

# Uses and Abuses of Models in Radiation Risk Management

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## Abstract

This article presents a high-level overview of managing risks to workers, public, and the environment. Next, the difference between a model and a hypothesis is discussed. The need for models in risk assessment is justified, and then it is shown that radiation risk models that are useable in risk management are highly simplistic. The weight of evidence is considered for and against the linear no threshold (LNT) model for carcinogenesis and heritable ill-health that is currently the basis for radiation risk management. Finally, uses and misuses of this model are considered.

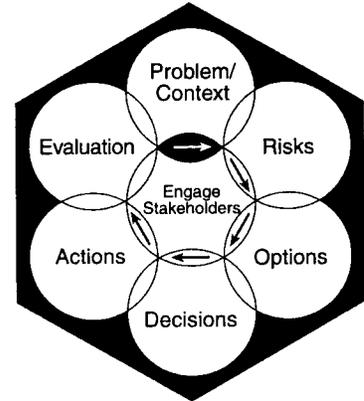
## Key Words

Biological effects  
Cancer  
Dose-response models  
Genetic effects  
Linear, non-threshold  
dose-response model (LNT)  
Risk  
Standards

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## Radiation Risk Management

Historically, radiation risks were at first denied or ignored by most. Thirty-three years elapsed between the discovery of x-rays in 1895 and the development of radiation dose limits for workers. During the Manhattan Project in the 1940s, workers were given little information on radiation risks or limits, and were "taken care of" by Project staff. With the development of the Atomic Energy Commission in 1946, the "decide, announce, and defend" mode of government standards setting for radiation risk management began. The radiation protection field was the first to attempt to base quantitative protection standards on quantitative risk assessments. The ALARA (as low as reasonably achievable) philosophy appeared in the late 1940s, and by 1956, the BEAR (biological effects of atomic radiation) Committee recognized both the need to limit the risk of heritable ill-health (also termed "genetic effects") and neoplastic disease such as cancer and leukemia. Only in 1983 did the entirety of quantitative risk assessment become formalized with the National Academy of Sciences' "Red Book" paradigm of hazard identification, exposure assessment, dose-response assessment, and risk characterization. But that paradigm still supported a risk management framework of "decide, announce, and defend." More recently, public (non-occupational), cultural and ecosystem risk assessments have been added, and in 1997 the Presidential/Congressional Commission on Risk Assessment and Risk Management ([www.riskworld.com](http://www.riskworld.com)) published its prescription for integrating stakeholder values into every stage of risk assessment and risk management (Figure 1).<sup>(1)</sup> Clearly,



**Figure 1.** Risk management paradigm of the Presidential/Congressional Commission on Risk Assessment and Risk Management<sup>(1)</sup>

though, science is only one of many inputs to risk management.

## Hypothesis, Theory, or Model?

One piece of terminology should be cleared up right away. Two or more quantifiable variables may have a *relationship* or an *association* (which may or may not be causal). If the relationship is single-valued and causal, one may be a *function* of the other. When a statistical association between two or more variables is suspected, one may develop a *conjecture*, *supposition*, or, more formally, *hypothesis*. Normally, we think of a hypothesis as something we test by experiment or observation. A *theory* is a formalism that can be used to make predictions. A *model* is usually a simplistic but useful description of observations that can be used for predictions. For example, we have climate models, economic models,

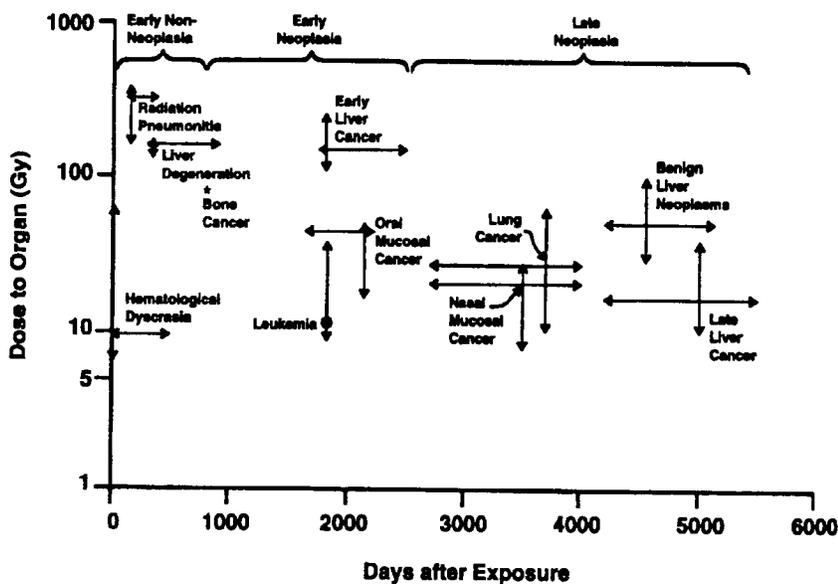


Figure 2. General categories of biological effects in 70 dogs after inhalation of  $^{144}\text{CeCl}_3$ <sup>[4]</sup>

environmental models, nuclear models (the Weizacker semi-empirical mass formula, for example, or the shell model predicting stability at "magic numbers" of nucleons). Another example is an article in *Nature* entitled "The Use and Abuse of Climate Models."<sup>[2]</sup>

No one expects models to be exact or completely correct, just useful. A favorite quote on the subject is "All models are wrong, but some are useful."<sup>[3]</sup>

### Radiation Risk Models Are Highly Simplistic

Radiation risk models are highly simplistic. First of all, let's consider four major kinds of health effects that have been observed in human beings as a result of exposure to ionizing radiation. Three of these fall into the category of somatic effects (from the Greek "soma," meaning "body") and the fourth is heritable ill-health, which are also known less precisely as genetic effects. Somatic effects include "deterministic" effects, whose severity and frequency are a function of the amount of radiation exposure

and which appear in every exposed person if the dose is high enough. Somatic effects also include developmental effects and in particular, teratogenic effects (those developmental effects that occur when a child is exposed *in utero* between conception and birth.) Finally, somatic effects include "stochastic" effects such as cancer, whose frequency (but not whose severity) is some function of radiation exposure.

Radiation dose (energy per unit mass) is a quantity with which physicists are comfortable. Dose quantities are measured in one of two special units in the International System (SI) of units: the gray (unit symbol: Gy; 1 Gy = 1 J/kg) and the sievert (unit symbol: Sv; 1 Sv = 1 Gy × a factor that depends on the microscopic nature of energy deposition). In this article, the word "dose" is often used generically.

### The 16 Variables of the Problem

People studying radiation effects talk about "dose-response" relationships. Unfortunately, "dose" and "response" are only two of 16 variables of a very complex problem. Most of these 16 variables are necessary to characterize each of the four broad

health effect categories, and they all apply to cancer. The variables, phrased as questions, are:

1. What measure is to be used (relative risk, absolute risk, severity, frequency. . .)?
2. What is the effect or health endpoint (heritable ill-health, reproductive health and developmental abnormalities, cancer, deterministic effects)?
3. Does the effect happen in the absence of radiation exposure, i.e., what is the background incidence?
4. What species is involved?
5. What subspecies is involved (genetic predisposition)?
6. Who is exposed, and who is affected?
7. What is the age at the start of irradiation?
8. What is the age at manifestation of effect: time between exposure and clinical effect?
9. What is the age at death and amount of life lost (lost life expectancy, LLE)
10. What is the gender of the subject?
11. What dose did the subject receive?
12. What was the [instantaneous] dose rate (inverse dose rate effect)?
13. What was the dose fractionation?
14. What portion of the organism was irradiated?
15. What was the radiation "quality?"; and
16. What other effect modifiers are there? Known modifiers include: diet; temperature; infection; combined injury: trauma, burns; state of organ function; other initiators, promoters, tumor progressors (smoking); oxygen; dehydration; and chemicals (antioxidants, free radical scavengers and drugs).

A detailed breakout of these variables is given in tabular form in the Appendix. Given the need to consider

these 16 variables, a "dose-response" curve is a partial derivative of response with respect to dose, holding the other 14 constant.

### Modeling Dose and Response and ...

Consider in some detail the variables enumerated above.

### Health Effect or Endpoint

One must first decide what endpoint or response one is interested in. Hahn and co-workers displayed various endpoints on a plane of time (days after exposure) and dose from  $^{144}\text{Ce}$  (in 70 dogs) (see Figure 2).<sup>(4)</sup>

### Radiation Quality

Concerning radiation quality, usually expressed as *linear energy transfer (LET)* in  $\text{keV}/\mu\text{m}$ , radiation risk assessors have usually used a *quality factor, Q*, and more recently, a *radiation weighting factor,  $w_r$* , to express the different biological effects of radiation. These factors are derived from biology experiments that yielded experimental values of *relative biological effectiveness, RBE*, the ratio of two doses of different kinds of radiation producing the same effect.

In the past 15 years, Bond and colleagues at Brookhaven National Laboratory have developed the concepts of *hit size effectiveness function (HSEF)* and the *distribution of hit sizes* for given radiation fields.<sup>[5,6]</sup> Hit sizes are the amounts of *lineal energy, y* ( $\text{keV}/\mu\text{m}$ ), deposited in a target of a specified volume, typically a  $1\ \mu\text{m}$ -diameter cell nucleus. The distribution of hit sizes is a characteristic of a given kind of radiation. There is additional insight in the June 1996 issue of *Health Physics*, which is entirely devoted to new directions in radiation risk assessment.

The Bond concepts are illustrated in Figure 3. Part (a) shows the distribution of hit sizes for low and

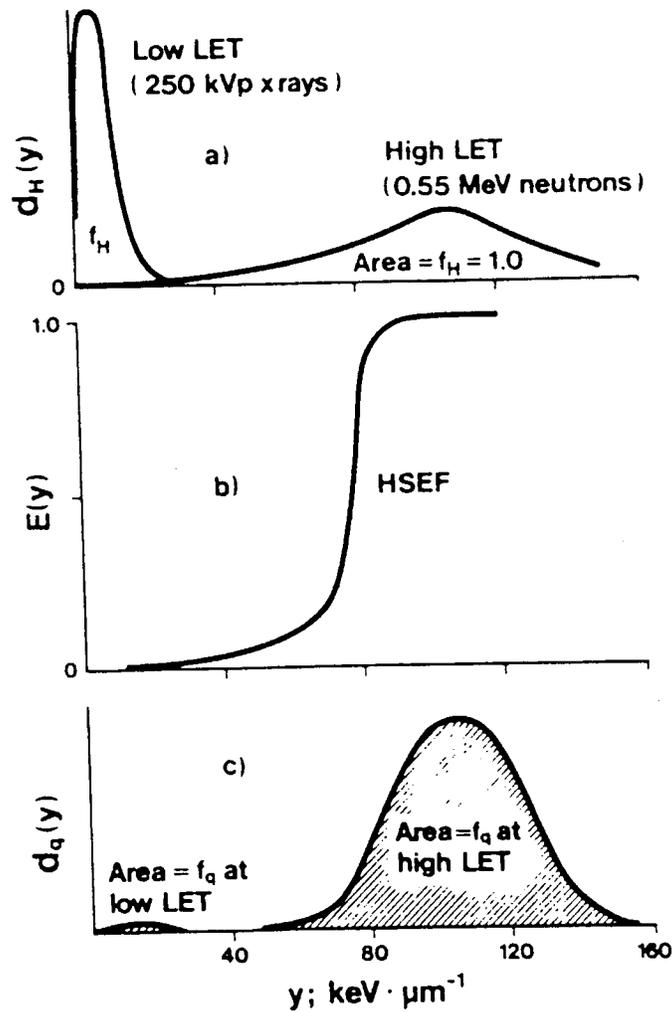


Figure 3. (a) Distribution of hit sizes,  $y$ , for low- and high-LET radiation; (b) Hit size effectiveness function; (c) Product of the two.<sup>[5]</sup>

high-LET radiations. Part (b) of Figure 3 shows a typical HSEF for some arbitrary endpoint as a function of  $y$ . The predicted effect is the result of multiplying the two together, as shown in Part (c) of Figure 3. Clearly, summarizing these effects as a radiation weighting factor is a gross simplification. The HSEF theory must be modified to incorporate repair and accumulation of damage to completely account for dose rate effects, since two small hits that occur near in space and time can combine to make a single larger hit which should be multiplied by a different value of the HSEF.

### Simultaneous Consideration of Dose and Dose Rate

It is worth considering the general location of a given irradiation in the 2-dimensional space of dose and dose rate. This can be seen in Figure 4. The effects labeled on the plane are defined in the key. The vertical scale covers 16 orders of magnitude of dose rate, and the horizontal scale covers 10 orders of magnitude of dose. Horizontal lines show the NCRP Report 64 (1980) "low dose rate" region ( $<5\ \text{rads/y}$ )<sup>[11]</sup> and "high dose rate" region ( $>5\ \text{rads/min}$ ). Vertical lines show NCRP's "low dose" ( $<5\ \text{rads}$ ) and "high dose" ( $>25\ \text{rads}$ )

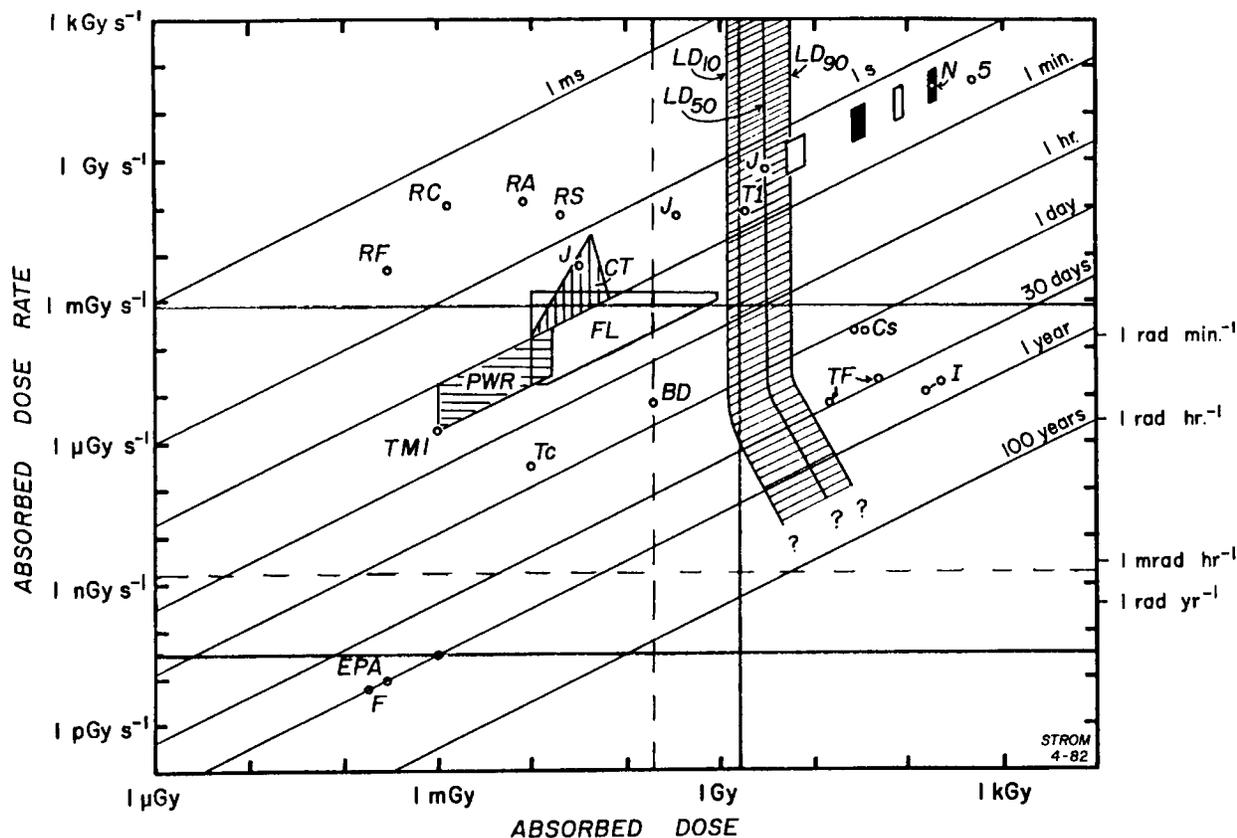


Figure 4. Locations of various low-LET irradiation experiences in the dose-dose rate plane. Isochrones are diagonal lines. An isochrone shows the range of total doses and corresponding dose rates during a given time period.

regions. The diagonal lines are "isochrones," lines of constant time, that show constant values of

$$t = D/\dot{D}$$

Note that the value of  $t$  for the Japanese bomb survivors and other nuclear weapon events is about 10 s, so that the variable was the dose rate, not the exposure time! Events that take longer than 100 years are not of interest, since that exceeds the life expectancy of a human being.

The point is our radiological experience covers a tremendous range of dose and dose rates.

#### Traditional Dose-Response Relationships

Biological effects are observed to increase in either severity (deterministic effects) or frequency (stochastic effects) with radiation dose. Relationships between dose and response are called *dose-response relationships*. Some non-threshold relationships are shown in Figure 5. For threshold effects, the dose-response may be sigmoidal or a Weibull function (e.g., Figure 6); for non-threshold effects, the dose-response curve may be a straight line (linear) or a curved line (linear-quadratic). There are many examples of radiation risk models. Plotting only response ("incidence" of cancer in this

case) versus dose, four alternative models were shown in the 1980 "BEIR III" report.<sup>[7]</sup> Note that in each, incidence initially increases monotonically with dose. Note also that in each case there is a response in the absence of any radiation exposure. The models are, clockwise from top left, general linear-quadratic with cell-killing at high doses; linear; quadratic; and linear quadratic. Note that none has a dose threshold, that is a dose below which there is no response. The one in the upper right hand corner is the linear, non-threshold dose-response relationship.

Figure 4 data

Code <sup>§</sup>	Experience	Absorbed Dose	Absorbed Dose Rate	Typical Time
FL	Fluoroscopy <sup>a</sup>	10-1000 mGy	17-1700 μGy s <sup>-1</sup>	0.1-15 min.
CT	Computed Tomography (CT) <sup>a</sup>	30-70 mGy	0.17-23 mGy s <sup>-1</sup>	2-60 s
Tc	Nuclear Medicine ( <sup>99m</sup> Tc) <sup>b</sup>	10 mGy	320 nGy s <sup>-1</sup>	8.7 h
Radiography: <sup>a</sup>				
RF	Finger	0.25 mGy	5 mGy s <sup>-1</sup>	0.05 s
RC	Lateral Chest	1.2 mGy	5 mGy s <sup>-1</sup>	0.01 s
RA	Angiogram	7.5 mGy	150 mGy s <sup>-1</sup>	0.05 s
RS	Lateral Lumbar Spine	20 mGy	80 mGy s <sup>-1</sup>	0.25 s
BD	"Bad Day" in the X Ray Department: Obese Patient, Vague Symptoms (Lumbar Spine, 20 mGy; Intravenous Pyleogram [IVP], 50 mGy; Arteriogram, 130 mGy) <sup>a, c</sup>	200 mGy	6.9 mGy s <sup>-1</sup>	8 h
Teletherapy, Linac <sup>a</sup> :				
T1	Single Fraction	2 Gy	67 mGy s <sup>-1</sup>	30 s
TF	Full 4-week course <sup>c</sup>	15-50 Gy	6-21 μGy s <sup>-1</sup>	4 weeks
Brachytherapy <sup>a</sup> :				
I	<sup>125</sup> I seeds	160-240 Gy	13 μGy s <sup>-1</sup>	87 d
Cs	<sup>137</sup> Cs	30-35 Gy	174 μGy s <sup>-1</sup>	2-3 d
Nuclear Weapons:				
J	Japanese A-Bomb Survivors	3 Gy	600 mGy s <sup>-1</sup>	5 s
J	Japanese A-Bomb Survivors	300 mGy	60 mGy s <sup>-1</sup>	5 s
J	Japanese A-Bomb Survivors	30 mGy	6 mGy s <sup>-1</sup>	5 s
5	2250 m from 5 MT Air Burst	500 Gy	50 Gy s <sup>-1</sup>	10 s
N	400 m from 1 kT Enhanced Radiation Weapon (neutron bomb)	180 Gy	36 Gy s <sup>-1</sup>	5 s (?)
Miscellaneous:				
TMI	Three Mile Island "Survivor"	1 mGy	1.7 μGy s <sup>-1</sup>	10 min.
EPA	EPA Fuel Cycle Limit (Increment)	-	8 pGy s <sup>-1</sup>	lifetime
F	Fish in 10 m Seawater	-	6 pGy s <sup>-1</sup>	lifetime
50	Dose Rate for 50 mGy in Working Year	50 mGy	7 nGy s <sup>-1</sup>	2000 h
PWR	Pressurized Water Reactor Steam Tube Jumper	1-15 mGy	3-100 μ <sup>-1</sup> Gy s	1-10 min.
NSD	Non-Stochastic (Deterministic) Death	1-15 Gy	any	< 100 y

<sup>a</sup>partial body exposure.

<sup>b</sup>Exponentially decaying dose rate, computed for average life of nuclide

<sup>c</sup>Fractionated exposures, average dose rate is of very limited meaning

§ Compiled by D.J. Strom University of North Carolina, Chapel Hill, 1982.

Sources:

FL, RF, RC, RA, RS, BD: Charles Burns, North Carolina Memorial Hospital (NCMH), Radiology Department

CT: Dr. David Washburn, Radiology Department, NCMH

T1, TF, I, Cs: David Huang, Radiation Therapy Department, NCMH

Js, 5: Glasstone and Dolan, eds., *The Effects of Nuclear Weapons*, 1977.

PWR: Dr. George Oliver, Carolina Power & Light NSD: Lushbaugh et al.,

The Impact of Estimates of Human Radiation Tolerance Upon Radiation Emergency Management,

Oak Ridge Associated Universities, 1981.

The BEIR-III generalized linear-quadratic dose-response model with cell-killing is given by:

$$F(D) = (\alpha_0 + \alpha_1 D + \alpha_2 D^2) e^{-\beta_1 D - \beta_2 D^2}$$

(1)

If health risk from radiation exposure increases directly with increasing dose without a threshold, this is called a linear, non-threshold (LNT) dose-response relationship.

In Figure 5, all curves also show a background incidence rate, that is, a non-zero incidence at zero dose.

Some dose-response relationships show a "threshold," a dose below which there is no response. Such relationships are typical of deterministic effects such as cataracts, erythema, epilation, nausea, leukopenia, and teratogenesis, as shown in Figure 6, where thresholds of about

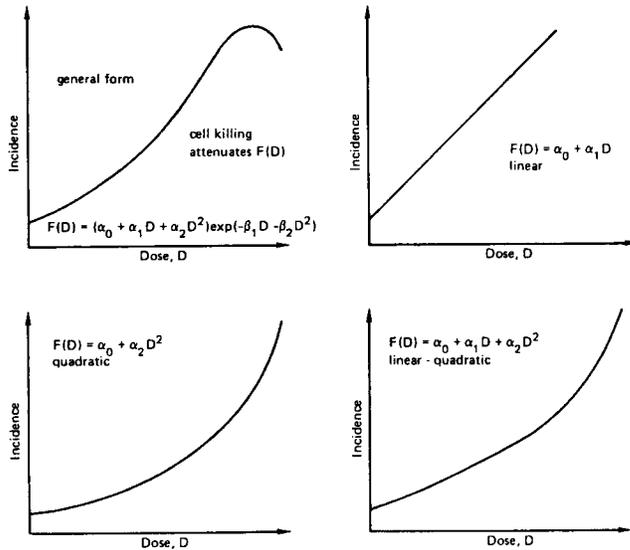


Figure 5. Traditional dose-response models from BEIR III<sup>[7]</sup>

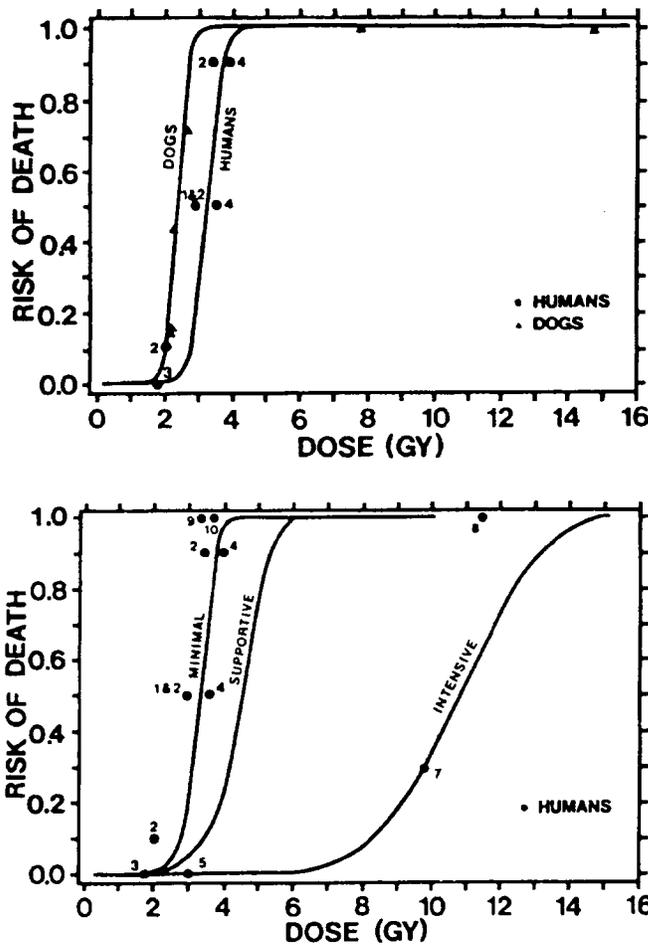


Figure 6. Top: Dose-effect curves for early mortality after brief total-body exposure of dogs and humans to low-LET radiations. Bottom: Dose-effect curves for various categories of medical treatment.<sup>[8]</sup>

1.5 Gy are seen. None of the curves in Figure 5 have a threshold, that is, even very small doses produce an increment of incidence.

Dose-rate effects are shown in a variety of ways. Sometimes two curves are used, as for the specific-locus mutation rates in male mice (Figure 7).<sup>[9]</sup>

### Considering Dose, Dose Rate, and Response Simultaneously: Surfaces

The mouse data can also be plotted in three dimensions as a function of dose and dose rate (Figure 8).<sup>\*</sup> The surface is truncated over a portion of the plane because doses in that dose rate region could not be delivered within the lifespan of a mouse.

Kellerer and Rossi developed a theory of dual radiation action in which microscopic lesions can be caused by either one or two hits and there is some repair characterized by a mean repair time  $\tau$ .<sup>[10]</sup> This leads to a linear-quadratic surface as a function of position in the dose-dose rate plane (Figure 9).

The surface shows the "high dose" and "low dose" regions from NCRP Report 64,<sup>[11]</sup> as well as the "high dose rate" and "low dose rate" regions from that report. At high dose and high dose rate, independent microscopic lesions can interact, giving rise to a dose-squared effect. The dual radiation action model holds very well for chromosome aberrations in circulating human lymphocytes, and is used as the basis for cytogenetic dosimetry.

### Dose Rate and Radiation Quality

Figure 10 shows dose-response curves for chromosome aberrations for several types of radiation. This figure illustrates the differences in biological effect for similar doses of different radiations.

\* Material presented on June 29, 1982, at the 27<sup>th</sup> Annual Meeting of the Health Physics Society, Las Vegas, Nevada.

*Dose, Dose Rate, and Dose Fractionation*

Fractionation of dose is the delivery of a given dose in fractional increments. This is common practice in radiation therapy, where it permits healthy tissue to repair somewhat more than tumor tissue between doses, with the ultimate goal of overwhelming the tumor and sparing the healthy tissue. This is shown dramatically in Figure 11 adapted from Fry for leukemia in mice.<sup>[12]</sup> As the number of fractions increases, the incidence decreases.

*Species, Average Dose Rate, Time to Death, and Endpoint*

Other ways of presenting data on radiation exposures and health effects are available. In 1980, Otto Raabe published a graph (Figure 12) showing time to death as a function of average skeletal dose rate.<sup>[13]</sup> Clearly this graph shows relationships that could not be shown on a dose-response plot.

More recently, Raabe has published a dose-rate, time-to-death, and frequency surface (Figure 13). The x-axis is the average dose rate over the remaining lifespan of the organism after exposure begins; the y-axis is the time to death in days, and the z-axis is the frequency of the outcome.<sup>[14]</sup>

*Type of Response Model, Age at Exposure and Sex*

Other important ways of showing dose and response data are to include age dependence, as shown by graphs from the recent paper by Pierce et al. on the Japanese bomb survivors (Figure 14 and Figure 15).<sup>[15]</sup>

The two graphs show models of the vast difference between excess relative risk (relative increase in cancer frequency as a function of dose, age, and sex) and excess absolute risk (absolute number of cancers as a function of dose, age, and sex). The additive risk model ("absolute" risk; Figure 15) was used by BEIR III, while the multiplicative risk model (excess relative risk) is now preferred by the

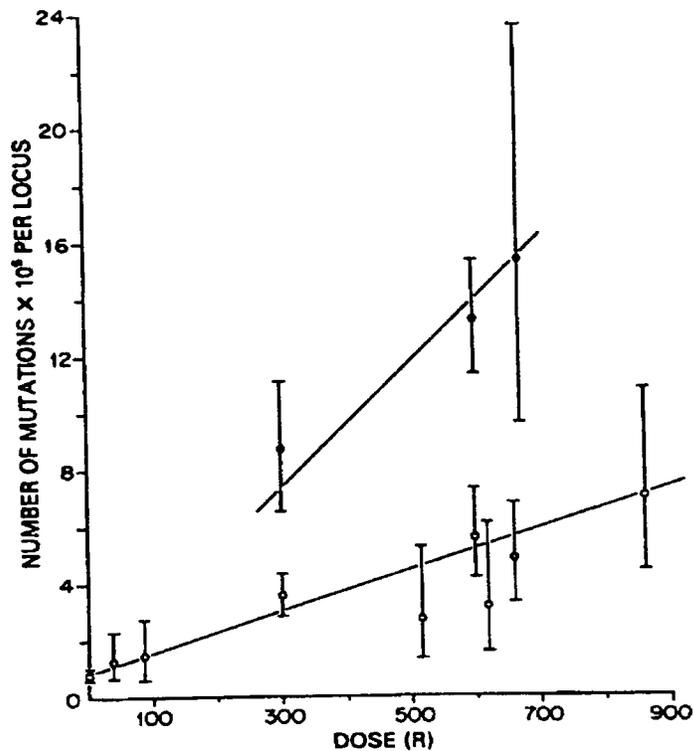


Figure 7. Specific-locus mutation rates for high (•) and low (◦) dose-rate irradiation of mouse spermatogonia with 90% confidence intervals<sup>[9]</sup>

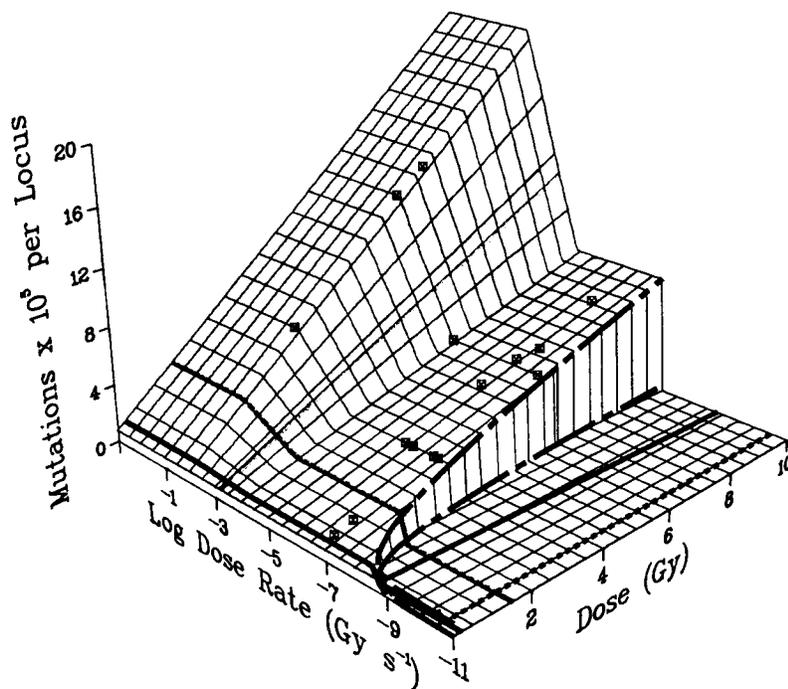


Figure 8. Russell and Kelly specific-locus mutation data plotted on a surface above the dose-dose rate plane<sup>[9]</sup>

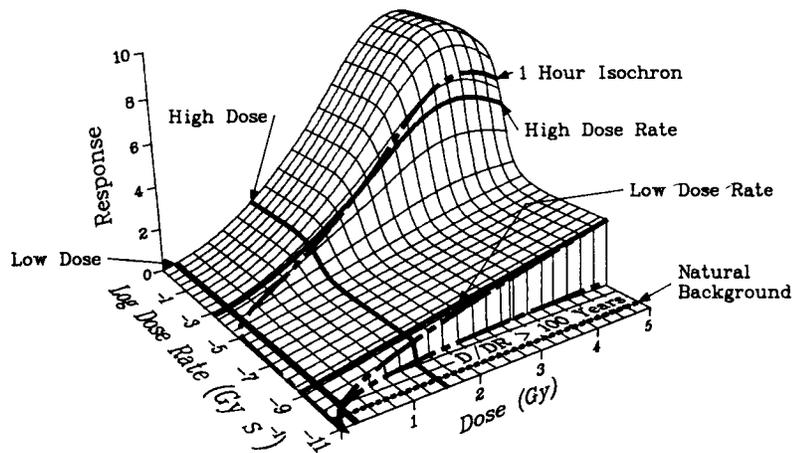


Figure 9. Kellerer and Rossi's 1972 theory of dual radiation action for arbitrary parameters and a 1-hr repair time<sup>[10]</sup>

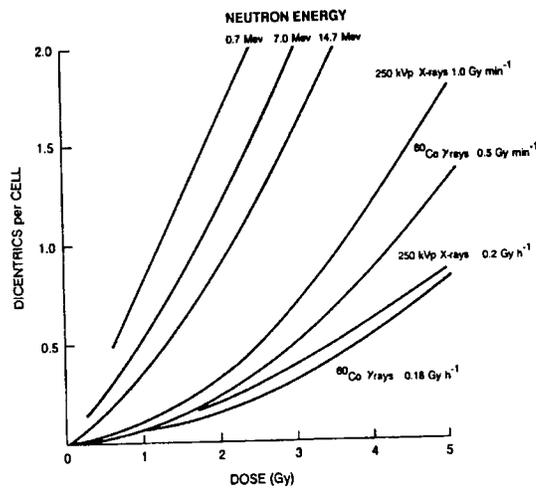


Figure 10. Frequency of dicentric chromosome aberrations in human lymphocytes irradiated in vitro in relation to dose, dose rate, and quality of radiation

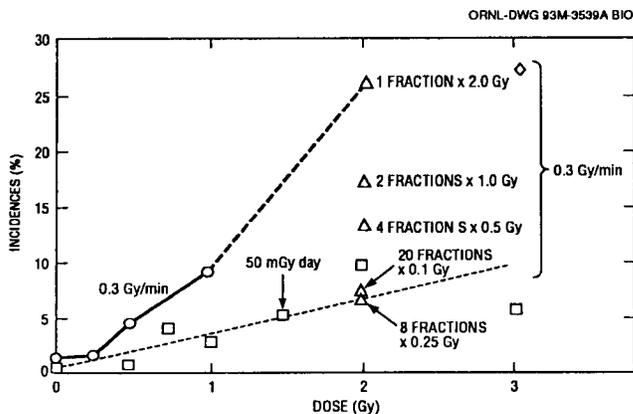


Figure 11. The incidence of myeloid leukemia in RFM male mice exposed to single doses (circles), fractions totaling 2 Gy (triangles), and 50 mGy d<sup>-1</sup> (squares)<sup>[12]</sup>

BEIR V committee, the ICRP, the NCRP, and the UNSCEAR. The BEIR V multiplicative risk model is given by:

$$\gamma(d) = \gamma_0(1 + f(d)g(\beta)) \quad (2)$$

where  $f(d)$  is the "dose-response function" and  $g(\beta)$  is a function of age and sex.<sup>[16]</sup>

The National Academy of Sciences' BEIR IV committee also adopted an age-dependent, time-since-exposure model, shown in Figure 16.<sup>[17]</sup> Exposures within five years of diagnosis are given zero weight, those between 5 and 15 years before diagnosis full weight, and those more than 15 years prior to diagnosis half weight. Exposures prior to age 55 are most important, while those between 55 and 65 are less important, and those after age 65 are least important.

In 1994, a National Research Council Committee showed the need to reassess the underground miner data.<sup>[18]</sup> Committee member David Brenner of Columbia University produced a dose and dose rate effectiveness function that accounts for the inverse dose rate effect seen in the miner cohorts (Figure 17).

#### Competing Effects: Adaptive Response Through Inducing Repair

In the past two decades, there has been considerable talk about radiation "hormesis" and "adaptive response" to radiation. Hormesis derives from the pharmacology concept of "sufficient challenge": a small amount of a toxin induces coping mechanisms, actually making an organism stronger. Adaptive response is the phenomenon of exposing an organism to a small "priming" dose of radiation, and observing that shortly thereafter the organism is much more resistant to high doses than control organisms that haven't been given a priming dose. Proponents of hormesis suggest a J-shaped or a U-shaped dose-response curve (Figure 18), where small doses of radiation show a protective effect, decreasing incidence to below background levels. Difficulties with this theory are discussed below.

## Issues in Developing or Choosing a Model for Radiation Risk Management

There are many issues to be considered in developing a model for radiation risk management. These issues include:

- the existence of a threshold or a practical threshold
- the shape of the functional relationship (linear; linear-quadratic; hormesis: U-shaped, J-shaped)
- repair of DNA
- adaptive response
- latent period for cancer
- relevance of *in vitro* and animal data to human health
- importance of heritable ill-health
- whether and how to extrapolate to doses below the range of statistically significant data
- validity of various epidemiological methods (in particular the ecological study design)
- whether a threshold for one kind of cancer implies a threshold for all
- what to do in the face of uncertainty or contradiction
- how to extrapolate: if one fits a linear relationship to the data, then one ends up with a linear relationship
- inference of causation from association
- determining what is prudent public policy
- choice of risk assessment models in the contexts of prevention (protection), prediction, and priority-setting<sup>[20]</sup>

## The Evidence and the Nature of Epidemiology

The evidence that can be brought to bear on these issues includes physical, molecular, cellular, *in vitro*, animal, and human (epidemiology)

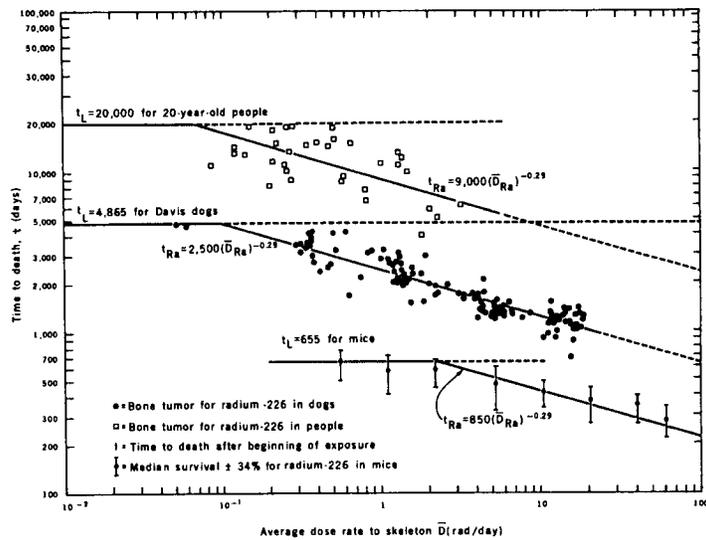


Figure 12. Primary bone cancer deaths from  $^{226}\text{Ra}$  for people, Davis beagles, and female  $\text{CF}_1$  mice<sup>[13]</sup>

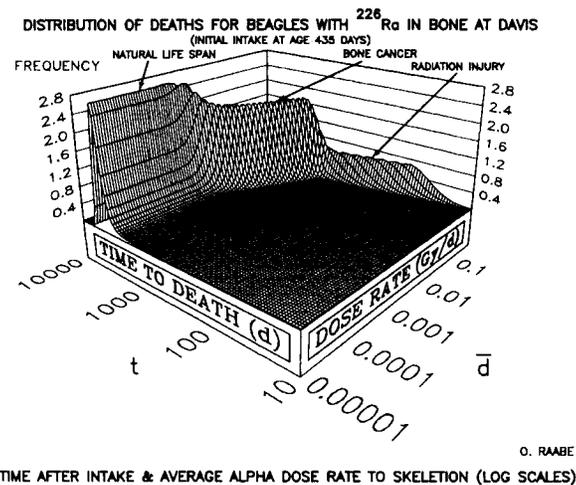


Figure 13. Distribution model of times to death for beagles from acute radiation injury, bone cancer, and old age as a function of average dose rate to skeleton from  $^{226}\text{Ra}$ <sup>[14]</sup>

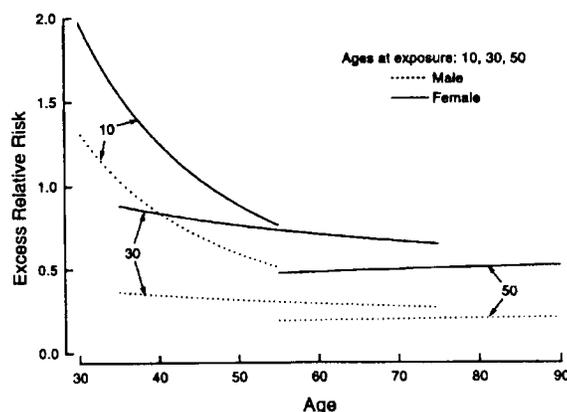


Figure 14. Multiplicative risk model of Japanese bomb survivor data<sup>[15]</sup>

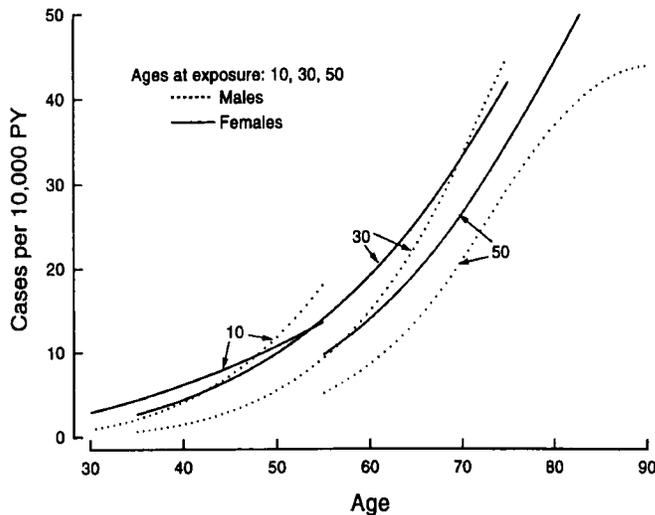


Figure 15. Additive risk model of Japanese bomb survivor data<sup>[15]</sup>

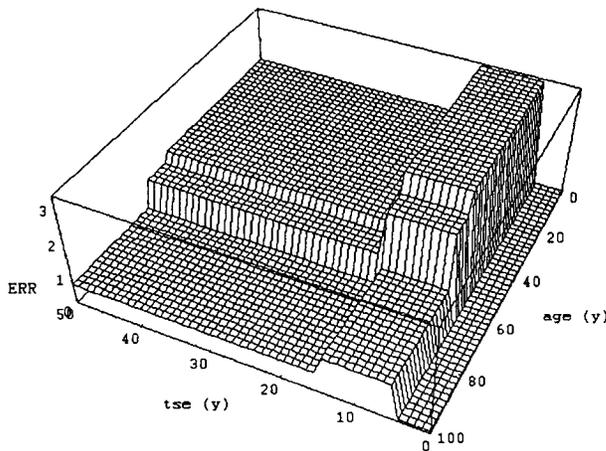


Figure 16. BEIR IV model for excess relative risk (ERR) of lung cancer following exposure to radon progeny as a function of age and time-since-exposure (tse; National Academy of Sciences 1988)<sup>[17]</sup>

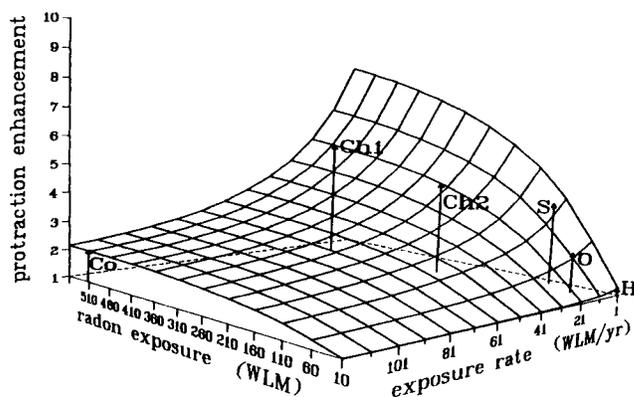


Figure 17. Protraction enhancement as a function of exposure in WLM and exposure rate in WL<sup>[18]</sup>

evidence. I will limit my discussions to the human evidence, or epidemiology. Epidemiology is the study of patterns of disease in human populations. It is very important to realize that some epidemiological studies are experiments, while virtually all radiation epidemiology consists of observational studies. What's the difference between an experiment and an observational study? In physics, an experiment is planned and designed to test a hypothesis. Data are collected and analyzed. In physics, an observational study involves no intervention or manipulation by the observer. Astronomy is purely observational.

In epidemiology, there is a hierarchy of study designs that ranges from the most compelling to the least. The best experiments are so-called double-blind randomized trials or clinical trials. In these, neither the researchers nor the subjects know who is in the exposed group(s) and who is in the control group. Ideally, there is a large enough number of subjects to be able to accept or reject the hypothesis under investigation. Observational studies are much less sensitive and subject to pitfalls yielding the wrong answers. Because of this, observational epidemiology for chronic diseases with long latent periods is an extremely blunt tool. It is insensitive and error-prone.

There are two broad categories of observational study designs. In the first category, individual health outcomes correlated with individual exposures. These are case-control and cohort studies. In case-control studies, the exposures are compared for persons having and not having a disease. For indoor radon, for example, persons having lung cancer are more likely to have been in high radon houses than persons matched on age and sex who don't have lung cancer. In cohort studies, groups are selected, their exposures categorized, and then their health history is ascertained. The uranium miners and the Japanese bomb survivors are cohort studies.

In the other broad category, group health outcomes associated with group exposures (or surrogates). In cross-sectional studies, one merely

looks at disease prevalence in a cross-section of a population. In the ecological study design, one examines the association between group health outcomes, such as lung cancer rates in counties, with exposure variables, such as radon measurements in counties. For a variety of reasons, such studies are much more prone to inferential pitfalls and spurious correlations. For the county radon-lung cancer study of Cohen,<sup>[21]</sup> the persons exposed to radon weren't the same as those who got the lung cancer and those who purchased the cigarettes. The exposures and deaths weren't even the same time! It is impossible to control for other factors, such as confounding, bias, and effect modification.

*Confounding* occurs when there is a factor associated with both exposure and health outcomes, e.g., diet differences are associated with ethnic groups and with health outcomes. *Bias* occurs when non-representative samples are used. For example, are all persons owning a telephone and willing to participate in a survey the same as all persons? No. All persons include many lower socioeconomic status persons (who have significantly poorer health) who cannot afford a phone or who don't have a permanent address. Those with phones but unwilling to participate in surveys also differ from the willing, for example, in English skills. A survey of only rich people is biased compared with a survey of all people. *Effect modification* occurs when some variable changes the effect of exposure. Common effect modifiers are age, immunization, and smoking.

Confounding, bias, and effect modification must be controlled for both in the design and analysis of epidemiological studies. Other inferential problems in epidemiology include the need to look for a small signal in a high level of noise. Experimental epidemiology has much better ability to deal with small signal-to-noise ratios than observational epidemiology. Many of the top epidemiologists suggest that looking for a relative risk (RR) or odds ratio (OR) less than 3 or 4 is tricky in environmental epidemiology.<sup>[22]</sup> [Note that American society wants regulation of

### WHOLE BODY MUTATIONS (MIS/UNREPAIRED DNA ALTERATIONS) From Low-Dose Radiation

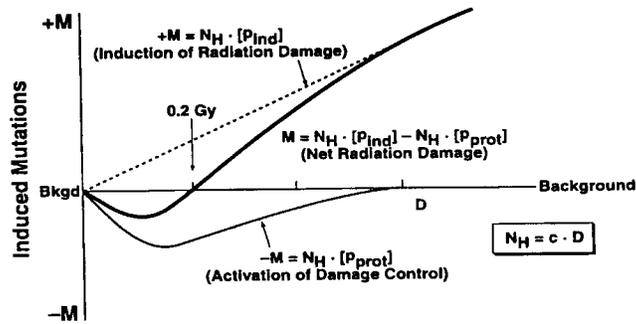


Figure 18. Dose-response curve showing effect of adaptive response<sup>[19]</sup>

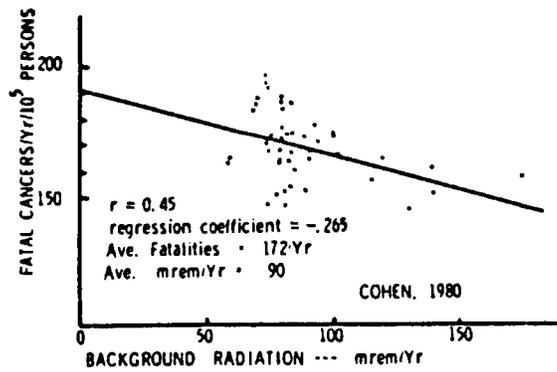


Figure 19. Ecological study design of fatal cancer rates in the USA as a function of terrestrial background radiation dose rates<sup>[29,30]</sup>

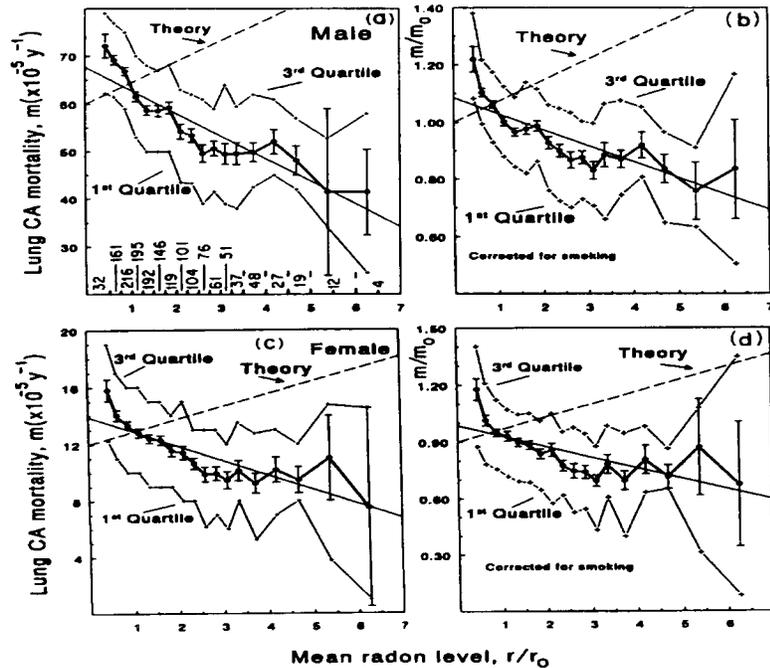


Figure 20. Ecological study of lung cancer mortality for US males and females, with and without "correction" for smoking, as a function of short-term average radon measurements in counties<sup>[21]</sup>

imposed risks at the lifetime fatal cancer risks of 1 in 1 million, that is,  $RR \approx 1.000005$  assuming a 20% underlying cancer fatality rate].

In 1877 Henle and Koch first addressed association and causation,<sup>[23]</sup> and their work was revisited two decades ago.<sup>[24]</sup> Sir Austin Bradford Hill published an influential work on association and causation.<sup>[25]</sup> Another perspective can be found in the work of Susser.<sup>[26]</sup> Canadian and U.S. leaders addressed the quality of epidemiologic evidence under the title "Hierarchy of Evidence."<sup>[27]</sup> Most recently, the Federal Focus expert panel explained why descriptive epidemiology studies don't get much respect among risk analysts when they try to come to quantitative conclusions.<sup>[28]</sup>

In the past, this author has been critical of the application of descriptive epidemiology (e.g., ecological studies) to quantitative problems.<sup>[31,32]</sup> "Descriptive studies are generally

viewed as useful for identifying or formulating causal hypotheses, but not sufficient to test such hypotheses, because they lack data on individuals, such as individual exposures, potential confounding exposures, factors affecting individual susceptibility, and potential biases. In contrast, studies generally termed 'analytic' aim to establish risk factors for populations and individuals by ascertaining individual exposures and controlling for other variables such as sex, age, race, or exposure to other agents that could affect risk estimates independently (potential 'confounders'), potential study biases, and variations in host susceptibility. There are two main types of analytic epidemiology: case-control and cohort studies..." This quote is from a new book written by an expert panel of risk assessors in 1995 entitled "Principles for Evaluating Epidemiologic Data in Regulatory Risk Assessment."<sup>[28]</sup> The panel consisted of an international group (mostly from the USA, however) of

well-respected, middle-of-the-road risk assessors from universities, governments, and industry groups. These principles can be found at [www.sph.umich.edu/group/eih/UMSCHPS/epidprin.htm](http://www.sph.umich.edu/group/eih/UMSCHPS/epidprin.htm).

The results of an often-cited study by Frigiero<sup>[29]</sup> of lung cancer mortality rates are shown in Figure 19. This study made no attempts to control for migration, bias, or confounding. The simplistic notion that no other agents (e.g., diet, air pollution, indoor radon) or conditions (e.g., ethnic make up of a population) that cause or prevent cancer are correlated with geography does not stand up to scrutiny.

Steve Wing and colleagues have published a reanalysis of TMI health effects data.<sup>[33]</sup> The Wing study, the work of B.L. Cohen (Figure 20),<sup>[21]</sup> and the Frigiero study are in a category of descriptive epidemiology, as opposed to analytical epidemiology.

Whether descriptive or analytic, virtually all occupational and environmental epidemiology studies are "observational" as opposed to "experimental" (a.k.a. clinical or interventional) studies. Since human experimentation, outside of closely supervised clinical trials, is out of the question, we are left with observational study designs which, unfortunately, are not the most cogent designs because of uncontrolled factors. Neither the Wing TMI study nor Cohen's study are "experiments," but compilations and analyses of whatever data are available.

Some tout Cohen's study as valid and useful (it claims that increasing exposure to radon is associated with decreased lung cancer risk), while decrying Wing's study as "junk science" (Wing et al. claim that the accident at TMI caused lots of excess disease, including acute radiation effects).<sup>[33]</sup> It is puzzling why descriptive studies are compelling in one case and not in the other. The bottom line is that neither have data for individuals, neither has meaningful control for confounders and biases, and no amount of statistical analysis will change that. Both fail to meet many of the criteria presented by leading risk analysts.

**Table 1. Mortality for selected causes,  $\geq 0.5$  rem group,  $< 0.5$  rem group, and NNW: Summary of Standardized Mortality Ratios (Table 4.1A from Matanoski)<sup>[34]</sup> LHC=lymphatic and hematopoietic cancers**

Cause	SMR	95% C.I.	SMR	95% C.I.	SMR	95% C.I.
	$\geq 5$ mSv		$< 5$ mSv		NNW	
All	0.76	0.73-0.79	0.81	0.76-0.86	1.00	0.97-1.03
Leukemia	0.91	0.56-1.39	0.42	0.11-1.07	0.97	0.65-1.39
LHC	0.82	0.61-1.08	0.53	0.28-0.91	1.10	0.88-1.37
Mesothelioma	5.11	3.03-8.08	5.75	2.48-11.33	2.41	1.16-4.43
Lung cancer	1.07	0.94-1.21	1.11	0.90-1.35	1.15	1.02-1.29

**Table 2. ACRP-18 findings on thresholds<sup>[37]</sup>**

Effect (Radiation) [Species]	Threshold?
Bone CA (Ra) Liver CA (Th) [human]	Yes;
Bone CA ( $\alpha$ , $\beta$ ) [human]	practical
Lung CA ( $\alpha$ ) [non-SMK dogs, rats; ? non-SMK human]	
Lung CA (fluoro) [CDN human]	Yes
Leukemia (A-bomb) [JPN human]	Perhaps
Tumors (any) [animals]	50-50 chance
Lung CA (Rn) [SMK human]	No
Solid CA (A-bomb) [human]	
Life shortening tumors (any) [animals]	No

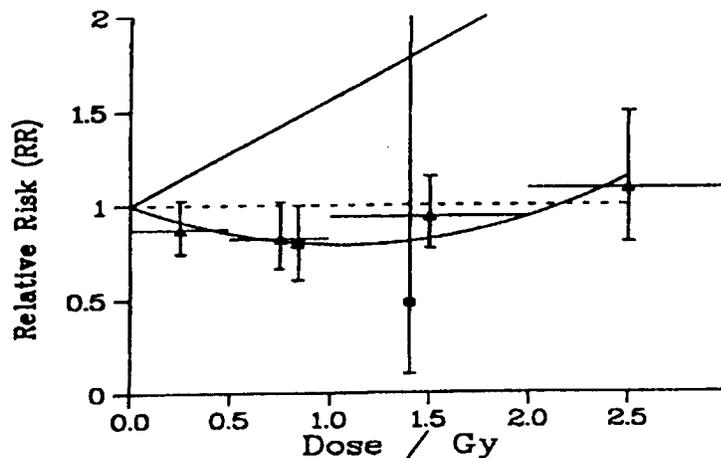


Figure 21. Relative risk (RR) of lung cancer in people exposed medically to low-LET radiation<sup>[38]</sup>

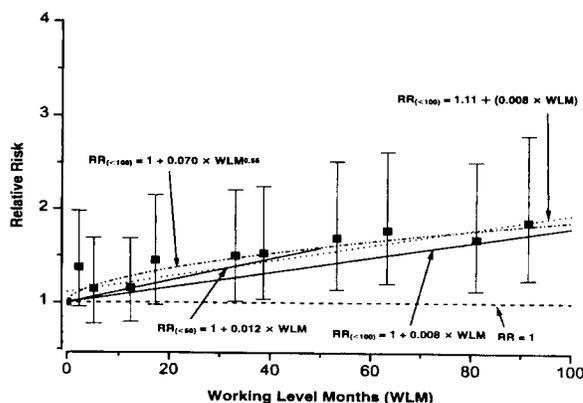


Figure 22. Relative risks (RRs) of lung cancer from pooled data for 11 cohorts of underground miners, restricted to <100 WLM or <50 WLM exposures.

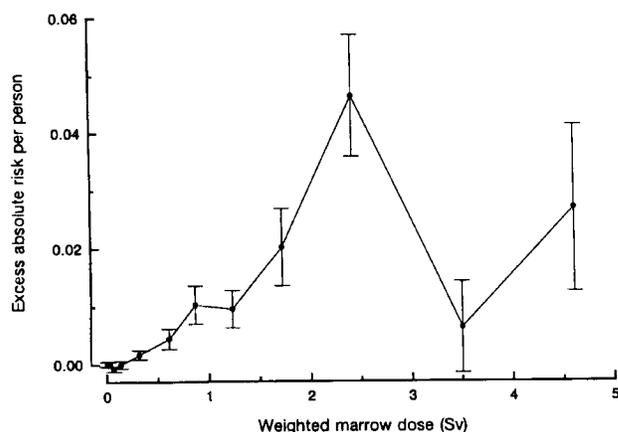


Figure 23. Excess absolute risk of leukemia in Japanese bomb survivors 1950-1990<sup>[16]</sup>

Matanoski's nuclear shipyard study is characterized by unhealthy control groups, making it one of the few studies in occupational epidemiology not to find a "healthy worker effect" (Table 1).<sup>[34]</sup> This odd finding challenges the consistency criterion and makes the entire study suspect.

In the LNT debate, there has been a lot of what I call "tobacco-company science": one begins with the conclusions one would like to have, and one only considers data or studies that support them. On the other hand, the national and international studies have considered all the studies, and weighed them on their merits.

Recent reviews that do not fall in the "tobacco company science" category include U.S. National Council on Radiation Protection and Measurements Report No. 121,<sup>[35]</sup> the UK National Radiological Protection Board document,<sup>[36]</sup> and the Canadian Advisory Committee on Radiation Protection.<sup>[37]</sup> All conclude that there are circumstances under which the linear, no-threshold (LNT) model is appropriate for use in radiation protection against stochastic effects. The latter study states, "Not all available data on radiation-induced cancers fit the linear non-threshold hypothesis." The ACRP finds no evidence for dose thresholds for heritable ill-health, and summarizes the evidence for dose thresholds for cancer as shown in Table 2. The ACRP concludes that, for some cancers such as bone cancer caused by radium, there is a definite threshold.

Another review not done by a committee shows an absence of lung cancer from low-LET radiation at doses below 2 Gy.<sup>[38]</sup> This study reviewed fluoroscopy patients, tuberculosis patients, and radiotherapy patients, as shown in Figure 21.

Since these three reviews were published, risk estimates have been updated for the two best characterized cohorts of human beings exposed to ionizing radiation, namely, the Japanese survivors of nuclear bombings<sup>[16]</sup> and eleven cohorts of underground miners (Figure 22.)<sup>[39]</sup>

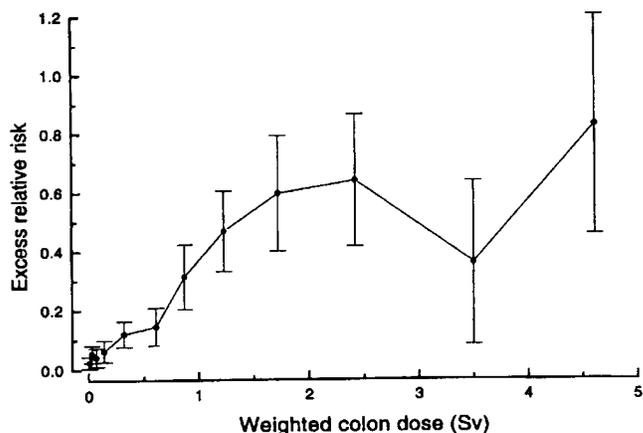


Figure 24. Excess relative risk of solid cancers in Japanese bomb survivors 1950-1990<sup>[16]</sup>

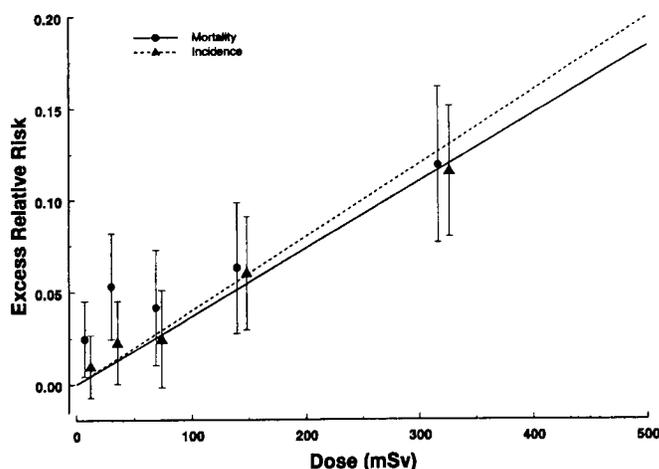


Figure 25. Solid tumor incidence and mortality in Japanese bomb survivors<sup>[40]</sup>

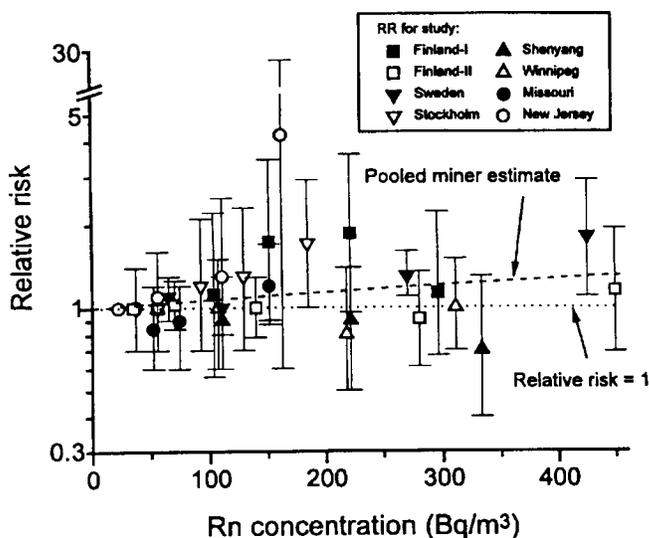


Figure 26. Meta-analysis of eight indoor radon case-control studies<sup>[42]</sup>

Both of those papers explicitly addressed the low dose region, and both document an inverse dose-rate effect. Lubin and co-workers tried several alternative models for excess relative risk (ERR) including the simple:

$$RR = 1 + \beta \times WLM;$$

the power law:

$$RR = 1 + \beta \times WLM^K;$$

and the adjustable intercept:

$$RR = \exp(\gamma)(1 + \beta \times WLM).$$

Models with adjustable intercept and adjustable power (exponent) did not fit significantly better than the simple linear ERR model.

The bomb survivors still show linearity for solid tumors (Figure 24) and a distinctly non-linear relationship for leukemia (Figure 23).

In response to repeated challenges to their analyses, Pierce et al. have recently provided a detailed explanation of their inference of linearity for solid cancers.<sup>[40]</sup> Simplistic analyses such as that of Cohen<sup>[41]</sup> that ignore variations in risk with age and sex and which, instead of using hypothesis testing, use nonstandard analyses, don't use all of the information in the data. Pierce et al. have shown that, while mortality is supralinear, the incidence is linear down to the lowest doses.<sup>[16]</sup>

A recent meta-analysis of indoor radon case-control studies has also shown consistency with extrapolations from high doses (Figure 26).<sup>[42]</sup> Both recent analyses show that these two well-characterized cohort studies have plenty of low-dose data in them.

The miner and indoor radon studies clearly rule out the protective effects suggested by the popular ecological study by Cohen (Figure 27). The ecological study design is simply not compelling because it cannot control for bias (in particular information bias) and confounding. This topic has been extensively discussed by various authors.<sup>[43,44,45,46,47,48]</sup>

Even within the ecological design genre, though, there are vast

differences in credibility. Jacob et al.<sup>[49]</sup> have published an ecologic study of thyroid cancer incidences between 1991 and 1995 in children in Belarus and Ukraine exposed at ages of 0-15 years to radioactive materials released from Chernobyl. This ecologic study is far more convincing than Cohen's<sup>[21]</sup> study because:

1. Confounding is much less of a problem because there are no competing causes of thyroid cancer (cigarette smoking is expected to cause ten times more lung cancer than radon).
2. The exposures occurred over a short period of time (a few weeks) instead of over lifetimes.
3. Migration (i.e., evacuation) of individuals is known.
4. Direct measurements were made on hundreds of thousands of thyroids at the time as a function of location.
5. Environmental measurements of the radioiodines in milk and soil were widely made.
6. Accuracy of diagnosis were independently verified.
7. An excellent control group was available (the same population, 1986-1988).
8. Strength of association was high.

Jacob et al. found statistically significant excess absolute risk at average thyroid doses as low as .05 Gy (in Kiev), with an observed to expected ratio of 6 (67 cases observed).<sup>[49]</sup> They found "no statistically significant deviation from a linear-dose response relationship," as shown in Figure 28.

In June 1998, a "large" case-control study (982 cases, >3000 controls) of indoor radon was published in the UK.<sup>[50]</sup> The study concludes that "the estimated excess relative risk associated with a 100 Bq/m<sup>3</sup> increase in residential radon concentration is 0.08 (with a 95% confidence interval of -0.03 to 0.20)". Note that the confidence interval on the slope is considerably narrower than that on any individual data point. This result is consistent with nine earlier case-control studies.

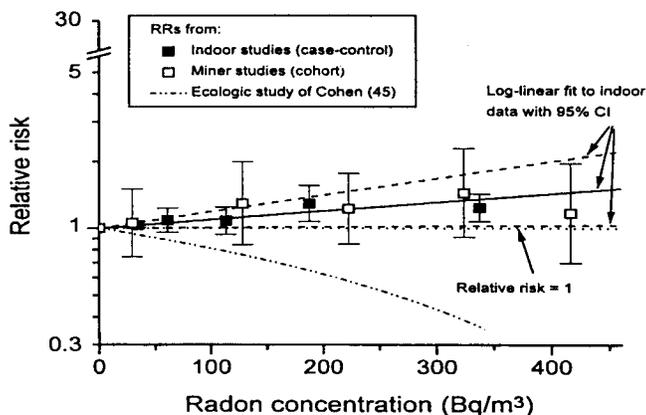


Figure 27. Lung cancer incidence in uranium miners and in indoor radon studies. The lower dashed line is Cohen's (1995) data, which appear to be curved on the semi-log vertical scale<sup>[39]</sup>

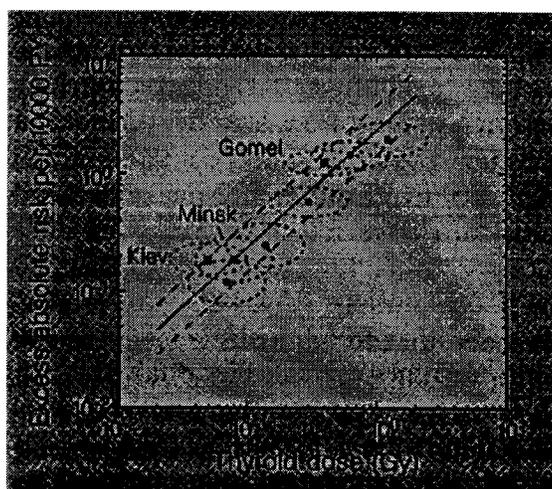


Figure 28. Excess absolute risk of thyroid cancer per 100,000 children exposed to emissions from the Chernobyl accident.<sup>[49]</sup> Note both horizontal and vertical uncertainty ellipses.

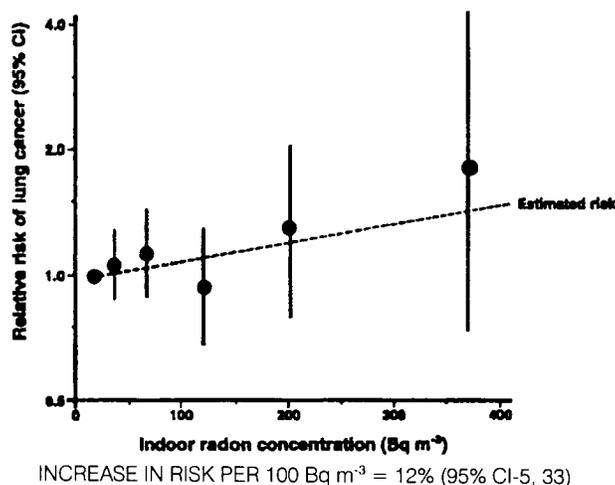


Figure 29. Relative risk of lung cancer v. indoor radon concentration in UK case-controlled study<sup>[50]</sup>

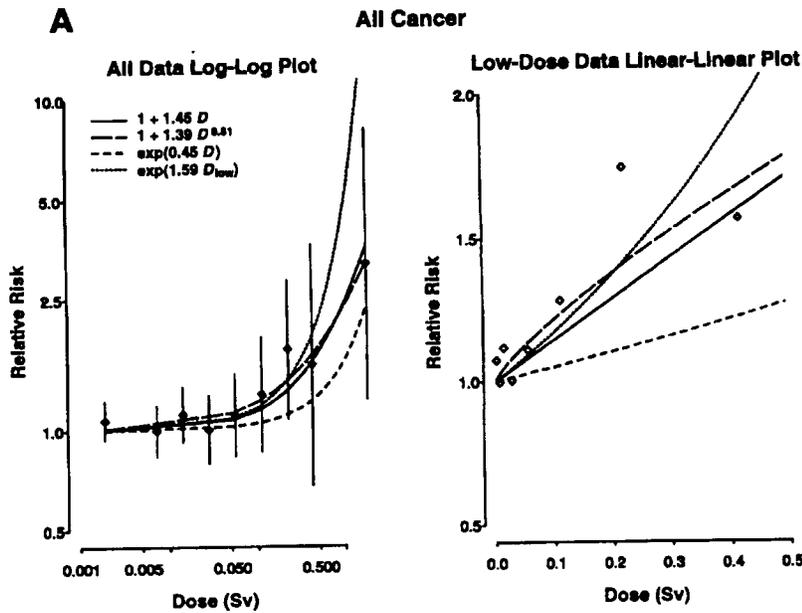


Figure 30. Fitted dose-response functions for all cancer. Point estimates ( $\diamond$ ) and 90% CIs (vertical lines)<sup>[52]</sup>

The page proof edition of BEIR VI report on radon (October 1998) recommends the use of the linear no-threshold model for radiation protection (Committee on the Biological Effects of Ionizing Radiation.<sup>[51]</sup> It also estimates that between 15,000 and 22,000 fatal lung cancers per year are due to radon progeny, with most of those being jointly caused by smoking. In a detailed discussion in an appendix, BEIR VI dismisses ecological studies as bases for risk estimation.

A recent combined analysis of Oak Ridge National Laboratory (X-10), the Oak Ridge Gaseous Diffusion Plant (K-25), and the Y-12 Plant studied 106,020 persons and 27,982 deaths. As expected, the all-cause standardized mortality ratio (SMR) was 0.80, and the all-cancer SMR was 0.87, which the authors termed a "strong 'healthy worker effect'."<sup>[52]</sup> The only notable excesses in SMRs were for lung cancer (SMR = 1.18, 1,849 deaths) and nonmalignant respiratory disease (SMR = 1.12, 1,568 deaths). The excess relative risk for all cancer was  $1.45 \text{ Sv}^{-1}$  (95% CI = 0.15-3.48). Fits to data are shown in Figure 30.

So the *scientific* evidence for thresholds for carcinogenesis in human beings is mixed.

#### Why use models at all?

Models are needed to extrapolate to low doses (< 50 mGy), low dose rates (< 50 mGy/y), and both. It is necessary to extrapolate below the range of statistical significance, because effects may still be very important below the range where they can be detected with statistical significance. The linear, non-threshold (LNT) model predicts that 1.2% of all deaths are cancer deaths due to background and technologically-enhanced radiation. Another 20-25% of all deaths are cancer deaths unrelated to radiation. The ubiquitous nature of radiation exposure and the long latency period for cancer makes environmental epidemiology very tricky indeed. It is thus necessary to use models to predict risk or the absence of risk.

Clearly, it is impractical to scientifically assess each individual's instantaneous risk each time he or she is to be assigned work on a particular

radiation work permit! Dose limitation for individuals must be set on the basis of predetermined rules based on models, whether there is a threshold or not.

#### Arguments for and Against the Linear, Non-Threshold Model

Having shown that the LNT model is far too simplistic to be "scientifically correct," this article will now review the various arguments for and against the use of the LNT model in radiation protection, that is, in the *management of radiation risks*. As described at the beginning of this article, risk management incorporates science, public policy, societal values, and practicality.

The use of the LNT model in radiation protection is only for stochastic effects, namely, cancer and heritable ill-health, not deterministic effects that clearly have thresholds and nonlinear dose-response relationships.

#### Scientific Arguments for LNT

There are a number of valid scientific arguments for the use of LNT as a basis for radiation protection against stochastic effects.

- *THE MONOCLONAL ORIGIN OF TUMORS*

One of the most compelling arguments for LNT is the monoclonal origin of tumors (tumors arising from a single transformed cell). This implies that one or more events occurred in that cell to initiate and promote the cancer, and cause it to progress to a tumor.

- *PERTURBATION THEORY*

A second argument is what physicists call perturbation theory: Radiation is merely a small perturbation of all the other nonradiological processes that occur in carcinogenesis. This theory was propounded by Crump and co-workers<sup>[53]</sup> and has recently been advanced again by Crawford and Wilson<sup>[54]</sup> and

Heitzmann and Wilson.<sup>[55]</sup> The basic tenet of the theory is that all thresholds, if there are any, for the various steps in a multistage carcinogenesis process have already been exceeded, and that any increment in radiation exposure produces a first-order perturbation of the process, leading to a linear increase in cancer risk.

- *CONSISTENCY OF MUCH HUMAN DATA WITH LNT*

A third argument is that the miner, Japanese bomb survivor, and many other human studies are consistent for most cancer endpoints. Exceptions to this are noted below.

- *HERITABLE ILL-HEALTH*

A fourth argument is that heritable ill-health (also imprecisely referred to as genetic effects) is very probably described by LNT.

#### *Scientific Arguments Against LNT*

There are two scientific arguments against the use of LNT as a basis for radiation protection against stochastic effects.

- *INCONSISTENCY OF SOME HUMAN DATA WITH LNT*

Some credible radiation data contradict LNT for a few cancer endpoints, as discussed above and shown in Table 2.

- *ABSENCE OF HERITABLE ILL-HEALTH IN BOMB SURVIVORS*

No statistically significant heritable ill-health has been seen in the Japanese bomb survivors. However, given the population size, and the predicted doubling dose of 1.7 to 2.2 Sv, this is consistent with predictions of animal and *in vitro* experiments (Neel in press).<sup>[56]</sup>

#### *Specious Arguments Against LNT*

Specious scientific arguments against LNT include the following:

- *"IF YOU CAN'T DETECT A HEALTH EFFECT, IT DOESN'T EXIST"*

The following posting was found on RADSAFE (an internet listserver devoted to radiation safety):

"Date: 25 Mar 1996 14:17:14 MDT

Subject: Threshold (was RE: Healthy Worker Effect vs. Hormesis)

It is certainly reasonable to conclude unobservable effects don't exist. However, those who espouse the LNT are not reasonable in that respect. They fear (emotion) that effects will be found some day and then they'd feel awful if they had let that happen because of their not insisting that their hypothesis was right. I have long advocated the idea of: "If you can't observe something, it doesn't exist." But, rationality sometimes takes a back seat to emotion (or to ulterior motives)."

This kind of specious reasoning is astounding nonsense, as illustrated by the story below.

- *A Story*

This is a tale of the health physicist at the "Swords to Plowshares" plutonium facility in the third world, where they make mixed oxide fuel for their domestic nuclear power program by recycling old weapons-grade plutonium donated by superpowers.

There is no containment in the processing facility where Pu is dissolved. The HP decides to conduct an air monitoring program. He has a limited budget, but plenty of donated air samplers. Workers breathing 20 liters per minute wear breathing zone air samplers operating at 1.8 liters per minute. Because of dust-loading, he can't use a filter more than one day. He's told that 0.1% of the plutonium by weight is Am-241, and by knowing the isotopic mix, he determines that 3.6% of the activity is Am-241. His only detector is a side-window GM tube (the shield is rusted in the closed position) connected to a rate meter that, given local background, can reliably distinguish

100 cpm above background from background itself. Since the shield is stuck in the closed position, the GM tube detects only the 60 keV photon from Am-241, emitted in 36% of transitions. The counting efficiency of the detector for 60 keV photons emitted from a standard 37mm air filter is 0.01 counts per photon emitted. Local regulations specify that the "50-mSv" ALI for this mixture of class W Pu (with Am) is 185 Bq (5 nCi). Day after day, he counts the air samples with his side-window GM and never sees anything that's 100 cpm above background. However, after a couple of weeks of Pu operations, the plant physician diagnoses radiation pneumonitis in several of the workers, and soon afterwards they die. He decides to compute the minimum detectable dose for his air monitoring system, and discovers that it corresponds to a daily intake of 144 kBq of the plutonium mixture, corresponding to a daily value of  $H_{E,50} = 39$  Sv. As the plant manager takes him out back, stands him up against a wall, and ties on a blindfold, he complains, "I was always told that if you can't measure it, it doesn't exist."

- *What Can Be Inferred When Nothing Is Observed?*

One well-known health physicist has "long advocated the idea of: 'If you can't observe something, it doesn't exist.'" Others state, "Below 10 rem ..., risks of health effects are either too small to be observed or nonexistent."<sup>[57]</sup> These arguments have been used to support claims that low doses of radiation are without risk. The arguments stem from the fact that epidemiology has failed to reveal excess or attributable cancer incidence or mortality at low doses (say, less than 10 mSv acute exposure).

Using epidemiology to detect cancer at low doses is like measuring radioactive materials with an insensitive instrument in the presence of an enormous background: the threshold for detection is too high. In the case of cancer, the enormous background is the more than 30% incidence rate of cancer and the roughly 20% mortality rate from cancer in human

populations. The insensitivity of the instrument arises from the fact that cohort and case-control epidemiology studies rarely have enough participants to have very much statistical power.

Statistical power is the probability of concluding that there's no effect when in fact there really is an effect, a Type II error. A Type II error for measuring radioactive material is falsely concluding that there is no activity present in a sample when indeed there is activity present. For conventional minimum detectable amount (MDA) calculations, we often choose to accept a 5% chance of making a Type II error when using a decision level (DL) that gives us a 5% chance of making a Type I error (concluding that there's activity present when there isn't). These two choices lead to the familiar  $MDA = 4.65 \sqrt{s_B}$ , where  $s_B$  is the standard deviation of the background measurement.

For our hapless third world health physicist, his DL of 100 cpm resulted in an MDA corresponding to an enormous daily dose. For cancer, sB is on the order of a couple of percent, given the fact that cancer mortality rates vary between 17% and 23% from one state to another, so detecting anything short of an epidemic is difficult.

- "IF YOU CAN'T DETECT A HEALTH EFFECT, IT IS OF NO CONCERN"

This line of reasoning is equally specious. Huge effects (e.g., 14,000 lung cancers per year attributed to indoor radon progeny) can't be seen with crude studies such as Cohen's,<sup>[21]</sup> but may be detectable with careful pooling or meta-analysis of better designed studies.<sup>[58]</sup> This argument is really about policy, not about dose-response models.

- *BOMB SURVIVOR AND MINER STUDIES ARE "HIGH DOSE" STUDIES THAT ARE INAPPROPRIATELY EXTRAPOLATED TO LOW DOSES*

The charge that the bomb survivor and miner studies are "high dose" studies is unfounded. Recent analyses of both of these cohorts have stressed that most members of both cohorts were exposed to low doses. Cancers observed in these groups are consistent with the LNT model, and in fact suggest an inverse dose rate effect.<sup>[16,18]</sup> Furthermore, the application of a dose and dose rate effectiveness factor (DDREF) of three is often done for low doses of low-LET radiation, to accommodate dose-rate effects. Thus, cancer risks from high doses are not blindly extrapolated to low doses.

- *OXIDATIVE DAMAGE IS THE SAME FOR RADIATION AND CHEMICALS*

The arguments that radiation acts solely through oxidative damage and is thus far smaller an effect than chemicals normally induce in cells<sup>[59]</sup> ignore the fact that no chemical can do what an alpha particle or electron at the end of its track can do to DNA. These events have been termed moderate, large and gross clusters (Figure 31).<sup>[60]</sup> The damage caused by ionization clusters is qualitatively different from the oxidative damage caused normally by chemicals. Claycamp and Luo<sup>[61]</sup> have shown that plutonium causes many orders of magnitude more oxidative damage as a chemical than it does radiologically, but the distribution of the chemical oxidative damage in space and time is inconsequential compared to the clustered distribution of ionization damage in space in time.

- *ADAPTIVE RESPONSE*

Adaptive response is induced DNA repair triggered by exposures to low doses of ionizing radiation.<sup>[19,62]</sup> However, adaptive response seen only for certain endpoints and for certain intervals after priming (it fades with time after exposure, over a period of days). Typically, a large priming dose, on the order of 150 mGy, is required

<u>Initial cluster (in or very near DNA)</u>	<u>DNA damage</u>	<u>Repair</u>	<u>Biological importance</u>
<b>Sparse ionization</b> • ~10-20 eV	== ssb or base	~100%	-none
<b>Moderate cluster</b> ••• ~100 eV in 2-3nm	== dsb + Some extra damage	Moderate	Mainly determines low-LET effects
<b>Large cluster</b> ••••• ~400 eV in 5-10nm	 dsb(s) + much associated damage (nucleosome?)	~None	Mainly determines high-LET effects
<b>Gross cluster</b> ••••••• ~800eV in 5-10nm	 gross damage to DNA and surrounds	None	Some effects unique to high-LET?

In General:

1. Clusters dominate the final effectiveness of all radiations.
2. Larger (~unrepairable) clusters dominate the final effectiveness of high-LET radiations.

Figure 31. Hypotheses on hierarchy of four classes of ionization cluster and their roles in biological effectiveness.<sup>[60]</sup> Ssb = single strand break; dsb = double strand break

to maximize the effectiveness of the adaptive response, and excess human cancers seen below this dose. Given these understandings, it is virtually inconceivable that any adaptive response can be sustained by chronic exposure to low levels of ionizing radiation at levels near background.

- *THRESHOLD ANALOGIES APPLIED TO DOSE INSTEAD OF HIT SIZE*

Threshold arguments applied to hit size make a lot of sense for analogies such as the one made by Otto Raabe in his 1996-97 presentations for the Health Physics Society.<sup>[63]</sup> The argument goes like this: if a storm with 160 kph winds kills 10 people, will a storm with 16 kph winds kill 1 person, or 10 storms with 16 kph winds kill 10 people? Clearly, injury in the form of physical trauma from a wind storm is a threshold phenomenon. If this argument is applied to hit sizes on a microscopic scale, as done by microdosimetrists like Goodhead (Figure 31), the threshold concept is apt and the argument valid. However, when such a concept is applied to a macroscopic quantity like dose, it fails to make sense because it fails to recognize that even at low doses some hits can be very large. For example, if an alpha particle traverses a nucleus, it produces a dose of roughly 250 mGy. So what does 1 mGy of alpha dose mean? It means that for every 250 cell nuclei in the radiation field, 249 nuclei have not been hit at all, and that one nucleus has received a dose of 250 mGy. So, even though on a macroscopic scale one can talk about a low dose, on a microscopic scale there is no such thing for high-LET radiation.

- *HORMESIS*

Hormesis is the phenomenon of "sufficient challenge" in pharmacology. Exposure to a small amount of a stressor has beneficial effects in a wide variety of circumstances, from exercise to selenium. If a human population gets very little exercise, or works like slaves building the great pyramids of ancient Egypt, that population will not live as long as a population with a similar diet but

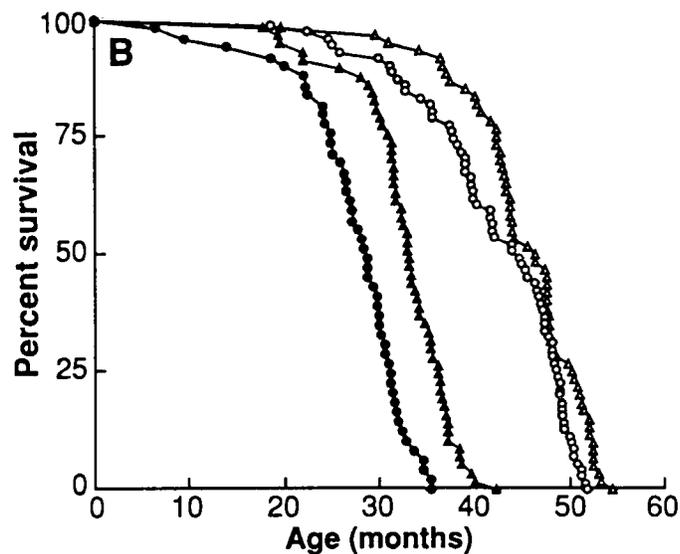


Figure 32. Survival of mice as a function of diet. • ad libitum; ▲ 85 kcal/wk; ○ 50 kcal/wk; △ 40 kcal/wk<sup>[64]</sup>

moderate exercise. In the first case, lack of exercise leads to a weak cardiopulmonary system, obesity, and increased risk of heart disease. In the second case, excessive exercise leads to people wearing out and dying of injuries. So, there is a balance point between inactivity and overwork.

Animal studies showing hormesis may fail to adequately control diet. Restriction of caloric intake lowers steady-state levels of oxidative stress and damage, retards age-associated changes, and extends the maximum life-span in mammals.<sup>[64]</sup> Thus, diet is a powerful risk factor for lifespan, leading to the question, "Is it the chemicals or the calories?" (Committee on Comparative Toxicity of Naturally Occurring Carcinogens of the National Research Council 1996).<sup>[65]</sup> Failure to control diet may completely mask much weaker effects on lifespan caused by radiation (see Figure 32).

- *SOME CHEMICAL CARCINOGENS HAVE THRESHOLDS*

The well-established fact that some chemical carcinogens have thresholds does not mean that all carcinogens have thresholds. Many chemicals act through mechanisms that can be understood in terms of

Ames's "mitogenesis is mutagenesis" hypothesis: excess cancer occurs when cell-killing forces mitosis to replace the dead cells.<sup>[66]</sup> Mitosis under chemical stress then leads to mutagenesis and cancer. So-called non-mutagenic carcinogens act in this way.<sup>[67]</sup>

- *ENERGY IMPARTED, NOT DOSE, IS THE INDEPENDENT VARIABLE*

Researchers have claimed that the energy imparted (i.e., total number of joules of ionization) should be predictive of stochastic effects, not massic energy, that is, dose (joules per kilogram).<sup>[68,69]</sup> This is a sensible argument. However, within the accuracy of current risk models, the mass of all adult human beings is the same (within a factor of 2 of a median of 70 kg), and so dose is simply energy imparted divided by a constant for people.

Perhaps of more interest is the question why elephants don't get more cancer than mice for a given dose, presuming that the mass of critical DNA in an elephant is significantly larger than in a mouse. The fact that cancer incidence does not scale with mass of DNA indicates that other factors, such as repair

fidelity and metabolic rates, differ among species of differing mass.

#### *Bogen's model*

Bogen has produced a two-stage cytodynamic model of radiation carcinogenesis that fits the county lung cancer data of Cohen.<sup>[70,21]</sup>

Cohen's design produces data that doesn't merit analysis (see BEIR VI),<sup>[52]</sup> but Bogen's model should be applicable to the underground miner cohorts and should be investigated.

#### *Policy Arguments for LNT*

There are a number of policy arguments for using the LNT model as the basis for a radiation protection system.

- *ERRING ON THE SIDE OF SAFETY*

First of all, if it errs at all, LNT probably errs on the side of safety, that is, it is a "conservative" model. Safety factors have traditionally been applied in the face of uncertainty, and radiation is no exception.

- *POLITICAL ACCEPTABILITY*

Since all US and international radiation protection systems are based on the LNT model, it has become a politically acceptable status quo. From a public policy standpoint, this is a virtue.

- *NO PROSPECT OF DIRECT MEASUREMENTS AT DOSES OF INTEREST*

We presently have no prospect of direct measurements of effects, i.e., epidemiology, at doses of interest. In the face of lingering uncertainty, a linear model seems prudent to many.

- *A PRACTICAL SYSTEM OF RADIATION PROTECTION BASED ON THE LNT MODEL HAS PROTECTED WORKERS*

The current LNT-based system of radiation protection, when it is followed, shows adequate worker

protection in epidemiologic studies.<sup>[71]</sup> After a history of acute and chronic radiation injuries and excess cancers in the first half of the twentieth century, the establishment of quantitative radiation protection standards has corrected an unacceptable situation.

#### *Policy Arguments Against LNT*

There are a number of policy arguments against a system of protection based on the LNT model.

- *EXPENSIVE RISK MANAGEMENT DECISIONS*

The use of the LNT model may lead to expensive risk management decisions when doses are projected over very long times or large numbers of people. The difficulty here is not the model used for radiation as much as it is the fact that such assumptions are not uniformly applied to other hazardous agents or human practices.

- *FAILURE TO OPTIMIZE*

It has been observed that the LNT model-based system of radiation protection would be acceptable if optimization were truly applied. In fact, in many cases optimization hasn't been carried out: the "R" in ALARA (as low as reasonably achievable) is ignored, leading to non-cost-effective risk management decisions.

Fiscally responsible use of the the LNT model in radiation protection requires optimization and *de minimis* dose concepts.

- *SIGNIFICANCE OF LIFE-SHORTENING*

Recently the argument has been made that the  $10^6$  lifetime fatal cancer risk may have insignificant life-shortening effects.<sup>[72]</sup> In this light, the ICRP would do well to reexamine its assumptions with respect to the number of years of life lost for cancers induced by low doses of radiation.

#### *Specious Policy Arguments on the Use of Alternatives to the LNT Model as a Basis for Radiation Protection*

Two specious policy, or at least nonscience, arguments regularly appear concerning the use of the LNT model in radiation protection.

- *OTHER SYSTEMS WON'T WORK*

A specious policy argument for LNT is that any other system of protection, such as a system based on a threshold model, is impractical. Radiation protection was based on the concept of the "tolerance dose" until the 1950s, and abandoning a system based on the LNT model would simply be a return to the tolerance dose system. Furthermore, industrial hygiene has been based on threshold kinds of controls since its inception. The only practical difficulty with a tolerance dose model is determining what a safe daily or weekly or annual tolerance dose is (given the existence of susceptible sub-populations). Such a determination would require the use of a model of some kind that included dose rate effects and fractionation.

- *CONSPIRACY*

A specious non-science argument against using the LNT model as the basis for radiation protection is that there is a conspiracy to promote the LNT model to protect the jobs of those with a vested interest in the current system of radiation protection. This thesis is unsupported, and certainly is not borne out by anyone in radiation protection known by the author. The accusation, for example, that the shipyard study was suppressed by the U.S. Department of Energy (DOE) because it would show that radiation was not dangerous would come as a great surprise to those who accuse DOE of hiding radiation's dangers. Many of the latter people are referenced in Taylor's discussion of non-scientific influences on radiation protection.<sup>[73]</sup> Those with sensational epidemiology findings, such as Steve Wing,<sup>[33]</sup> would also be surprised by DOE's covering up the putative fact that 'radiation is good for you.'

The conspiracy theorists are well known to readers of the Health Physics Society's *Newsletter*, participants in the electronic bulletin board RADSAFE (from listserv@romulus.ehs.uiuc.edu), and visitors to the web site <http://www.junkscience.com>.

- *SCIENCE AND THE "SCIENTIFIC METHOD" AS THE ONLY VALID INPUT TO RISK MANAGEMENT*

It is abundantly clear from many recent publications on risk that science is only one of many inputs to risk management decisions.<sup>[74,75,76,77,78]</sup> For radiation protection, the science is neither simple nor consistent.

- *THE LNT MODEL CAUSES FEAR*

To those who make this claim, such as Rockwell (1997),<sup>[79]</sup> one simply has to demand the evidence. According to a leading researcher in the field of risk perception, Paul Slovic, there is little or nothing in the way of social science research to support this theory.\* Those who claim that the statement "any increment in dose carries an increment in risk" automatically translates to "there is no safe dose of radiation" and to irrational fear should produce some research to support their hypothesis. This point leads directly to the truly "hard problem" addressed in below: what is an acceptable risk when the risk is imposed?

### Uses and Misuses of Models in Radiation Risk Management

Having reviewed the nature of the problem to be modeled, the various kinds of evidence used as input to models, and having established the seemingly contradictory points that models are wrong and models are necessary, it is finally time to consider the *uses* and *misuses* of models in radiation protection.

\*Personal communication to Daniel J. Strom, April 3, 1997.

Stephen L. Brown has elucidated three distinct uses of risk assessments, of which models are an important part.<sup>[20]</sup> Brown's "3 P's" include prevention (protection), prediction, and priority-setting. He establishes the need for different kinds of risk assessments for different uses.

In setting standards for prevention of ill-health (prevention and protection), it is appropriate to deal with uncertainty by incorporating conservatism in the form of safety factors or their equivalent model assumptions. By contrast, for assessing prospective or retrospective individual risks (prediction), such as in a probability of causation determination, it is clearly inappropriate to use a "one size fits all" model such as the ICRP's "5% per sievert" risk factor averaged over all ages and both sexes. In fact, the 1985 radioepidemiological tables use different models for different cancers, with age and sex dependence and smoking.<sup>[80]</sup> Finally, for priority-setting or risk ranking, Brown also urges that models with the best point estimates be used.

There should be no argument that using the LNT model for prediction of individual risks is irresponsible and bad science.<sup>[81]</sup>

### The Real Challenge: What Constitutes an Acceptable Imposed Risk?

Members of the Health Physics Society see poor risk management decisions being made about issues involving radiation, and scientifically unsound decisions being made in courts of law. The problem stems not from the linear hypothesis, but rather from its misuse and perhaps misinterpretation. There are clearly *de minimis* levels of imposed risk. Equally clearly, there are levels of imposed risk where society, through its regulators, has the right and responsibility to compel the expenditure of resources to reduce the risks imposed on an individual by others. When resources are committed to managing small risks from radiation while larger or unknown risks from other sources are not managed, members of the Health

Physics Society are upset. However, the Health Physics Society should not "make an end run" around the need for affordable *de minimis* risk levels by trying to establish the existence of a threshold for stochastic effects. By citing radiation studies showing thresholds or hormesis without considering the more compelling science of the bomb survivor and miner studies that do not show thresholds or hormesis, we risk losing the trust of the public and the Congress.

### Summary and Conclusions

All models are wrong but some are useful. Even though we know them to be simplistic, models are needed for managing radiation risks. Different models are needed for different purposes.

In formulating models, the evidence must be *weighed* critically, not on the basis of wishful thinking. There is a lot of poor-quality science that seems to be supplying answers that many people in the Health Physics Society *want* to hear. Scientifically, the LNT model is simplistic, wrong for some cancers, right for some cancers, and probably right for heritable ill-health. The LNT model is acceptable for risk management if applied with ALARA and *de minimis* concepts.

The linear, no-threshold (LNT) dose response model is simplistic for stochastic effects, but is currently the best choice for prevention (standards setting). The LNT model is inappropriate (wrong) for individual prediction (e.g., probability of causation). With appropriate assumptions (e.g., a DDREF), it may be appropriate for priority-setting.

For those who wish to further evaluate evidence, bear in mind there are motives and tactics being used that reflect not a love of science or truth or public health, but anger and outrage over the demise of nuclear power in the USA and the almost unceasing bad press that radiation gets.

Regarding the "real problem" of determining an acceptable imposed

risk, a favorite piece of advice is offered:

"I know of no safe depository of the ultimate power of the society but the people themselves; and if we think them not enlightened enough to exercise their control with a wholesome discretion, the remedy is not to take it from them, but to inform their discretion."

*Thomas Jefferson*

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**Appendix: Variables Affecting Characterization of Health Effects Categories**

	<b>Heritable Ill-Health</b>	<b>Reproductive Health and Developmental Abnormalities</b>	<b>Cancer (a family of diseases)</b>	<b>Deterministic Effects and Somatic Effects Other than Cancer</b>
Measure	rate per live birth "serious," e.g., survival "not serious," e.g., cosmetic lost life expectancy (LLE)	rate per conception rate per live birth lost life expectancy (LLE)	incidence rate (frequency) mortality rate (frequency) primary or secondary "absolute" or "relative" risk attributable risk (excess risk) lost life expectancy (LLE)	rate (proportion or frequency) severity lost life expectancy (LLE)
Effect	non-lethal mutations: <ul style="list-style-type: none"> <li>▪ change in immune system</li> <li>▪ change in gene expression</li> <li>▪ change in gene function</li> </ul>	permanent sterility temporary sterility decreased fertility damage to transient germ cells lethal mutations in germ cells failure to implant spontaneous abortion malformations (microcephaly) mental retardation epigenetic effects (changes in expression of genetic information at the transcription, translation, or post-translation levels) decreased vigor impaired immune system retarded growth	bladder brain breast colon esophageal kidney leukemia (bone marrow; CML, CLL, etc.) liver lung cancer (adenocarcinoma, small cell, oat cell, mesothelioma, etc.) lymphoma osteosarcoma (bone surface) ovary skin stomach thyroid "remainder"	death (sterilization) <ul style="list-style-type: none"> <li>▪ cerebrovascular syndrome</li> <li>▪ gastro-intestinal syndrome</li> <li>▪ hematopoietic (bone marrow) syndrome</li> </ul> hematological effects (immune system compromise) necrosis (localized tissue death; the desired outcome for cancer therapy) burns erythema alopecia cataract fatigue nausea disorientation fever chromosome aberrations
Does effect happen in the absence of radiation exposure?	yes	not all; some are unique effects	yes; no unique effects	most are unique effects there is a background of chromosome aberrations
Species	human, primate, dog, rat, mouse, other species; plants; microbes. Example: Harderian gland tumors			
Sub-species: genetic predisposition	?	?	pre-disposing genes, e.g., BRCA-1	immune system differences
Who's exposed, and who's affected?	mother and or father exposed; future generations affected	for teratogenesis, mother is exposed, child is <i>physically</i> affected most for post-natal effects, individual who is exposed is affected	exposed individual is affected	exposed individual is affected
Age at irradiation	irradiation of future parent must precede conception metabolically active ovum, between ovulation and fertilization, may be more susceptible	extremely age-dependent Bergonie and Tribondeau: <ul style="list-style-type: none"> <li>▪ rapidly-growing tissues more susceptible</li> <li>▪ undifferentiated tissues more susceptible</li> </ul>	susceptibility depends strongly on age at irradiation	young and old most susceptible Bergonie and Tribondeau: <ul style="list-style-type: none"> <li>▪ rapidly-growing tissues more susceptible</li> <li>▪ undifferentiated tissues more susceptible</li> </ul> point in cell cycle is critical for single cells
Age at manifestation of effect: time between exposure and clinical effect	may appear in next generation or may not appear for many generations may appear for many generations or forever may be self-extinguishing	probably evident fairly soon	2-10 years for leukemia in humans 5 years for thyroid cancer following Chernobyl 10-40+ years for solid tumors in humans for lung cancer in Uranium miners, risk decreases beyond 15 years after exposure	seconds to years, depending on the effect acute doses manifest effects in weeks at most, with decreasing time associated with increasing dose

	Heritable Ill-Health	Reproductive Health and Developmental Abnormalities	Cancer (a family of diseases)	Deterministic Effects and Somatic Effects Other than Cancer
Age at death and amount of life lost (lost life expectancy, LLE)	can be all, none, or in between ICRP 60 uses 20 years LLE	can be all, none, or in between	cancer is usually a disease of old age average LLE is 15 years; ranges from 9.8 (bladder) to 30.9 (leukemia)	non-lethal effects may not shorten life death may be virtually immediate
Sex	? recovery seen in female mice, not in males	teratogenesis: pregnant women only shedding of damaged sperm: men only	significant differences between men and women breast cancer: ♀ > 100×♂ thyroid cancer: ♀ > ♂ leukemia: ♂ > ♀	little difference, except for reproductive organs and breast
Dose	linear, non-threshold model seems to apply, with additivity	almost certainly all threshold effects	some have practical thresholds some non-linear with dose (leukemia in A-bomb survivors)	most are threshold effects, with a sigmoidal or Weibull dose-frequency relationship chromosome aberrations described by dual radiation action model (linear-quadratic)
[Instantaneous] dose rate; inverse dose rate effect	repair and multiple hits; induction of defense and repair mechanisms damaged or destroyed defense and repair mechanisms		multi-stage carcinogenesis: does radiation play a part in more than one stage? "wasted" dose: dead cells don't get cancer	
Dose fractionation	repair and multiple hits		multi-stage carcinogenesis: does radiation play a part in more than one stage?	
Portion of organism irradiated	must be gonads abscopal hypothesis unlikely	reproductive organs embryo, fetus for teratogenesis placenta?	tissue at risk must be irradiated for primary tumors abscopal hypothesis for secondary tumors (e.g., lung metastasis)	causal chain may be simple (cataracts) or complex (kidney failure following beta burns in Chernobyl firemen)
Radiation "quality"	density of ionization <ul style="list-style-type: none"> <li>▪ densely-ionizing radiation (alpha particles, fast neutron secondaries, fission fragments)</li> <li>▪ sparsely-ionizing radiation (beta, photon)</li> <li>▪ ultra-sparse effects (chemical production of free radicals)</li> </ul> dramatically affects repair; microdosimetric considerations required for understanding hit sizes, hit size effectiveness functions at high doses, makes less and less difference; e.g., Q = 7 for high dose alpha radiation, 2 for high dose neutrons			
Other effect modifiers:			other initiators, promoters, tumor progressors (smoking)	oxygen effect hyperthermia radiosensitizers radioprotectors (anti-oxidants, free radical scavengers)
<ul style="list-style-type: none"> <li>▪ diet</li> <li>▪ temperature</li> <li>▪ infection</li> <li>▪ combined injury: trauma, burns</li> <li>▪ state of organ function</li> <li>▪ other initiators, promoters, tumor progressors (smoking)</li> <li>▪ oxygen</li> <li>▪ dehydration</li> <li>▪ chemicals, drugs</li> </ul>				

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Dr. Strom attended the University of Connecticut, where he earned a BA in physics and French in 1971, an MS in physics in 1973, and continued graduate study through 1976 in the physical and life sciences. He earned a PhD in Environmental Sciences and Engineering at the University of North Carolina at Chapel Hill in 1983, assessing occupational radiation monitoring records for use in the DOE Health and Mortality Studies. Dr. Strom was certified by the American Board of Health Physics in 1980 and was Chair of the ABHP Comprehensive Panel of Examiners for the 1993 exam, and served on the Board of Directors of the American Academy of Health Physics from 1996-1998. He has been an Associate Editor of Health Physics since 1995. His work experience includes being Radiation Safety Officer at the University of Connecticut Health Center, 1973-76; Radiation Safety Officer, Old Dominion University and Eastern Virginia Medical School, 1978-80; Associate Professor of Health Physics in the Department of Radiation Health, Graduate School of Public Health at the University of Pittsburgh, 1984-91; and Adjunct Associate Professor in the Department of Environmental Sciences and Regional Planning, Washington State University - Tri-Cities, 1994-present. Dr. Strom has been employed at Pacific Northwest National Laboratory since 1991 as a Staff Scientist, currently in the Risk Analysis and Health Protection Group.

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