the sympathetic-parasympathetic innervation of many organs, including the heart. Such systems are self-regulating and are unlikely to be linear over a wide range and may even represent dynamical systems, capable of showing chaos under certain circumstances (Scott, 1991). The actions and reactions of the animal or human body to a variety of stress situations has been studied in great detail. In terms of exposure to chemicals, it is well known that organisms may increase their ability to metabolize and detoxify an exogenous chemical and also that exposure may lead to the depletion of endogenous substances which are protective, such as glutathione, vitamin C or vitamin E. The converse is also possible - metabolism may lead to toxification and some exposure may increase the production of protective substances. It is even possible for protective substances to lead to increased damage, e.g., an antioxidant which is oxidized to a free radical, the detoxication pathway for which has been depleted ("traitors").

The potential importance of the defense-response phenomenon emerged for us from recent research on phenobarbital and dieldrin, because these substances not only induce the production of free radicals of oxygen (invaders) from the P450 system of mice, but like other enzyme inducers, they also increase the synthesis rate of vitamin C (defenders) or glucaric acid in other species. The increased urinary excretion of either vitamin C or glucaric acid has been used as an indirect measure of enzyme induction in animals and humans. Dieldrin and phenobarbital induce DNA synthesis in liver cells of some species, an effect which may be inhibited by vitamin E, vitamin C or glucaric acid by analogy. The DNA synthesis response to phenobarbital in the rat is only transient and

may reflect a shift in the balance between invaders and defenders occurring with time.

Food constituents such as sucrose, vegetable oils and animal fats have been shown to promote tumor formation in mouse livers, mammary glands and other organs. A potential mechanism for this is by depleting defenses, or removing defense substances from the diet rather than a genotoxic effect. For example, sucrose has been used experimentally to deplete glutathione both *in vitro* and *in vivo.*

THE CONCEPT OF "INVADERS" AND "DEFENDERS"

Sielken (1987) used the term "invaders" and "defenders" in demonstrating that linearity at low doses is not inevitable. We have found that these terms have the advantage that the concepts are readily understood by non-scientists, who quickly appreciate that individuals may have the capability of changing their personal balance by acting on some widely known recommendations such as increasing the intake of fruits and vegetables.

If health, including the lack of cancer, is regarded as a favorable balance between these two opposing forces, then a somewhat different concept from the conventional low-dose linearity emerges. The point of balance is defined initially by genetic factors, but the organism has the ability to load or unload the "pans" of the balance by behavioral practices or exposure patterns. Diet is one of the more important modulators of the balance. An example is provided by SchmÑhl et al. (1979) who dosed rats with a constant amount of carcinogen and then determined the response to a range of diets. Not only was the time of death significantly impacted by diet, but also the tumor types were altered. Thus, the dose-response is not only a function of exposure to a carcinogen, it can be altered dramatically by other factors. In some cases, such as childhood cancers, the genetic component may be overwhelming. However, for the majority of tumors, the impact of "environmental" factors is a key element (in this context, "environmental" is defined as everything that is not incorporated in the genetic code). An example of the importance of such factors is provided by epidemiology studies such as those of Enstrom (1989) on Mormon populations in California. He showed that the standardized mortality rates for cancer can be only half of the control population living in the same area, if some relatively modest life-style modifications are implemented. Current regulatory strategies in the U.S.A. strive to reduce the marginal risk but ignore large risks which could be reduced by life-style changes.

MODELING TO INCORPORATE THE CONCEPT OF INVADERS AND DEFENDERS INTO THE DOSE METRIC

The concept of "invaders" and "defenders" can enter the dose-response modeling process by becoming a part of the determination of the dose scale used for dose-response modeling, that is, the dose metric. If the net amount of cellular activity corresponding to a given delivered dose to the target tissue depends on the number of "invaders" and "defenders," as well as their efficiency in dealing with the opposition, then this dependence can be incorporated into the determination of the dose metric corresponding to the biologically effective dose. The latter can be either positive or negative in this concept; i.e., it may result from either the addition or subtraction of "invaders" or "defenders."

Hormesis, which is a non-specific beneficial effect which may be seen at low exposures of agents which at higher doses may be toxic, may be explicable in part by the mobilization of defenses in excess of those needed strictly to deal with current insults.

The biologically effective dose should reflect the number of "invaders" that break through the "defenders" and, hence, become free to do their damage. The number of such breakthroughs depends on the number of "invaders" (NI), the number of "defenders" (ND), the probability (p) that a "defender" defeats an "invader," and the rules of "combat" (e.g., whether or not defeat of one "invader" at least temporarily reduces the number of "defenders" by one). For example, the probability that an "invader" breaks through ND "defenders" each with an efficiency p, is (1-p)ND, and the probability that the "invader" is defeated by the third "defender" it encounters is (1-p)2 p. Computer programs evaluating the probabilities associated with each possible outcome of the struggle between multiple "invaders" and "defenders" or simulating the struggle using Monte Carlo techniques have been written.

The impact of the concept of "invaders" and "defenders" on the number of breakthroughs (and, hence, on the biologically effective dose) can be explored simply by considering what happens with different numbers of each, not only in terms of their proportions, but also in terms of their functional efficiency. Figure 1 illustrates the number of breakthroughs when the chemical affects only the number of "invaders" or "defenders" but not both simultaneously. The case on the left shows the growth in breakthroughs (biologically effective dose) when the number of "invaders" is increased while the number of defenders is held constant. The case on the right shows what is predicted for a constant number of "invaders" as the number of the "defenders" is decreased (from 55 to 25 on the abscissa). In Figure 1 the two dose-response slopes have similarities. Figure 1 also shows that, if the defenses have no chance of success, then the response to increasing numbers of "invaders" is linear. However, even a seemingly small

chance of success by an individual defender has a dramatic effect on the number of breakthroughs and introduces low-dose nonlinearity into the dose-response relationship. A threshold-like shape is obtained at higher defender efficiencies which would mean non-response for carcinogens at doses less than the minimum dose corresponding to a significant probability of a breakthrough.

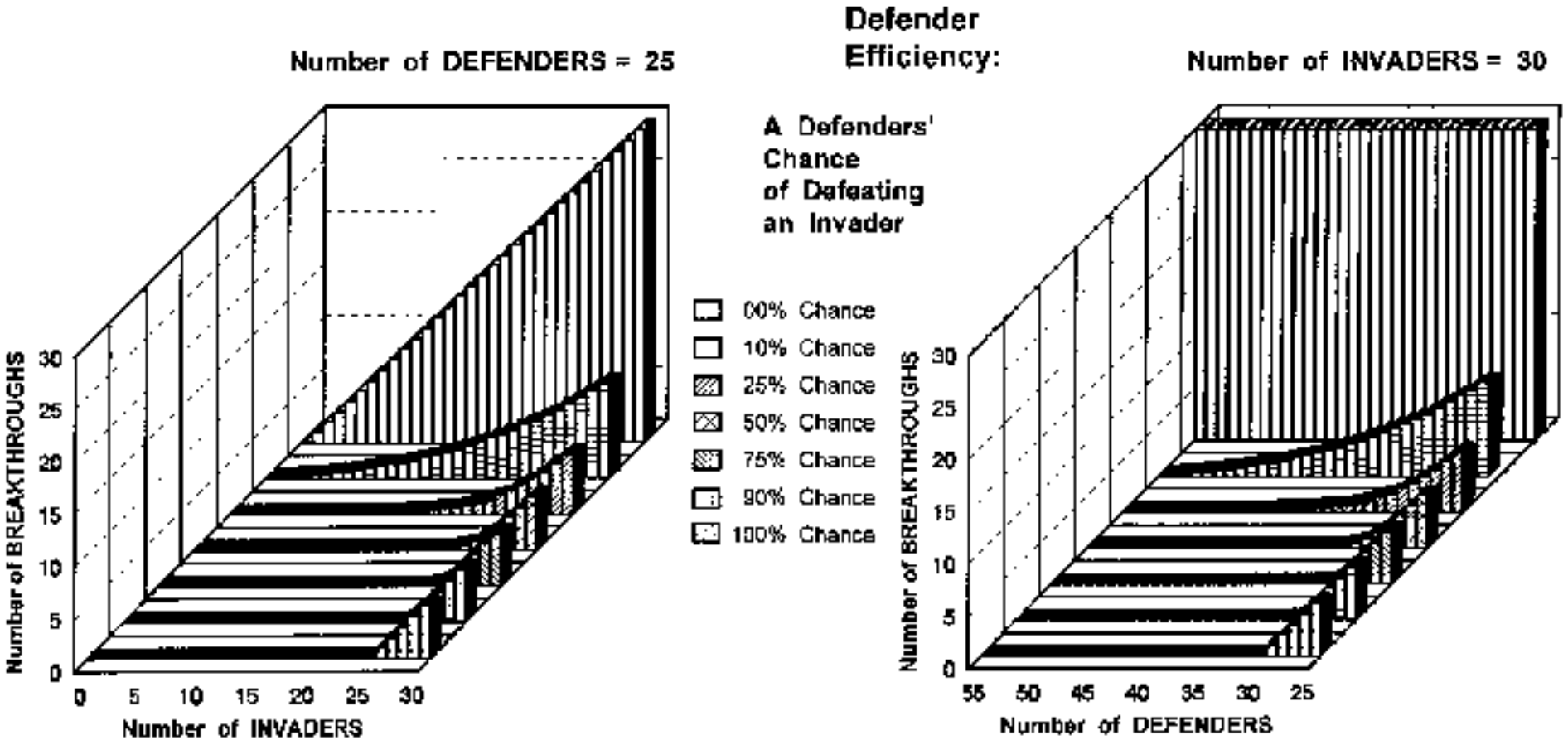


Figure 1. The Dependence of the Number of Breakthroughs on the Interaction Among the Number of Invaders, Number of Defenders, and Defender Efficiency

The cases shown in Figures 1 represent the simple situations where dose only affects either the number of "invaders" or "defenders" but not both. Figure 2 provides an example in which the chemical is assumed to have a dual action; that is, the dose affects both the number of "invaders" and either the number of "defenders" or their efficiency. The figure shows that a hormetic effect can occur when dose affects both "invaders" and "defenders." The hormetic effect on the number of breakthroughs would correspond to a hormetic effect on the cancer probability in any dose-response model in which the cancer probability is essentially proportional to the "biologically effective dose." For example, the cancer probabilities in any one-hit or linearized multistage model where "administered dose" has been replaced by "biologically effective dose" would decrease as long as the administered dose resulted in a decreasing number of breakthroughs. In Figure 2, the number of invaders is increasing linearly with dose while the number of defenders has a moderate, saturable increase with dose. The figure shows the results of 10,000 simulations for 40 doses and a control. It should be noted that even a modest saturable increase in the number of "defenders" around doses 3-8 produced a hormetic effect even though the number of "invaders" was increasing linearly in this same range. This example assumed a saturation of the increase in the number of defenders at a low dose whereas a non-saturable linear increase in the number of "defenders" would have produced a greater hormetic effect or even non-response.

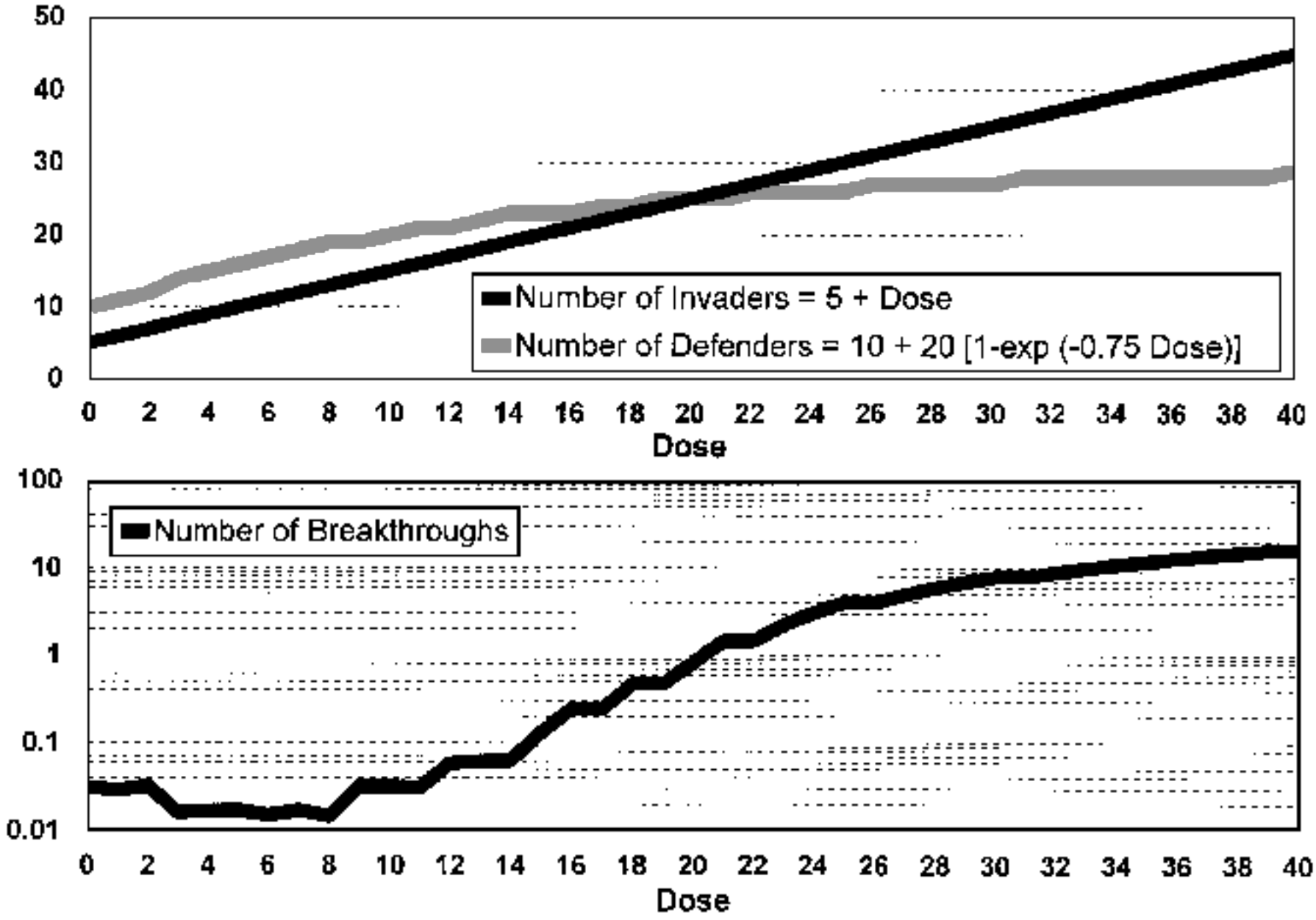
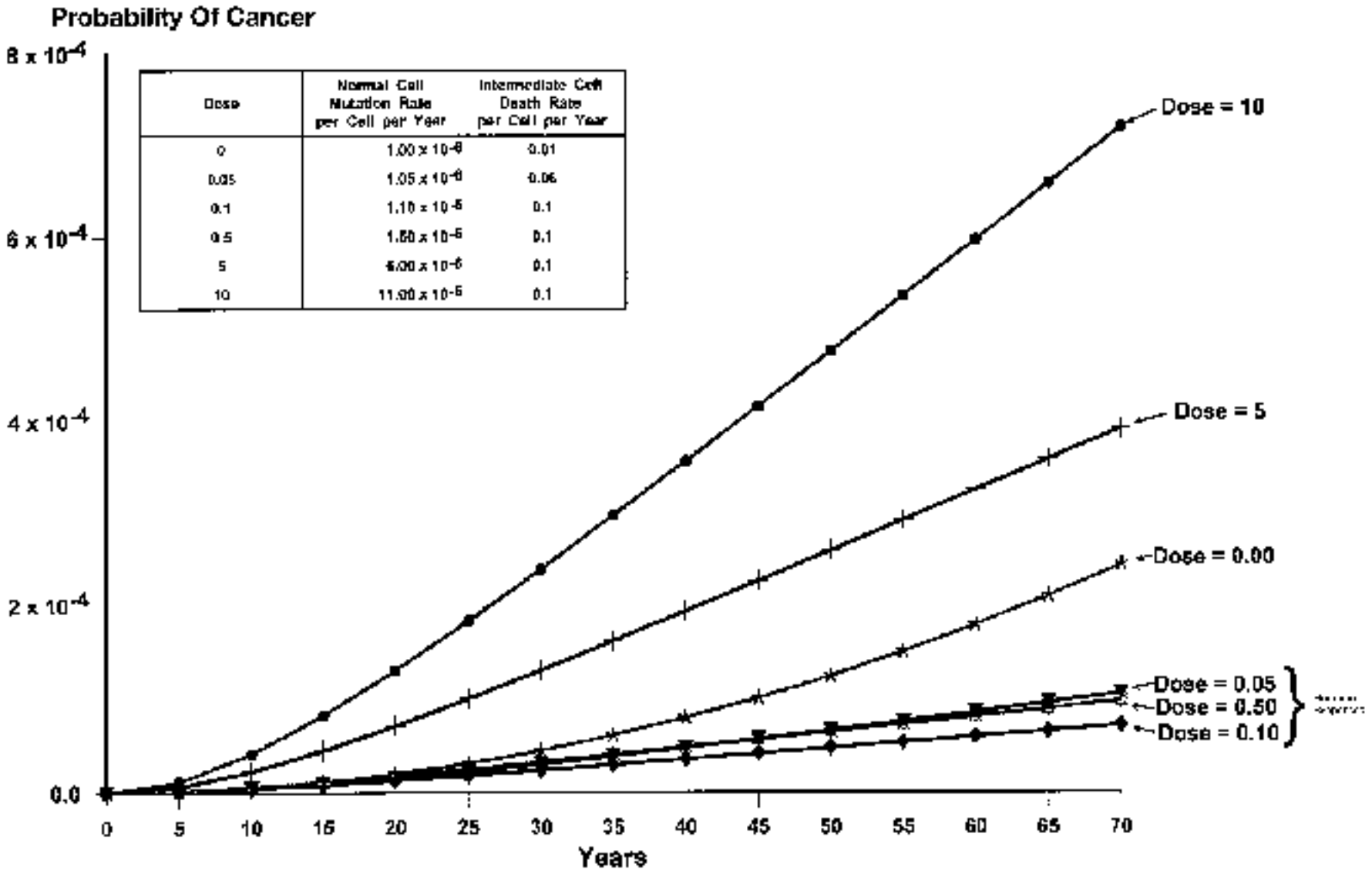


Figure 2. An Example of a Hormetic Effect on the Number of Breakthroughs Associated with a Linear Increase in the Number of Invaders with Dose Being Accompanied by a Saturable Increase in the Number of Defenders

A wide variety of different relationships between dose and the number of "invaders," number of "defenders," and the "defender" efficiency can exist, and the corresponding impact on the number of breakthroughs and cancer probability can be quantified. Only by focusing on a hypothesized increase in the number of "invaders" and neglecting other components of the carcinogenic process can low-dose linearity be assumed.

MODELING TO INCORPORATE THE INTERACTION BETWEEN MULTIPLE COMPONENTS IN A TWO-STAGE CARCINOGENIC PROCESS

Because the death of cells containing a mutation may also be considered a defense mechanism, this possibility was examined in a two-stage model of the Moolgavkar-Venzon-Knudson (MVK) type. In Figure 3, the normal cell mutation rate increased linearly with dose while the initiated cell death rate increased in a saturable fashion from 1% to a maximum of 10% per year. In this example, only the two highest doses showed a positive response, while the lower three doses exhibited hormesis. In a typical bioassay, with only a maximum tolerated dose (MTD) and a second dose at one-half the MTD, any such hormetic effect would have been missed. It is striking that even a modest increase in the initiated cell death rate can have a dramatic effect on the response frequency. Of course, it is also evident in this example that a linear increase in a mutation rate does not necessarily correspond to a linear increase in cancer probability (low-dose linearity).



Dose	Normal Cell Mutation Rate per Cell per Year	Intermediate Cell Death Rate per Cell per Year
0	1.00×10^{-6}	0.01
0.05	1.05×10^{-6}	0.06
0.1	1.10×10^{-6}	0.1
0.5	1.50×10^{-6}	0.1
5	6.00×10^{-6}	0.1
10	11.00×10^{-6}	0.1

Figure 3. An Example of a Hormetic Effect on the Cancer Probability in a Two-Stage Growth Model Associated with a Linear Increase in the Normal Cell Mutation Rate Being Accompanied by a Saturable Increase in the Intermediate Cell Death Rate

The example in Figure 3 is just one of many possible examples in which the joint dose-dependence of two or more parameters can result in a cancer dose-response model without low-dose linearity.

DISCUSSION AND CONCLUSIONS

The concept of "invaders" and "defenders" is presented to stimulate interest in the multifactorial nature of the dose and dose-response modeling of carcinogens and to highlight the fact that the "defenses" can play a major role in the determination of the carcinogenic response. It can be predicted, for instance, that an increase in tumor incidence may occur without additional exposures to carcinogens if the defenses are depleted. This side of the balance is not normally considered in the modeling of the carcinogenic process. We have been surprised by the number of factors which may produce hormetic effects in simulations. This suggests that hormesis may be more widespread than generally recognized, but that it may be confined to a range of doses which may fall below those commonly employed in chronic bioassays, particularly if only the MTD and half this dose are used.

It has been assumed with less than critical reasoning, that low-dose linearity is a general phenomenon. The "invaders-defenders" model indicates that even if the formation of DNA adducts is linear, there are many other factors which may lead to low-dose nonlinearity or even hormetic responses.

The concept of "invaders" and "defenders" has a high degree of practical importance for the evolution of attitudes towards the reduction of the incidence of cancer. It demonstrates that attention to factors which increase defenses may be as important as the search for environmental carcinogens. It also leads to the realization that cancer may not only be the result of exogenous exposures - if there is a steady stream of endogenous invaders derived from normal metabolic processes, depletion of defenses will also result in disease. It is not generally recognized how often this may occur, for non-specific insults such as stress are capable of doing just this.

We now have the modeling tools to explore the variety of factorial combinations that may lead to a range of dose-response shapes. It is hoped that this short note will stimulate interest in further

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RADIATION HORMESIS: AN EVOLUTIONARY EXPECTATION BASED UPON EXPOSURE TO BACKGROUND RADIATION

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SUMMARY
A fundamental tenet of evolutionary biology is that organisms are adapted to the environments or habitats in which they normally occur. This means that highest survival or fitness is expected when organisms are exposed to background radiation levels. Therefore radiation hormesis is an evolutionary expectation. However, most claims for radiation hormesis are based on short intense exposures which therefore are "artificial habitats" and cannot contribute to the evolutionary argument. An exception comes from some whole-of-life experiments in unicellular organisms at exposures including background; these experiments are suggestive of radiation hormesis. There is a need for additional whole-of-life studies around background exposures in organisms such as nematodes, insects and small mammals. On evolutionary grounds the results obtained may be applicable to humans and hence to radiation protection criteria.

INTRODUCTION
Criteria for radiation protection are largely based on the linear extrapolation of the harmful effects of radiation at high doses and rates to low doses and rates. This linear no-threshold model assumes that there is no threshold below which harmful effects are reduced or do not occur. Since much of the debate on radiation protection concerns quite small changes in radiation exposure and rare events such as specific genetic defects and carcinomas, it becomes almost impossible to assess the effects of small variations in radiation exposures especially around background levels. In the discussion to follow I consider an approach based upon an expectation from evolutionary biology that organisms are best adapted to live at background radiation exposures (see also Parsons, 1989, 1990, 1992).

THE ENVIRONMENT AND THE EVOLUTIONARY EXPECTATION

The fitness of organisms - or their capacity to survive, reproduce, grow and contribute to future generations - should be maximal in the habitats or environments in which they normally occur. This is a fundamental tenet of evolutionary biology as developed by Charles Darwin and subsequently refined by evolutionary biologists to this day. Since radiation is part of our normal environment, it follows that fitness should be highest at around background exposures. These are commonly 2 - 2.5 mSv y-1 but up to ten times higher in certain regions of the world. One implication is that fitness at exposures close to zero radiation should be lower than around background exposures. This means that radiation hormesis is expected on evolutionary grounds.

There are many claims for radiation hormesis in experimental organisms covering a wide range of taxa including plants, invertebrates and vertebrates (Luckey, 1982). These studies are almost universally based on short and intense exposures, so that connections with natural background exposures cannot be directly made. For the testing of the evolutionary expectation these are therefore "artifical habitats" and cannot be used as a valid test for radiation hormesis in free-living populations. In contrast whole-of-life studies are needed to replicate the habitats or environments in which organisms normally occur.

For the experimental testing of the possibility of radiation hormesis the following considerations are important:

(1) Whole-of-life studies are needed including exposures around background levels.

(2) For comparisons with background levels, a set of data is required close to or at 0 exposure using radiation-shielding devices.

(3) The practical estimation of fitness differences which may be quite small is not simple. It involves all individuals in a population rather than a small minority as in many studies of rare genetic defects and carcinomas in populations.

These criteria suggest that short-lived rapidly breeding organisms not taking up excessive space should be used.

For instance, Planel et al (1987) carried out studies on growth rates in the unicellular protozoan, Paremecium tetraurelia, at three exposures of gamma-radiation:

(1) Background background radiation, 1.75 mSv y^{-1}

(2) Using using a 10cm Pb shield giving, 0.3 mSv y^{-1}

(3) The the shielded chamber in (2) but with the addition of the radionuclide ^{232}Th giving 7 mSv y^{-1}

All other environmental conditions were standardized. Based upon the evolutionary argument the growth rate in (2) should be <(1). Furthermore, since background radiation levels exceed that of (3) in many parts of the world, the growth rate in (2) should also be <(3).

In three experiments the growth rate in (2) turned out to be around 2/3 of that in (1) and (3). In other words creating an artificial environment close to 0 exposure reduced fitness. This is in accord with the evolutionary expectation and suggests radiation hormesis.

In any organism where such tests can be carried out parallel predictions apply. However, because of the need for radiation shielding and for large numbers of organisms to be grown under controlled laboratory conditions for fitness estimates, the possible organisms for such studies are restricted. Candidate organisms may include the nematode, *Caenorhabditis elegans*, the vinegar fly, *Drosophila melanogaster*, and the house mouse *Mus musculus*.

UNDERLYING MECHANISMS

Hormesis is a deviation from the linear extrapolation model of radiation effects. Mechanisms leading to such deviations include the enhancement of DNA repair, increase of free radical scavengers and the stimulation of antigen production (Wolff, 1989; Sagan and Cohen, 1990).

Mechanisms underlying hormesis are however more readily understood for some organic metabolites than for radiation. An example is acetaldehyde, an intermediary in the metabolism of ethanol to acetic acid, which is normally regarded as highly toxic in insects, rodents and humans. However, it is a metabolite of high intrinsic activity and low

concentrations occur in nature, even if transiently. Hence there is an expectation of higher fitness at low concentrations than at zero concentration. For instance, in the fruit fly genus Drosophila exposure to 0.1% acetaldehyde doubled the longevity of flies compared with 0%. However as concentrations are increased this extension of longevity rapidly fell so that at concentrations just above 1% flies died rapidly. Furthermore, larvae were attracted to low acetaldehyde concentrations, and repulsion occurred at concentrations where acetaldehyde became toxic based on adult longevity data (Parsons, 1989).

This is an example of habitat-related chemical hormesis where the underlying mechanism is clearer than for radiation. If the biological effects of low levels of ionizing radiation were equivalently well understood, this would assist in debates on the validity of radiation hormesis.

EXTRAPOLATING TO HUMANS?

Although controlled experiments involving esposure to radiation cannot be carried out in humans, data sets can be very large permitting epidemiological studies. For instance, some U.S. and Chinese populations have been surveyed for relatively rare events such as various carcinomas in relation to varying background radiation levels. Some of these data sets are incompatible with the linear no-threshold model for the effects of exposure to radiation. Indeed, Hickey et al (1981) drew attention to the possibility of hormesis arguing for its likelihood because of exposure to background radiations in the environment that have occurred throughout biological evolution. However, unknown corelated effects can lead to interpretative difficulties in epidemiological studies so these results can be regarded as no more than suggestive.

The A-bomb survivors in Japan have been studied extensively and radiation hormesis has been claimed. For instance, survivors exposed to 500-1490 mSv showed significantly lower mortality from non-cancerous diseases than unmatched controls (Mine et al, 1990), and similar patterns have been established for various cancers especially leukemia but at somewhat lower exposures (Kondo, 1990). However, the A-bomb caused short intense exposures so the survivors cannot be validly used as a test for radiation hormesis in natural populations. The dilemma is that as the exposure to the A-bomb survivors approaches background, the sample size needed exceeds that available. This is highlighted by Vogel (1992) who comments "the bulk of the evidence points to only small effects of low or moderate radiation doses, effects that will probably be buried in the background noise of changeing patterns of human morbidity and mortality".

In view of the difficulties of accurately measuring the biological effects of low levels of exposure to ionizing radiation in humans, there is a need for experiments to seek evidence for hormesis in multicellular organisms that can be handled experimentally under controlled conditions. This is because the evolutionary expectation of hormesis is similar irrespective of taxa. In other words if a case for radiation hormesis were established in various invertebrate and vertebrate taxa at similar whole-of-life exposures, they should be applicable to humans as a first approximation. Such results could therefore assist in considerations of exposures in the context of radiation protection.

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