LINEAR VERSUS NON-LINEAR: A PERSPECTIVE FROM HEALTH PHYSICS AND RADIOBIOLOGY

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ABSTRACT

There is a vigorous debate about whether or not there may be a "threshold" for radiation-induced adverse health effects. A *linear-no threshold* (LNT) model allows radiation protection practitioners to manage putative risk consistently, because different types of exposure, exposures at different times, and exposures to different organs may be summed. If we are to argue to regulators and the public that low doses are less dangerous than we presently assume, it is incumbent on us to prove this. The question is therefore whether any consonant body of evidence exists that the risk of low doses has been over-estimated. From the perspectives of both health physics and radiobiology, we conclude that the evidence for linearity at high doses (and arguably of fairly small total doses if delivered at high dose rate) is strong. For low doses (or in fact, even for fairly high doses) delivered at low dose rate, the evidence is much less compelling. Since statistical limitations at low doses are almost always going to prevent a definitive answer, one way or the other, from human data, we need a way out of this epistemological dilemma of "LNT or not LNT, that is the question". To our minds, the path forward is to exploit (1) radiobiological studies which address directly the question of what the *dose and dose rate effectiveness factor* is in actual human bodies exposed to low-level radiation, in concert with (2) epidemiological studies of human populations exposed to fairly high doses (to obtain statistical power) but where exposure was protracted over some years.

INTRODUCTION

In the debate about whether or not there may be a "threshold" for radiation-induced adverse health effects, one must distinguish between the *practice* of radiation protection and the *science* of radiation protection. A *linear-no threshold (*LNT) model is useful because it allows radiation protection practitioners to manage risk consistently; different types of exposure, exposures at different times, and exposure to different organs may be summed. The risk coefficients recommended for making radiation protection decisions about public or occupational exposure to radiation are intended to be reasonable and conservative. Their values are nominal, and should not be expected to predict the consequences to the tissues and organs of particular individuals or groups under all possible combinations of dose and dose rate. It should therefore be expected that some particular circumstances may reveal data apparently inconsistent with a single all-encompassing LNT model. In this paper, we examine the data for and against linearity and a threshold, and suggest research that would help to resolve the issues.

THE RELEVANT ISSUES

High doses at high dose-rate definitely increase cancer

The most important source of information about this is the Japanese A-bomb survivor (ABS) population. In the latest update (Pierce, Shimizu *et al*., 1996), the uncertainty in the lower dose categories has in fact been decreased since the last analysis (which covered up to 1985). A LNT model remains a credible fit.

There is no statistically significant non-linearity in the range 0-3 Sv for excess solid cancers. (Above 3 Sv, the slope decreases somewhat; this may reflect cell-killing). The excess absolute risk (EAR) per sievert for mortality from solid cancers, for persons exposed at age 30, is estimated as 0.10 for males [10% per Sv] and 0.14 [14% per Sv] for females. The risks for someone exposed at age 50 are about one-third the preceding.

Models which were linear in dose raised to a coefficient k were used to provide an assessment of linearity as a "fit" to the data. The authors reported that models with $k < 1$ generally provided a worse fit than a linear ($k = 1$) model (Pierce, Shimizu *et al.*, 1996) and that the new data do not provide any evidence to support a contention that there is a threshold below which no excess risk exists. It is this absence of statistically significant non-linearity which led them to quote risk over the whole range of exposures in terms of risk per Sv.

"Threshold models" have been tested quite extensively, by others also, to see if there is any evidence for curvature in the cancer incidence dose-response curve for the Japanese atomic bomb survivors (see, *e.g.*, Muirhead and Little, 1997). Threshold-linear and threshold-linear-quadratic models were fitted to the solid cancer data and to the leukemia data. There was little evidence for curvilinearity for solid cancers overall; this more extensive analysis confirms the RERF conclusion. For example, if a threshold-linear model is fitted, the threshold dose below which there is assumed not to be any elevated risk does not differ significantly from zero, although the point estimate was 40 mSv. For leukemia, there was evidence for curvilinearity, both here for incidence (Muirhead and Little, 1997) and in the mortality data (Pierce, Shimizu *et al.*, 1996). The main insights from such direct "threshold analyses" are : (1) If there is a threshold, it is relatively small one, in the order of a few tens of mSv; and (2) Such studies set fairly tight upper bounds ($\approx$ 200 mSv; Muirhead and Little, 1997) on just how large any putative dose threshold could possibly be.

The observational basis for a non-threshold (*i.e.*, linear) model is far wider than merely the A-bomb survivors. Not only the ABS results, but as well various other studies of elevated radiogenic cancer in cohorts exposed to enhanced levels of ionizing radiation (usually acutely), when taken together, indicate a consistent story of elevated radiogenic risk (UNSCEAR, 1994a), and are consistent with a monotonic increase in effect with increasing dose. The issue of whether there exists some level of dose for high dose rate exposure below which risk diminishes or vanishes is not a profitable area for argument: as Sir Richard Doll notes "a linear dose-response relationship will not suddenly dive to zero immediately below the lowest level at which a statistically significant excess is observed" (Doll, 1997).

In addition, a significantly increased excess relative risk (= 1.4) has been demonstrated in the case of irradiation of 10 mGy to the fetus *in utero* (Wakefield, Doll *et al.*, 1997). This relatively low dose for significance is possible not because of any super-sensitivity of the fetus, but rather because the natural or "spontaneous" incidence of effects were so low. This intrauterine irradiation study is sufficiently powerful to be able to exclude any value of threshold (assuming that one may exist) above about 5 mSv.

Risks at low dose and low dose rate are the issues for radiation protection. The ABS results are a guide, but only a guide, to how we might assess the risk of low doses from radiation received either in a highly fractionated or protracted manner. The question for radiation protection is whether a single value of two for the *dose and dose rate effectiveness factor* (DDREF; ICRP 1991) suffices for most practical purposes. Currently, it should be appreciated, because of the inclusion of the DDREF, the nominal population-wide risk is taken to be curvilinear with dose, approaching a slope at the lowest doses half of that observed at high doses and dose rates. The explicit recognition of non-linearity by incorporating a single value of DDREF, of course, still leads to linearity for the low doses and low dose rates, albeit with a different slope than for high doses and dose rates.

In contrast to the relatively low uncertainty for the high dose rate results, studies of the degree to which there may be elevated risk in humans exposed to low dose rate radiation tend to be somewhat equivocal (see, *e.g.*, Gentner 1996 for a summary). In studies where low-level radiation [LLR] risk has been assessed as a function of dose categories, a wide range of risk values exists (UNSCEAR, 1994a; Table 34). The majority have confidence intervals so wide that they prove or disprove very little. Not only can they not reject the ICRP nominal risk coefficient, they are consistent (at their upper confidence limit) with a nominal probability coefficient which is much higher than ICRP's; at the lower confidence limit, some studies are consistent with the possibility of there being no radiation risk at all. The issue we have to address and rectify is in large part to narrow the band within which estimates of any risk at low doses and low dose rates must lie. Untenable generalizations will not help.

It is difficult to prove that "no risk" exists

There is no study of persons exposed to low dose and/or low dose-rates which is able to prove that the overall radiation risks for all individuals are less than the nominal risk coefficient implies. Evidence that no significant effect is seen (one way or the other) ought not to be misconstrued as evidence that there is no effect. Thus, despite claims to the contrary, most low dose studies are not "proof of no effect" but rather "no proof of effect". It is misleading to suggest there is a coherent body of data which suggests otherwise.

The set of results from comparisons of cancer incidence in inhabitants of high compared with control 'low' natural radiation background areas is one case in point. This sort of comparison has been performed for groups in the UK, USA, China, Sweden, France and Japan. The conclusion is that "None, including the largest, that in China, has produced statistically significant associations" [UN94a]. While within studies slight differences in site-specific cancer mortality rates do exist between the high- and low- radiation-background areas, overall the differences are not significant statistically, and hence no

results to date provide clear evidence for either the presence or absence of detriment due to LLR.

A second case in point relates to using SMR's for cancer in occupationally exposed persons to bolster a claim that they show less risk from cancer as a result of their occupation. Such a claim seems unsustainable. Results from studying groups of nuclear industry workers tend to be somewhat equivocal (UNSCEAR, 1994a). A standardized mortality ratio of <1 for a worker population, by itself, proves nothing other than that the risk is not huge. In Table 1, for fifteen cohorts of nuclear energy workers the arithmetic and geometric means of the SMR's for deaths due to "all causes" are 0.84 and 0.83; for "all malignant neoplasms" the values are 0.89 and 0.88. (This "healthy worker effect" [HWE] certainly makes it more difficult to interpret SMR's, which is partly why many studies do an internal analysis, where they look for a trend in risk with increasing dose—i.e., the lesser-exposed persons serve as controls.)

Table 1
Standardized mortality ratios for all causes of death and for malignant neoplasms for nuclear energy workers. (Adapted from Table 33 of UNSCEAR 1994a.)

	Standardized mortality ratios for deaths due to		
Nuclear installation	**All causes**	**All malignant neoplasms**	**Leukemia**
UK Atomic Energy Authority	0.76	0.78	1.2
Sellafield	0.96	0.96	0.83
UK Atomic Weapons Establishment	0.73	0.79	0.44
United Nuclear	0.83	0.97	1.19
Pantex	0.72	0.63	1.34
Rocky Flats	0.63	0.71	0.75
Portsmouth	0.78	0.96	0.88
Oak Ridge National Laboratory	0.73	0.80	1.50
Oak Ridge, Y-12 (1943-1947)	1.00	0.96	1.04
Oak Ridge, Y-12 (after 1947)	0.89	1.01	0.50
Oak Ridge federal nuclear plants	1.11	1.05	1.13
Hanford	0.78	0.85	0.71
Linde Air Products	1.18	1.12	-
Savannah River	0.75	0.74	1.50
Naval shipyards	0.76	0.99	0.91
Arithmetic mean	0.841	0.888	0.994
Geometric mean	0.828	0.877	0.936

The SMR for "all causes of death" in nuclear shipyard workers compared with non-nuclear shipyard workers is significantly low (SMR = 0.76 in Table 1; UNSCEAR 1994a; Matanowski 1991), but this value is significantly low primarily because the non-nuclear workers (the comparison, control group) had a higher incidence of deaths from disease other than cancer (UNSCEAR 1994a). Both groups had lower death rates than the general US population for leukemia, and for lymphatic and haemopoietic cancers

(UNSCEAR 1994b, Table 41), but it would be misleading to attribute this to a protective effect of radiation: a low dose sub-cohort tends to be weighted towards younger employees, and the HWE is known to decrease with increasing length of employment. The apparent deficit of leukemia in the low dose group, in any event, is not significantly different from unity [no effect]. In fact, this naval shipyard worker group has SMR = 0.99 for "all malignant neoplasms" (UNSCEAR 1994a; see also Table 1 above), a value sufficiently far above the "all causes" SMR of 0.76 that a case could be just as well argued that the HWE was masking occupationally-related cancer in the naval shipyard nuclear workers, as could a case that the low SMR for “all causes” reflects a hormetic effect of radiation.

DNA repair

Active DNA repair processes certainly exist which restitute most of the initial radiation-induced lesions. It is the residual damage that can lead to the development of cancer which is of concern. DNA repair capability is coded for in DNA, varies among persons and is inducible (in some individuals at least) in response to damage.

The existence of DNA repair capability does not allow one to argue *a priori* that risk necessarily short-circuits to zero below some threshold value of dose. The issue is whether or not DNA repair efficacy reaches or approaches 100% if the rate or amount of damage input is sufficiently low. This is difficult to 'prove" one way or another, but the weight of experimental evidence seems to be against the operation of a totally error-free DNA repair process at low doses of the sort which could substantiate a threshold for induction for induction of mutations (Lloyd, Edwards *et al.*, 1992; Thacker, 1992), such as initiate oncogenesis (UNSCEAR 1993).

But what if some extra DNA repair capability is induced? The phenomenon of adaptive response has been raised as a mechanism which could decrease risk to zero at low doses, or conceivably even act on spontaneous damage (DNA damage by agents other than radiation) so as to provide a net benefit greater than the putative radiation detriment. But the adaptive response (UNSCEAR 1994b) has not been found in all biological systems, nor in all donors; genetic disposition is likely to be an important variable. There is no evidence of its influence on radiogenic cancer induction. While the adaptive response is relatively reproducible, it is a laboratory phenomenon (the best evidence is at the cellular level) and well-defined experimental conditions are needed for it to be observed. There is a window for any adapting dose that is narrow in time and value: since the doses received by nuclear industry workers in what are likely relevant periods are below the values of priming doses observed for the phenomenon, it is not at all clear whether an adaptive response would be relevant to risk assessment or radiation protection. The 1994 UNSCEAR conclusions—that extensive data "provide no evidence to support the view that the adaptive response in cells decreases the incidence of late effects in humans after low doses", and that "at this stage it would be premature to draw conclusions for radiological protection purposes" (UNSCEAR 1994b)--remain valid.

Physical nature of the radiation event

The physical nature of a radiation event in a cell has important implications. One millisievert (mSv) from gamma radiation represents on average about one event or track per cell. At low dose rates of the order of a few mSv per year (or less) one has therefore

to consider the impact of a few events per cell per year; i.e. only a small fraction of the body's cells are hit in any day. (The fraction is much smaller for higher LET radiation, but the dose to the cell is much larger). This means that the question of import for threshold versus non-threshold is whether a single track of ionizing radiation can induce the necessary damage in a target tissue. (Note that it is not necessary that every such single track be able to do this, only that the there be a non-zero probability). Evidence exists for all types of ionizing radiations that a single track can induce a wide array of lesions in DNA, including the double-strand breaks implicated as critical damage (see, *e.g.*, Goodhead, 1994).

Radiation exposure has no unique signature in the cancers it induces, nor is it possible at present to determine unambiguously if a given cancer was radiogenic or not, other than probabilistically. Moreover, radiation accomplishes no step in the neoplastic process which cannot be accomplished in some other way. Thus, another way in which the nature of the biological target, and of processes affected by a radiation event, and the natural course of cancer development, argues for linearity is as follows. The 'background' rate of cancer in human populations is appreciable (about 25% mortality). Therefore all steps in the cancer development process can and do proceed "spontaneously" for reasons which have nothing to do with radiation. The radiation action in exposed humans may be to augment those ongoing processes which result in cancer in the normal course of events. Where radiation-related increases have been observed, in fact the increase per unit dose appears to be proportional to the normal incidence--the "constant relative risk" model.

If a cell does respond in any way to one event, then for there to be any dose rate effect (that is, a non-linearity) there has to be interaction between spatially- or temporally-distant events. Such interaction may result in a different response (for example, enhanced repair) to a later event compared with that to an earlier one--an adapted response. With the time and spatial separation of radiation events when there are only small increments on the background dose rate the possibility of such interactions seems remote; one would therefore expect a "linear" relationship between number of events (dose) and deleterious effects stemming directly from those. However, a radiation event may affect how the cell or its associated tissue handles non-radiation-related but potentially deleterious events that occur sufficiently soon and close enough. One could therefore have an increase in some deleterious effects, and a reduction in others because of a general increase in repair capability. What the net effect might be depends on many biological variables so that simple generalizations one way or the other are unlikely to be valid.

Radiation- and cancer-sensitive persons

Radiocarcinogenesis is a complex process, and its progress should not be expected to be the same in all potential target organs. There seem to be some tissues at least where radiogenic damage is clearly "less repairable"; there also exist persons with various syndromes associated with diminished repair capability, including for ionizing radiation-induced damage. Hence risk in some persons, and possibly in some tissues in most persons, may well extend down to very low doses.

A considerable array of genes has been identified which is associated with increased risk of cancer. Only a portion of these seem to relate to DNA repair. These cancer genes (present in a fraction of the population) may account for a considerable fraction of human cancer. Cells of tissues in people who have one or more of these genes may already be

some steps along the multistep path to cancer, reflected in such people having a higher risk per unit radiation dose, and no practical threshold that might otherwise arise because of the slow progress through initial steps.

We conclude therefore that even if the overall risk might decrease to zero in some persons at low doses and/or low dose-rates, it is unlikely to be the case for all persons, and it may well not be the case for the subset of persons who may normally give rise to most cancers in a population. That is, there likely will always be some individuals at enhanced risk, however low the dose.

The "problems" the LNT hypothesis cause are addressable

The "problems with LNT theory" mainly relate to what are seen as excessive costs for protection against radiation versus other risks to human health. The issue as we see it is that the attention given to low doses of radiation is excessively high *even if the LNT-based risk coefficients were to be correct*. This is the issue we have to continue to address and rectify. It is this cost of a theoretical cancer death prevented which is out-of-whack; public misperception and whatever leads to this misperception—not LNT—is to blame for this. To be effective, it is the perception issue that has to be addressed.

THE PATH AHEAD

There are two main ways to address this question of narrowing the bounds within which any estimate of risk of low doses at low dose rates must lie.

The first type of approach would be epidemiological, focused on low dose rate studies but at relatively high total doses. One study of this type, illustrating the principles involved, concerns lung cancer in TB patients receiving fluoroscopic examinations: these highly fractionated exposures were associated with an excess relative risk for lung cancer of 0.0, with fairly narrow confidence intervals—sufficient to exclude any level of risk higher than about 18% of the value from the LSS (Howe, 1995). The study achieved its statistical power because of an average dose (1.04 Sv) some four-times that of the A-bomb survivors; the average patient received 92 examinations, separated by days to weeks, of 11 mSv each. However, while the lung cancer risk was negated by this fractionated exposure, it must be emphasized that no such protection was seen for breast cancer: this cohort exhibited a risk comparable with that seen in the ABS, and there was no evidence of protection by dose fractionation (Howe and McLaughlin, 1996). This type of epidemiological study requires that data be built up on a tissue-by-tissue basis; to do this, the populations exploited were generally irradiated for medical reasons.

Another type of cohort which promises to substantially illuminate the low dose/low dose rate question concerns persons who received substantial whole body exposures, generally from the early days of the weapons production program in the former Soviet Union. Epidemiological follow-up is resuming of residents along the Techa River (Kossenko, Degteva *et al.*, 1997); Figure 1 gives a preliminary look at the Techa River cohort's risk of solid cancer and leukemia compared with the mortality experience of the ABS. The leukemia rate of the Techa River cohort looks to be about one-third that of the ABS. The solid cancer rate in the Techa River cohort seems to be substantially less than in the ABS; if confirmed, it could be powerful support of a hypothesis that a DDREF = 2

over-estimates the risk of ionizing radiation delivered chronically (even when the total doses are quite high).

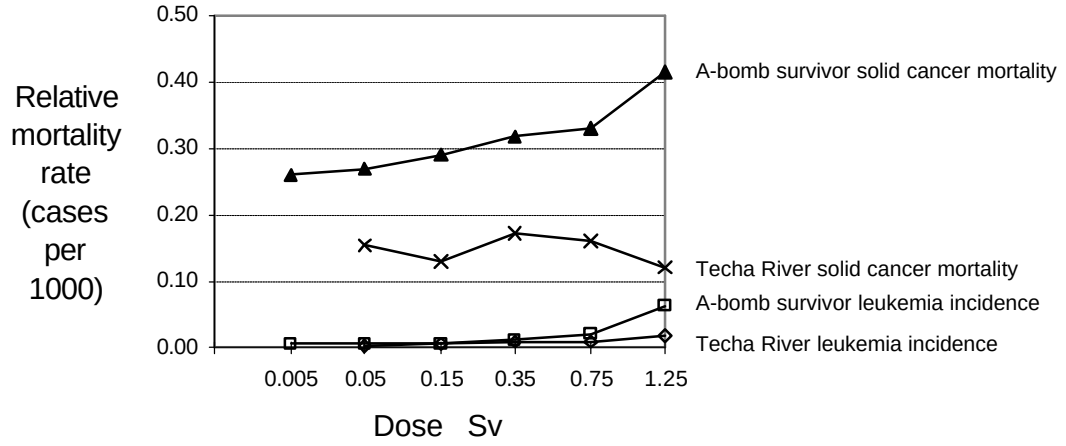

Figure 1
Comparison of the preliminary epidemiological data from the Techa River cohort with the data from the A-bomb survivors plotted from data in Kossenko, Degteva *et al.* 1997.

A second approach could focus on the DDREF: if a larger value for the DDREF could be demonstrated, this would be akin to decreasing the radiation risk. The issue for radiation protection therefore becomes whether there exists any consonant set of data which suggests that the two-fold lower (that is, by the DDREF factor) coefficient for LLR demonstrably over-estimates risk. Epidemiological studies may not suffice: even consolidated studies organized for the purpose of garnering increased statistical power are unable to demonstrate this. For example, the International Agency for Research on Cancer (IARC) study of cancer mortality rates among nuclear industry workers in the UK, USA and Canada (Cardis, Gilbert *et al.*, 1995) was a high-visibility attempt to address this question in occupationally exposed persons. The excess relative risk for leukemia (excluding chronic lymphocytic leukemia) was 2.18 per Sv, with 90% confidence intervals (CI) of 0.1 and 5.7. This is the only statistically significant result. In comparison, when the A-bomb survivor cohort was analyzed in a strictly comparable way, the resultant value of ERR/Sv was 3.67 (90% CI: 2.0, 6.5).

For "all cancers excluding leukemia", the ERR in the IARC study was -0.07 per Sv (90% CI: -0.4, 0.3). Unfortunately, while providing no proof that there was an increased risk of solid cancers, the result also lacked sufficient statistical power to prove that the risk for solid cancers was in any whit lower than the estimate from the A-bomb survivor data (an ERR/Sv of 0.24, calculated in a corresponding manner); worse, the IARC result was unable to exclude the possibility that the true risk might be even higher.

To do better, and to garner the requisite statistical power, we may have to invoke biological indicators of exposure *in vivo*. A recent study compared the physical dosimetry of 81 workers in five dose categories (58 having exposures ranging from 173-1108 mSv,

with 55 being >500 mSv) at the Sellafield facility of British Nuclear Fuels with stable chromosomal aberration frequencies (translocations and insertions) measured by fluorescence *in situ* hybridization, or "chromosome painting" (Tucker, Tawn *et al.*, 1997). The slope of the dose response curve (number of aberrant cells per 100 cells examined, per Sv) for the Sellafield workers was about one-sixth of the corresponding slope for samples from the A-bomb survivors. Such a result, for this real-life situation, suggests that the DDREF value is effectively 6. This is three-times the value assumed to hold.

These are the type of results which will help correct misperceptions.

Even with new results from studies in these directions there will still be the need to extrapolate to some circumstances of low dose rates and low doses. Here, there will have to be reliance on having sufficient knowledge of the mechanisms involved and their relevance to the responses that can be observed in these regions of dose and dose rate.

IF A THRESHOLD EXISTED, WOULD IT CHANGE THE WAY WE DO THINGS?

Even if there was a small threshold, it would be unlikely to change the way in which we manage worker exposures. We do not know for any particular small increment in dose, what the actual ultimate influence on biological state will be--only its bounds. In any population the effects on individuals of small additions in the day-to-day radiation doses will be varied, both in time for a given individual and between individuals, depending *inter alia* on the individuals' genetic make-up and the spatial and temporal distributions of cellular doses. Eventually, a combination of sufficiently large doses and dose rate from natural background, medical and other man-made sources to people in a population could result in a biological response that is deleterious to some individuals.

How, then, do we achieve protection against the possible effects of exposure from man-made sources? If there is a "freebie" area (effectively a threshold, for possibly some proportion of the population), how do we apportion "credit" for doses that correspond to this area? How do we take account of doses received elsewhere?

First, we would have to make the practical assumption that we do not have a detailed accounting of any individual's complete personal dose history, nor of their genetic make up, nor of their individual cellular responsiveness to radiation at any particular time.

Then, given the multitude of factors influencing radiation response, the only practical and equitable approach is to associate with increments of radiation dose from man-made sources (or any other) a probability of advancing an individual (whose position in the distribution we do not know) towards a deleterious biological response. *The only reasonable assumption for a hypothetical individual somewhere in the distribution is that the bigger the dose, the proportionately bigger the likelihood of an advance towards an effect*. (Note, this does not preclude that in some individuals from any particular additional radiation dose, there may be no actual effect, a much greater actual deleterious effect, or a beneficial actual effect, or even both some deleterious and some beneficial effects.). Such an approach protects the hypothetical average individual, accepting that we do not know the characteristics of each individual, only the estimated bounds of response from epidemiology.

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