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Topics under Debate

IS THE LINEAR-NO-THRESHOLD HYPOTHESIS APPROPRIATE FOR USE IN RADIATION PROTECTION?

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INTRODUCTION

There are few things more important to the practice of radiation protection than the basic assumptions regarding the actions of ionising radiation at low levels. As well, there are few things that have caused more consternation among investigators due to the fact that data relating to the biological effects of low levels of ionising radiation have such large uncertainties. Given the data have large uncertainties; it is useful to consider whether the simple hypothesis of a linear-no-threshold relationship is appropriate for use in radiation protection. The two participants in this debate have extensive experience in research on the biological actions of ionising radiation, and the implications of those actions for radiation protection.

David Brenner is Professor of Radiation Oncology and Public Health at Columbia University, and is Director of the Columbia Radiological Research Accelerator Facility. His research is divided between low dose and radiotherapeutic applications. In the low-dose realm, he has focused on mechanisms of chromosome aberration formation, and on methods to apply what is known from radiobiology to radiation risk estimation. He is the author of about 150 peer reviewed papers and two books. He has been the winner of the Radiation Research Society Young Investigator Award. He is currently a member of the NCRP and is a co-author of NCRP Report No. 136, *Evaluation of the Linear-Nonthreshold Dose-Response Model for Ionizing Radiation.*

Otto Raabe is Professor of Radiation Biophysics and Environmental Engineering in the Institute of Toxicology and Environmental Health, the Department of Veterinary Molecular Biosciences, and the Department of Civil and Environmental Engineering at the University of California, Davis. He served as President of the Health Physics Society and the American Academy of Health Physics, and he was awarded the Distinguished Scientific Achievement Award from the Health Physics Society in 1994. Professor Raabe is author or co-author of over 250 scientific publications. He is internationally known for his research in radiation biology and biophysics, radiological health, radionuclide toxicology, radiation risk assessment, aerosol science, airborne particle characterisation, airborne toxics, inhalation toxicology, properties of radioactive airborne particles, internal radiation dosimetry, and the dose-response relationships for internally deposited radionuclides. He is editor of the textbook, *Internal Radiation Dosimetry*, published 1994 by Medical Physics Publishing Co., Madison, WI.

FAVOURING THE PROPOSITION: D. J. Brenner

Argument

At very low doses, say below 10 to 100 mGy, the reality is that we do not know the shape of the appropriate dose-response curve, because the signal to noise ratio of epidemiological or even laboratory data becomes too small. All the dose-response relations shown in Figure 1 are possible descriptors of low-dose radiation oncogenesis – and indeed, as we shall discuss, different endpoints (e.g. carcinoma *vs.* sarcoma induction, breast- *vs.* lung-cancer induction) may well show qualitatively differently shaped responses.

It will be argued that, for an overall description of low dose radiation-induced cancer, the weight of evidence is for curve *a* (linear / no threshold [LNT]). There are certainly scenarios, each of which probably applies to some endpoints, where a linear extrapolation could *underestimate* some low-dose risks (e.g., curve *b* [downwardly curving]), and also where a linear extrapolation could *overestimate* some low-dose risks (curves *c*, *d* or *e* [upwardly curving, threshold, or hormetic]). However, for overall cancer induction at low doses, there is no preponderance of evidence suggesting that either of these classes of non-linear dose responses have a greater, or even as great, a general applicability as does an LNT dose response.

At the low and intermediate doses that are generally amenable to investigation (typically 100 mGy to 1 Gy in epidemiological studies, 10 mGy to 1 Gy in the laboratory), there are a wealth of data, both from epidemiological studies and from laboratory studies of mutation and chromosome aberration induction, that are consistent with a linear dose-response relation (curve a in Figure 1). The data are extensively reviewed in the recent NCRP Report 136[1] which concluded "*although other dose-response relationships for the mutagenic and carcinogenic effects of low-level radiation cannot be excluded, no alternate dose-response relationship appears to be more plausible than the linear-non-threshold model on the basis of present scientific knowledge*".

At still lower doses, one necessarily must rely on biophysical arguments. The biophysical arguments for linearity (curve a) are essentially[1]:

1. Tumors are largely of monoclonal origin;
2. High doses of ionising radiation can produce sufficient damage in a given cell to start the process of oncogenesis;
3. Because of the unique nature of ionising-radiation energy deposition, the effect of decreasing the dose in the low-dose region (i.e., where few cells are hit by more than one radiation track) is just to proportionately decrease the number of cells in which this sufficient damage occurs, even down to very low doses;
4. Therefore a linear extrapolation for the risk of radiation carcinogenesis down to very low doses is justified.

Let us examine cases where the LNT hypothesis over-estimates low-dose risks. Notwithstanding the above arguments, non-linear responses are conceivable if, for example, other cells or cell systems modify the probability that any given radiation-damaged cell becomes the clonal origin of a cancer, in a manner which is non-linear with dose; or there may be situations where a single cell requires traversal by several radiation tracks to produce a given endpoint. Such processes could result in curves like d (threshold) or even e (hormesis). An example is radiation-induced sarcoma, where non-cycling cells need a large dose to stimulate them to cycle - so low doses of radiation generally do not induce sarcomas[2]. Another example is the phenomenon of induced radioresistance, which has sometimes – though not always - been observed for some endpoints[3]. There is no evidence, however, for any such non-linear processes which are 'universal' in nature.

Upwardly-curving dose-effect relations like curve c in Figure 1 provide a good description of acute dose-effect relations for radiation-induced leukemia in man[1] (in the A-bomb data, though only, of course, at epidemiologically-tractable doses), and also of acute dose-effect relations for chromosome aberration induction[1]. These dose-response data have been extensively analysed with mechanistically-motivated models, using linear-quadratic or related approaches; such upwardly-curving dose-effect models generally reduce to simple linear models at sufficiently low doses.

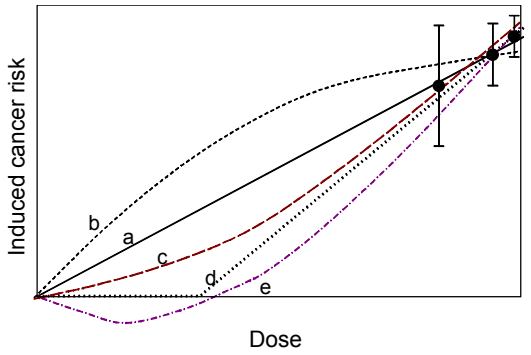

Figure 1. Schematic showing different possible extrapolations of induced cancer risk from some (hypothetical) intermediate-dose epidemiological data, down to low doses. The different curves are each discussed in the text.

CASES WHERE THE LNT HYPOTHESIS *UNDERESTIMATES* LOW-DOSE RISKS

Consider now downwardly curving dose-effect relations (curve b). The evidence for dose-response relations like curve b is quite persuasive, both from an experimental and a theoretical standpoint. Experimentally, the most recent low-dose A-bomb survivor cancer mortality data[4] (Figure 2) do appear to exhibit this shape – though of course the shape of the dose-response at these low doses (5 to 150 mSv) cannot be unequivocally established by epidemiological studies, and certainly not at still lower doses. Likewise, the extensive data on *in-vitro* oncogenic transformation also show this downwardly-curving shape at low doses[1].

Further evidence, at least at high LET, for downwardly curving dose relations comes from the existence of inverse dose-rate effects (increased effect with increasing protraction) for radon exposure[5]. Essentially all analyses of inverse dose-rate effects, irrespective of their biophysical basis, involve an underlying acute dose-response relation which is downwardly curving, so that repetition of the initial part of the curve will produce an increase in effect[6].

In brief, at intermediate acute doses, say in the 100 mGy to 1 Gy range, the evidence for linearity in many relevant biological systems (including the A-bomb data for solid cancers) is reasonably strong. However, the nature of low-dose epidemiological or laboratory studies means that we cannot be sure of the appropriate dose response relation to use at lower doses or at low dose rates. The current weight of evidence, however, is that none of the alternate models shown in Figure 1 are more plausible than the LNT model as a generic descriptor of radiation carcinogenesis at low doses and low doses rates.

So given our current state of knowledge, an assumption of linearity for low-dose radiation protection seems the most reasonable one that can be made. In light of the evidence for downwardly curving dose responses (see, for example, Figure 2), a linear approach is surely not the *most* conservative approach, as has sometimes been claimed [7], and it is possible that it will result in an underestimate of some radiation risks - and an overestimate of others. Given though, that it is supported by experimentally grounded, quantifiable, biophysical arguments, a linear extrapolation of risks from intermediate to very low doses is currently the most appropriate approach for use in radiation protection.

Rebuttal

As Professor Raabe points out, there are certainly some endpoints, such as radiation-induced sarcoma, where there are dose thresholds below which the risk could well be zero. The situation for sarcomas is well understood theoretically, relating to the need to stimulate non-cycling cells into cycle. The evidence, however, does not allow one to generalise this conclusion to the common carcinomas, and I have described situations where a linear non-threshold (LNT) extrapolation may underestimate as well as overestimate the low-dose risk.

Professor Raabe suggests that the key data regarding the LNT are from the A-bomb survivors. One can argue whether these low-dose data are indeed statistically significant (in common with the authors of those data, I suggest they are, see Figure. 2), but his point is well taken that there will always be *some* dose below which the risks are not statistically distinguishable from the background. That is the nature of low-dose risks. However, that a risk is not statistically distinguishable from background is not, in itself, evidence that the risk is or is not zero, and so is not evidence for or against the applicability of the LNT.

That is why we must rely on models to extrapolate risks to very low doses. For all its uncertainties, the LNT is a *bona-fide* model, with testable hypotheses (schematised, for example, in my section entitled 'Linear Responses') and testable predictions.

The core of Professor Raabe's case lies with his assertion that "the addition of a few additional [DNA] alterations by low dose irradiation may not contribute to any meaningful increase in cancer risk". I know of no evidence to support this statement, and Professor Raabe does not provide any. Of course at very small doses any increase in risk will be very small, but that does not make the risk 'not meaningful', particularly if that very small risk is applied to a very large number of people.

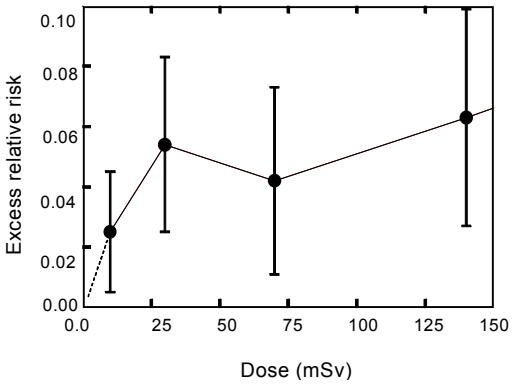

Figure 2. Estimated radiation-related excess relative risk, and standard errors, for solid-cancer related mortality (1950 – 1990) among atomic-bomb survivors[4]. Each data point shows a significant radiation-related increased cancer mortality risk.

With our present state of knowledge, using the LNT to estimate low-dose risks seems appropriate both on a theoretical and practical level. It has at least some theoretical basis, and it also represents a compromise between a variety of data suggesting that it overestimates or alternatively underestimates low-dose risks.

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OPPOSING THE PROPOSITION: O. G. Raabe

Argument

The linear-no-threshold (LNT) hypothesis has been used to attempt to estimate the possible risk of cancer induction that might be associated with exposure to ionising radiation at doses for which there are no measurable or known effects. The LNT approach uses simple linear mathematical relationships that assume that unknown cancer risks at low doses, down to zero risk at zero dose, are dosimetrically proportional to observed risks at higher doses. Experimental and epidemiological data that are often highly imprecise are used to fit two-dimensional risk versus dose LNT models. It is then assumed that risk estimates can be made with these speculative mathematical models by linear extrapolation down to zero dose. However, the LNT concept is actually not a systematic theory that can be used to predict risk from various forms or modes of exposure to ionising radiation.

The LNT approach is based on an inappropriate conceptual model that conflicts with modern cancer biology. Since the occurrence of some simple mutations has been observed to be proportional to radiation dose, it is assumed that cancer induction has a similar pattern. However, a single mutation or an isolated event in a single cell is an unlikely basis for induced cancer in a whole organ or person. In the milieu of about a million metabolic and oxidative DNA alterations that normally occur every day in each cell of the human body[1], the addition of a few additional alterations by low dose irradiation may not contribute to any meaningful increase in cancer risk. This phenomenon suggests a curvilinear or effective-threshold cancer risk model in which the risk drops precipitously to negligible levels at low doses. Considerable radiation carcinogenesis data do not follow the LNT model. The fact that high linear energy transfer (LET) alpha radiation can produce unique multiple double-strand DNA lesions is sometimes used to support the LNT idea, but cancer from alpha radiation is well-known to be a highly non-linear, threshold-like phenomenon[2].

The key data sustaining the LNT hypothesis are the solid cancer mortality data as analysed by the Radiation Effects Research Foundation of the life span studies (LSS) of the Japanese survivors of the 1945 atomic bomb detonations at Hiroshima and Nagasaki who received acute gamma (and some neutron) irradiation (Figure3)[3]. At doses smaller than about 0.2 Sv, the observed relative risks are statistically indistinguishable

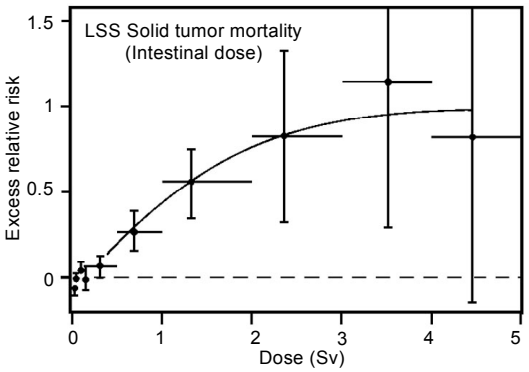

Figure 3. Observed solid tumor mortality excess relative risk (±SE) for Japanese 1945 atomic bomb survivors[3].

from zero and the shape of the dose-response relationship is uncertain[4]. LNT models have been fit to these data[5]. However, using these same LSS data, Hoel and Li found that a nonlinear threshold model fits equally well with a threshold at about 0.05 Sv[6]. Pierce *et al.*[7], observed a significant slope below 0.05 Sv, but this significance is lost when higher dose subjects are added to the analysis.

If the LNT hypothesis for ionising radiation carcinogenesis were correct, proportionally increasing cancer risk would be observed as dose increases with protracted exposure to internally deposited radionuclides or to external radiation. Instead, non-linear response relationship with life span effective thresholds were found for radiation-induced cancer from protracted exposures in lifetime studies of beagles after intake by injection, ingestion, or inhalation of radionuclides (including high LET alpha emitters ^{226}Ra, ^{239}Pu, ^{238}Pu, and ^{241}Am and low LET beta emitters ^{90}Sr, ^{91}Y and ^{144}Ce) and in people after intake of ^{226}Ra[2, 8-12]. A clearly impressive effective threshold response was observed in lifetime studies of beagles with skeletal burdens of ^{90}Sr (Figure 4)[12].

Raabe *et al.*[10-11] used life-span normalisation to scale response relationships from laboratory animal species to human risk predictions. In this analysis a life span effective threshold for bone cancer is predicted at a skeletal dose of about 3.5 Gy (70 Sv) for ^{226}Ra in bone; there was actually no bone cancer occurrence for any cumulative skeletal dose less than 11.6 Gy (232 Sv) among the US radium cases[2, 13]. These results inductively rule out LNT models of radiation risk at low doses. Risk estimates based on collective dose (sum of doses received by individuals in a group) are invalid because it is clear that small doses do not yield effects that are proportional to large doses.

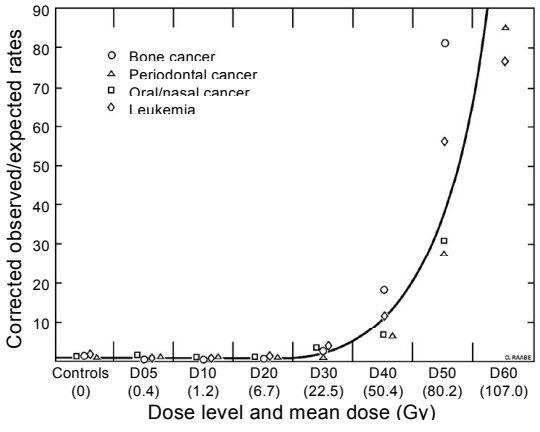

Figure 4. Incidence of fatal cancer as a function of dose group in beagles fed ^{90}Sr at the University of California, Davis[12].

Possible beneficial effects of low-level ionising radiation exposure have been described including reduced cancer rates[14-15]. Radiation exposures may increase the rate of DNA repair, possibly reducing the carcinogenic risk in a distinctly non-linear fashion. States in the USA having the highest background radiation levels (e.g., Colorado at 8 mSv.y^{-1} effective dose equivalent) have among the lowest cancer rates. Cohen studied radon levels in homes and lung cancer rates in 1601 counties in the United States and found a significant inverse relationship where those counties with higher average radon levels in homes (up to 130 Bq.m^{-3}) had lower average incidence of lung cancer[16].

Current dose-based radiation protection standards have been found to be sound. They are based on a century of experience with occupational and accidental exposures to ionising radiation. The most reliable studies of health among radiation workers are unable to detect any significant effects for lifetime exposures below 0.1 Sv[17]. There is no need to use the speculative LNT hypothesis to attempt to describe unobservably small risks even if they exist. So then why should it be used in radiation protection? Forty years ago it seemed to be useful in radiation protection as a means of postulating a possible upper limit in cancer risk associated with radiation protection standards. Unfortunately, about twenty years ago, it started to be used as a means of counting imaginary bodies. There is a delusion that radiation protection standards are 'risk-based', but they are not. How can there be a risk-based system for low dose occupational and environmental exposures to ionising radiation if the true risk, if any, is not really known and may be zero?

On the other hand, the use of the faulty LNT hypothesis to attempt to predict cancer risk is counterproductive and disruptive. It confuses the public into believing that there are significant hazards associated with exposure to low dose radiation. It misleads health protection personnel, aids the antinuclear extremists, and results in unwarranted reductions in allowable dose limits and environmental radioactivity standards that result in unnecessary and expensive remediation or counter measures. Money spent on such unnecessary remediation would be better used in cancer research or some other useful purpose.

LNT is not a specific theory since it does not proceed from any coherent comprehensive underlying analysis of the process of radiation carcinogenesis and does not accurately predict unknown radiation carcinogenic relationships. Unfortunately, simple linear models can be quite seductive and very misleading. When they are fit to imprecise grouped data spanning a selected range of doses they often 'look good'. In fact, the LNT hypothesis is neither appropriate nor logical, and it is not needed to provide sound radiation protection stan-

dards. Ironically, a simple fallacy (LNT) is often more acceptable than the more complicated truth.

Rebuttal

The three 'biophysical arguments' presented for the LNT hypothesis and for extrapolating cancer risk estimates to low doses are inadequate. First, the fact that each primary tumor is usually monoclonal is a description of how malignancy develops rather than of the nature of the dose-response relationship that leads to malignancy.

Second, although high doses of ionising radiation can damage cellular DNA, it is not known what is 'sufficient damage in a given cell to start the process of oncogenesis'. The term 'given cell' suggests results of studies of cells in culture, but it is the response of multiple cells in the whole body that controls carcinogenesis.

Third, the idea that the underlying cause of radiation carcinogenesis is a single radiation 'track' in a single cell that results in 'sufficient damage' has not been shown and conflicts with current knowledge of the processes involved in radiation carcinogenesis. This idea is just a restatement of the unacceptable single point-mutation theory. Since the underlying basis of radiation carcinogenesis involves much more complicated intercellular responses including effects observed in cells that are not even irradiated (bystander effects), a non-linear effective threshold model is clearly more appropriate than the single-track, single-change linear model.

Bone sarcoma is not a special insensitive type of cancer that has a threshold and is fundamentally different from carcinoma and other types of cancer. In the US human radium studies, about one-third of the fatal radiation induced cancers were not sarcomas but rather carcinomas of the mastoid and sinus regions of the head. Head carcinoma cases also showed a strong effective threshold for alpha irradiation with none occurring in persons with skeletal doses less than 8 Gy (160 Sv). Also, in the ^{90}Sr beagle studies, shown in Figure 4, all forms of cancer exhibited a strong thres-hold response including leukemia, periodontal carci-noma, and oral-nasal carcinoma, not just bone sarcoma.

The linear models used for human exposure to radon decay products in underground mining are the classic example of assembling highly imprecise data with varying degrees of large uncertainty and appropriating best fit linear models. Since no person in these studies wore a radon dosemeter, all doses used are approximate. The confounding by cigarette smoking is substantial. Using a linear conceptual model perpetuates support for the faulty LNT hypothesis. The 'inverse dose-rate effect' occurs with all alpha radiation induced cancer including bone cancer and does not prevent the occurrence of a nonlinear lifetime effective threshold[8,12].

Figure 2 shows some estimated 'excess relative risk' (ERR) values for low-dose atomic bomb survivors from Pierce *et al.*[7]. None of the values shown are statistically different from zero so there is actually no significant downward curving. Also, Pierce *et al*. noted that these values are probably high because of death certificate bias. Their comparative cancer incidence values from the more accurate tumor registry put the first three points on Figure 2 very close to zero ERR with SE's that cross over zero indicating a threshold-like response for cancer incidence. Also, the position of the baseline (zero ERR) is based on the lowest dose survivors not a separate control group. As explained by Pierce and Preston[18], those lowest-dose survivors who were closer than 3,000 m to the blast hypocenter have a significantly lower cancer rate than the lowest-dose survivors who were >3,000 m from the blast. When all of the low-dose survivors are used to establish the baseline the low dose data fall randomly above and below the baseline indicating a classical effective threshold for radiation carcinogenesis.

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SUMMARY

Our debaters have presented us with many ideas that resonate with the interpretations and opinions of a large part of the radiation protection community. We all tend to agree on the dose-effect relationship at high doses, but at low doses it is difficult for all of us to be sure about the precise nature of such effects. The need for additional research directed toward understanding biological effects at low doses is something that all of us can undoubtedly agree upon. However, it is certainly understandable that strong opinions are voiced about the implications of the LNT hypothesis. If the recommendations of our national and international radiation protection commissions are misinterpreted or overly-interpreted by regulatory agencies, then those agencies are not following, or not understanding, the additional recommendation that points out the need to take economic and social factors into account when setting radiation protection policy. In time, we will have additional scientific information regarding the nature of biological effects at low doses, but we may need to work as quickly as possible to better educate our regulatory agencies.