STROM/1996I

The Linear, No-Threshold Dose-Response Model: Both Sides of the Story

Continuing Education Lecture Presented at the 41st Annual Meeting of the Health Physics Society, July 24, 1996; rev.7/25/96

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1 What Is the Linear, No-Threshold Dose-Response Model?

1.1 Model, Hypothesis or Relationship?

For our purposes, a ***hypothesis*** is a statement of a relationship between or among variables whose truth can be tested, at least in principle, experimentally or observationally. An example of a hypothesis is "the period of a pendulum is independent of the amplitude of its swing." A ***model***, on the other hand, is a statement of a relationship between or among variables that is used to predict values of one or more of the variables. For example, we use biokinetic models and metabolic models to predict the fate and transport of radioactive chemicals within the body, or climatic models to predict weather or global warming, knowing that they are imperfect but perhaps useful. A true ***relationship*** between or among variables may well exist but be different from our hypothesis or our model. In some cases, a true relationship may be known but may be of no use because it is too complex to implement in a model. Examples include many-body problems in physics fluid dynamics, lightning, and so on.

This word study is intended as an introduction to a key point of this presentation: radiation protection is not science even though it has roots in science, politics, societal values, economics, and risk management.

1.2 Linear, Non-Linear; Threshold, No-Threshold

The linear, no-threshold (LNT) dose-response model is one of several types of models that could be chosen to predict health effects of radiation (National Research Council 1980). Models can be linear or non-linear with dose, and can exhibit a dose

threshold or no threshold, or a "practical threshold." "The concept of a practical threshold implies an accumulated dose below which no excess cancers are likely to appear within the normal life span of humans..." (Advisory Committee on Radiological Protection 1996). Furthermore, models usually account for some background incidence of effects in the absence of dose.

Currently, radiation protection against stochastic effects, whose probability is a function of dose, is based on the linear, no-threshold *model*. It is notable that radiation protection against deterministic effects (formerly non-stochastic effects) is firmly based on non-linear, yes-threshold models, always has been, and always will be.

1.3 Additive (Absolute), Relative (Multiplicative), and Other Risk Models

I remember being confused when I first came into the radiation protection business about the various kinds of models. Additive (absolute) and relative (multiplicative) risk models do not refer to the dose response curve, but rather to what response is being modeled: an absolute excess or a relative excess risk, in the case of cancer. The absolute excess is just some number of cancers produced in a population by a dose; such models are additive in the sense that the radiation effect simply adds to whatever effect occurs in the absence of radiation exposure, regardless of how large the background effect is. The relative excess is a fractional increase in the number of cancers produced in a population by a dose; such models are multiplicative in the sense that the radiation effect multiplies whatever effect occurs in the absence of radiation exposure. Cohen has postulated many other models that may be more apt than either the additive or multiplicative models (Cohen 1987).

The results of a multiplicative model can be expressed as an absolute increase in cancer incidence once the age distribution and underlying incidence of cancer in a population is specified.

Thus the attributes linear (non-linear), threshold (no-threshold), and additive (or multiplicative or ...) are all independent, and don't even refer to parallel concepts.

2 The Tyranny of Two-Dimensional Thinking: Dose and Response Aren't Enough

The entire concept of a dose-response relationship is so utterly simplistic that it cannot possibly be good *science*. On the other hand, the LNT model may well be good *risk management*. Health effects and radiation represents about a 16-dimensional problem, rather than a two-dimensional (dose, response) problem. Here's a list of the dimensions:

1. What measure (relative, absolute, severity, frequency, ...)?
2. What effect or health endpoint?
3. Does the effect happen in the absence of radiation exposure?
4. What species?
5. What sub-species: genetic predisposition?
6. Who's exposed, and who's affected?
7. What is the age at 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 sex?
11. What dose?
12. What [instantaneous] dose rate (inverse dose rate effect)?
13. What dose fractionation?
14. What portion of organism irradiated?
15. What radiation "quality?"
16. What other effect modifiers are there? (e.g., diet; temperature; infection; combined injury: trauma, burns; state of organ function; other initiators, promoters, tumor progressors (smoking); oxygen; dehydration; chemicals, drugs)

2.1 What is the relevant "dose?"

Dose itself is far too simplistic a concept to be useful at low doses. There is a large literature on microdosimetry (Bond et al. 1995; 70; Bond et al. 1985; Cameron 1992; Feinendegen et al. 1994; Goodhead 1992. Goodhead 1988; Harley 1988; ICRP 1991; Kellerer and Rossi 1984; Rossi and Zaider 1991; Steel 1996; Zaider and Brenner 1985) including a number of papers in the June, 1996 issue of *Health Physics*. Very clearly, at low doses, the discrete, quantum nature of radiation interactions must be acknowledged in order to have any biological understanding. The concepts of lineal energy (ICRP 1991), hit size (Bond et al. 1985), and cluster size (Goodhead 1992.) all improve our understanding of the microscopic nature of radiation effects. Given the understandings detailed in the documents above, "dose" in the sense of energy per unit mass, is a macroscopic quantity that cannot be very predictive of effects at levels of 100 mGy or less.

2.2 What is "risk?"

There are a variety of health effects to be considered under the grouping of risk. The LNT model, if it is applicable anywhere, is applicable to cancer and heritable ill-health.

2.3 Dose as a surrogate for risk is simplistic: It's a 16 × 4 dimensional problem

To what extent is "risk" or "response" related to "dose?" What is a dose-response hypothesis or dose-response model? Consider the 16 rows and 4 columns in the following table:

	Heritable Ill-Health	Reproductive Health and Developmental Abnormalities	Cancer (a family of diseases)	Deterministic Effects and Somatic Effects Other than Cancer
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: • change in immune system • change in gene expression • change in gene function	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) • cerebrovascular syndrome • gastro-intestinal syndrome • hematopoietic (bone marrow) syndrome 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 *physically* affected most for post-natal effects, individual who is exposed is affected	exposed individual is affected	exposed individual is affected

	Heritable Ill-Health	Reproductive Health and Developmental Abnormalities	Cancer (a family of diseases)	Deterministic Effects and Somatic Effects Other than Cancer
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: • rapidly-growing tissues more susceptible • undifferentiated tissues more susceptible	susceptibility depends strongly on age at irradiation	young and old most susceptible Bergonie and Tribondeau: • rapidly-growing tissues more susceptible • undifferentiated tissues more susceptible 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 U 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
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)

	Heritable Ill-Health	Reproductive Health and Developmental Abnormalities	Cancer (a family of diseases)	Deterministic Effects and Somatic Effects Other than Cancer
[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 metastases)	causal chain may be simple (cataracts) or complex (kidney failure following beta burns in Chernobyl firemen)
Radiation "quality"	density of ionization • densely-ionizing radiation (alpha particles, fast neutron secondaries, fission fragments) • sparsely-ionizing radiation (beta, photon) • ultra-sparse effects (chemical production of free radicals) 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: • diet • temperature • infection • combined injury: trauma, burns • state of organ function • other initiators, promoters, tumor progressors (smoking) • oxygen • dehydration • chemicals, drugs			other initiators, promoters, tumor progressors (smoking)	oxygen effect hyperthermia radiosensitizers radioprotectors (anti-oxidants, free radical scavengers)

3 The Motives, the Issues, and the Tactics

Parties on the two sides of the debate concerning LNT in radiation protection have differing motives as well as differing views on the basic issues.

3.1 The Motives

Those defending LNT believe they are acting in the best interests of workers, public and the environment. Those opposing LNT have similar beliefs! What, then is the difference?

The defenders, claim the opponents, are unable to get out of their box. The defenders are seen as the "establishment," while opponents see themselves as revolutionaries or paradigm-busters. (If one takes a longer term view, the opponents of LNT want a return to the previous paradigm, that of "tolerance dose" that was the basis of radiation protection up through the 1940s; thus they are really counter-revolutionaries.) Some opponents are motivated by scientific truths they believe are being ignored. Other opponents intend to rehabilitate the nuclear power industry in the USA or to counteract misunderstandings or false beliefs on the part of press and public (Peterson Jr. 1993.). There have been abuses of the LNT that cost ridiculous amounts of money or obstruct or prevent needed activities such as disposal of low-level and high-level radioactive waste. Opponents in many cases have financial interests at stake in terms of stock holdings; defenders have been accused of supporting LNT because it gives them job security.

3.2 The Issues

One might think that the only issues are

- the existence of a threshold or a practical threshold; and
- the shape of the functional relationship (linear; linear-quadratic; hormesis: U-shaped, J-shaped).

However, there are many other issues underlying the debate, however, including

- repair of DNA
- adaptive response and hormesis
- 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 epidemiologic methods (in particular the ecologic 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 analyze data: 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

3.3 The Tactics

Several tactics have been used in the controversy, some valid, some questionable.

- The tactic of reasoned examination of all the evidence: Review all evidence that is germane to the problem over a period of years in an organized fashion and print a consensus report. This tactic has been used by the ICRP, the NCRP, the UNSCEAR, the National Research Council, the United Kingdom's National Radiological Protection Board (NRPB), and Canada's Advisory Committee on Radiological Protection (ACRP).
- The one-sided tactic: Quote only the evidence that supports one's position and ignore evidence that is equivocal or supports the other position. This tactic has been called "tobacco company science," "concentration camp science," or "Ferengi science," a reference to a greedy, do-anything-to-make-a-dollar humanoid species on *Star Trek*. The one-sided tactic has been practiced by opponents of nuclear power, food irradiation, and many other contemporary safety issues. This tactic has been used by both sides of the LNT controversy.
- The ad hominem tactic: If one cannot make one's case using reason and data, then one makes personal attacks on one's opponents, using insults and insinuations or impugning dark motives and conspiracy to one's opponents. This tactic has been seen on the RADSAFE bulletin board, and has led one prominent health physicist to characterize RADSAFE as "the AM talk radio of health physics." Such unprofessional muckraking should be beneath professionals.
- The simplistic argument tactic: provide a simple, appealing rationale for one's own side of an issue.

An example of this tactic is claiming "If you can't detect it, it doesn't exist."

- The reductio ad absurdum tactic: extrapolate to an absurd limit to falsify a proposition. An example is the claim that LNT implies that one ionizing event can cause a fatal cancer.

- The tactic of making exaggerated claims based on flimsy data. The recent radon study from Finland is an example.

- The tactic of misleading presentations: showing graphs without error bars, or not discussing weaknesses of analysis.

- Counting studies instead of weighing evidence.

4 The Quality of Science: Who and What Should You Believe?

Some people are not as critical of radiation biology and radiation epidemiology as they should be.

4.1 Advocacy or Weighing the Evidence?

Too many works on LNT quote only the evidence that supports one position and ignore evidence that is equivocal or supports the other position. When influenced or blinded by advocacy, objectivity suffers and conclusions are biased.

4.2 Specious Arguments: One Event Can Cause Cancer

The argument that one ionization can cause cancer has been presented (Goldman 1996). There are two senses in which this is a specious argument. First, the kinds of radiations of interest include 5-keV tritium beta particles to 5-MeV alpha particles to x-rays with energies in the tens of keV. If a few tens of eV are required to produce an ion pair (34 eV in air, only a few eV in germanium), then one never encounters a single ionization. A weak beta produces hundreds of ionizations, and a typical alpha produces a hundred thousand or more. Second, single ionizations and single-strand DNA breaks are probably of no consequence whatever (Trosko 1996; Goodhead 1992.), and really have nothing to do with LNT. The concept of a single "hit" is somewhat simplistic in the light of Goodhead's cluster sizes.

4.3 Specious Arguments: There's No Way to Implement a Threshold System

The chairman of the ICRP, Roger Clarke, has recently claimed that it would be impractical to implement a scheme of radiation protection based on a threshold concept (Clarke 1996). Of course it's practical: that's precisely what we do for protection against deterministic effects, and it's precisely what is done in most of the profession of industrial hygiene; it's how we manage many of life's problems, from highway speed limits to credit limits. There may be some difficulty in achieving universal agreement that there *is* a threshold, and then *what value* the threshold ought to have, but there should be no difficulty in implementing it.

4.4 What, No Error Bars?

Particularly troublesome are those who present results without error bars. A recent article in *Nuclear News*, which received a good deal of press, trumpeted the Japanese data with no indication of the uncertainties at low doses (Muckerheide 1995). This masked the fact that the data are also consistent with LNT.

5 The Limits to Epidemiology

"With epidemiology you can tell a little thing from a big thing. What's very hard to do is to tell a little thing from nothing at all" (Michael Thun, quoted by (Taubes 1995)). In randomized trials, where the study is designed in advance and is a controlled experiment, effects as small as a few tens of percent can be reliably detected with large studies. In observational studies, many respected researchers distrust findings that aren't a factor of 3 or more. "In the past 30 years, the methodology [of epidemiology] has changed a lot. Today people are doing much more in the way of mathematical modeling of the results of their study, fitting of regression equations, regression analysis. But the question remains: What is the fundamental quality of the data, and to what extent are there biases in the data that cannot be controlled by statistical analysis? One of the dangers of having all these fancy mathematical techniques is people will think they have been able to control for things that are inherently not controllable" (Norman Breslow, quoted by Taubes (1995)). "The data are like a captured spy: if you torture him long enough, he will tell you anything you want to hear" (Anonymous). "There is nothing sinful about going out and getting evidence, ...about seeing if that evidence correlates, ... about checking for confounding variables. The sin comes in believing a causal hypothesis is true because your study came up with a positive result, or believing the opposite because your study was negative" (Sander Greenland, quoted by Taubes (1995)).

5.1 Association and Causation

Here are some of the major factors to consider before inferring that a statistical association is a causal one (Hill 1965):

1. Strength: a large effect, e.g., 32-fold lung CA

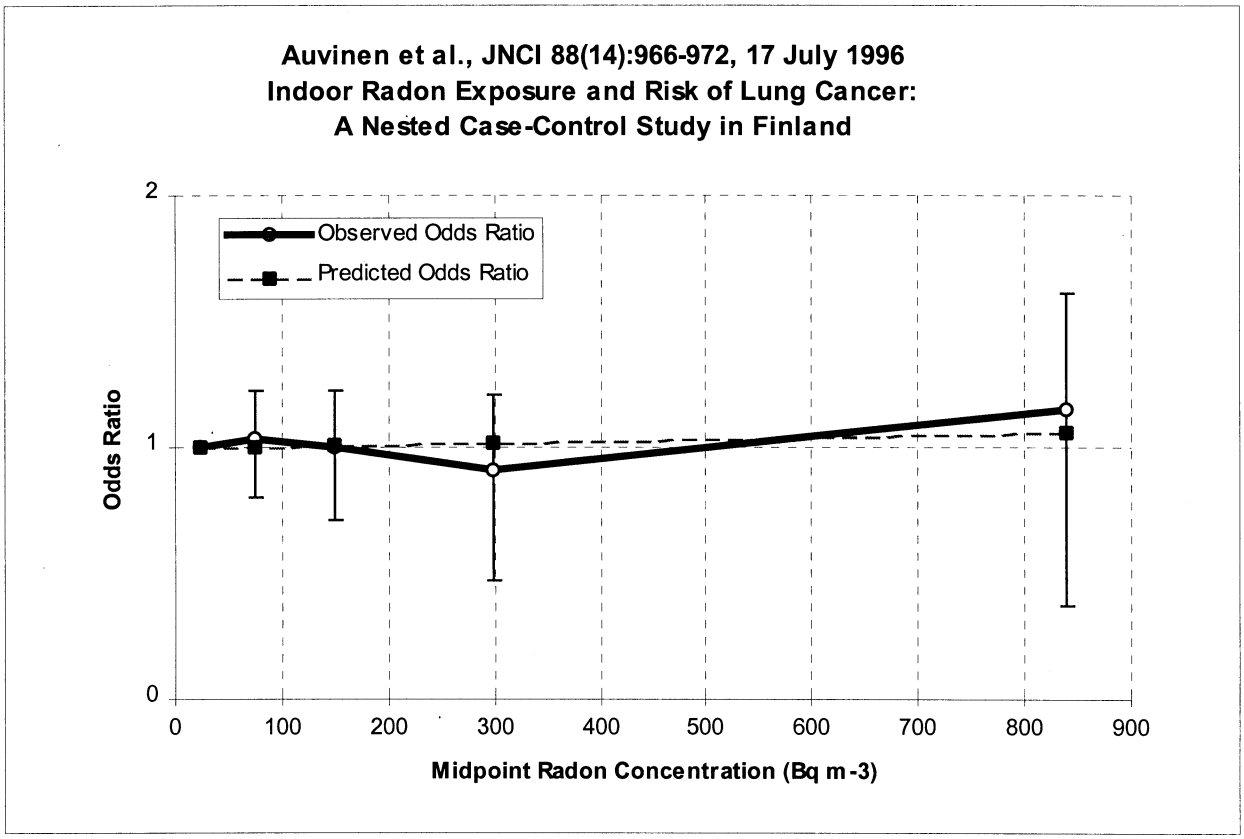
increase in heavy smokers.

2. Consistency: is effect consistently observed across studies?

3. Specificity: specific workers, particular sites and types of disease.

4. Temporality: exposure must precede disease.

5. Biological gradient: dose-response curve.



6. Plausibility: biological plausibility depends to some extent on how much biology one knows.

7. Coherence: cause and effect inference should not seriously conflict with generally known facts of the natural history and biology of the disease.

8. Experiment: does intervention reduce or prevent?

9. Analogy: do other, similar agents produce the effects?

BOTTOM LINE: STRONG STATISTICAL ASSOCIATION ALONE DOES NOT PROVE CAUSATION.

My colleague Dwight Underhill offers the following humorous example of causal inference: "In the winter I wear galoshes. In the winter I get colds. Therefore, galoshes cause colds." This, too, may be a 20-standard deviation effect, but it doesn't prove that galoshes cause colds. And it will take more than an ecological study to convince some of us that radon exposures protect against lung cancer.

Other work on the difficulty of making a causal inference from a statistical association has been published by respected authors (Rothman 1976; Lave and Seskin 1979; Lowrance 1974; U.S.Surgeon General's Advisory Committee on Smoking and Health 1964; Wagner et al. 1989; Taubes 1995)

5.2 An Egregious Example: Radon in Finland

The recent study of radon in Finland provides an example of the unwarranted conclusions that people draw from epidemiology studies (Auvinen et al. 1996). While this is a well-designed study, its statistical power is inadequate to accept or reject the null hypothesis of no effect. I have plotted the odds ratios from the paper on the figure below. While the data are consistent with no effect from radon, they are also consistent with hormesis and with significantly higher risk than predicted by the "establishment," namely, BEIR IV, ICRP 65, UNSCEAR and Lubin et al. (Lubin et al. 1994).

"Background: Inhaled radon has been shown to cause lung cancer among underground miners exposed to very high radon concentrations, but the results

regarding the effects of residential radon have been conflicting. Purpose: Our aim was to assess the effect of indoor radon exposure on the risk of lung cancer. Methods: To investigate this effect, a nested case-control study was conducted in Finland. The subjects of the study were the 1973 lung cancer case patients (excluding patients with cancers of the pleura) diagnosed from January 1, 1986, until March 31, 1992, within a cohort of Finns residing in the same one-family house from January 1, 1967, or earlier, until the end of 1985 and 2885 control subjects identified from the same cohort and matched by age and sex. In September 1992, a letter was sent to all study subjects or proxy respondents explaining the purpose and methods of the study. After giving informed consent, the study participants were asked to fill out a questionnaire on smoking habits, occupational exposures, and other determinants of lung cancer risk and radon exposure. The odds ratio (OR) of lung cancer was estimated from matched and unmatched logistic regression analyses relative to indoor radon concentration assessed by use of a 12-month measurement with a passive alpha track detector. Results: Five hundred seventeen case-control pairs were used in the matched analysis, and 1055 case subjects and 1544 control subjects were used in the unmatched analysis. The OR of lung cancer for indoor radon exposure obtained from matched analysis was 1.01 (95% confidence interval [CI] = 0.94-1.08) per 2.7 pCi/L (100 Bq m^{-3}) after adjustment for the cigarette smoking status, intensity, duration, and age at commencement of smoking by subjects. For indoor radon concentrations 1.4-2.6, 2.7-5.3, 5.4-10.7, and 10.8-34.5 pCi/L (50-99, 100-199, 200-399, and 400-1277 Bq m^{-3}, respectively), the matched ORs were 1.03 (95% CI = 0.84-1.26), 1.00 (95% CI = 0.78-1.29), 0.91 (95% CI = 0.61-1.35), and 1.15 (95% CI = 0.69-1.93), respectively, relative to the concentration below 1.4 pCi/L (0-49 Bq m^{-3}). The unmatched analysis yielded similar results with somewhat smaller CIs. In the analyses stratified by age, sex, smoking status, or histologic type of lung cancer, no statistically significant indications of increased risk of lung cancer related to indoor radon concentration were observed for any of the subgroups. Conclusions: Our results do not indicate increased risk of lung cancer from indoor radon exposure. Implication: Indoor radon exposure does not appear to be an important cause of lung cancer" (Auvinen et al. 1996).

On the graph above, I calculated the predicted odds ratio using standard assumptions: 1 WL per 3700 Bq·m^{-3} at equilibrium, equilibrium factor of 0.4, 75% of time spent at home, 5 effective mSv/WLM, and 5% fatal cancer incidence per effective sievert (ICRP 1993). When you look at the authors' own error bars on the graph above, do you conclude that "indoor radon does not appear to be an important cause of lung cancer?" I conclude that the study does not have the power to show anything one way or the other.

5.3 Ecologic Studies: Radon Somewhere Else at Some Other Time

To those of us who debate it, it seems as if the issue of ecologic studies has been beaten to death (Alexander 1995; Cohen 1991; Cohen 1994; Cohen 1995a; Cohen 1995b; Conrath 1990; Greenland and Robins 1994a; Greenland and Robins 1994b; Howe 1991; Jablon et al. 1991; Lubin et al. 1990; Patterson 1995; Piantadosi 1994; Puskin and Nelson 1995b; Puskin and Nelson 1995a; Stidley and Samet 1993; Stidley and Samet 1994; Strom 1995; UNSCEAR 1993; UNSCEAR 1994). The ecologic study design examines the association between health outcomes (for example, lung cancer deaths in counties) and characteristics of a region in which those health outcomes occurred (e.g., radon concentrations in counties). The papers of Bernard Cohen concerning radon, lung cancer, and the linear, no-threshold dose response model are of the ecologic design (Cohen 1995b). Despite Cohen's claims to the contrary, there is no way to control for migration, smoking, and changes in radon concentrations over time in this design. The pitfalls of observational epidemiology, as opposed to randomized trials, are only exacerbated by the ecologic design (Taubes 1995) An ecologic study is not necessarily a "garbage in, garbage out" problem; even if the input data on health effects and exposure variables are good, the inferential mechanism suffers from a fundamental flaw: the people getting the disease aren't the same ones who got the exposure, the exposure they got was at some other time, and they have many other risk factors that cannot be accounted for. Bias and confounding simply can't be controlled.

5.4 Radiation Epidemiology Is Like Counting Plutonium Air Samples with a Side-Window GM

5.4.1 Unobservable Effects Don't Exist?

Found on RADSAFE:

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 LNTH 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).

5.4.2 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 count 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."

5.4.3 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 are non-existent (Mossman et al. 1996)." These arguments have been used to support the claim that low doses of radiation are without risk (Goldman 1996). The arguments stems 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 $MDA = 4.65 \cdot s_B$, 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, s_B 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.

5.4.4 Acceptable Risk

If even a small fraction of a percent of people die of cancer that would be attributed to a specific cause if there were a sensitive instrument to study it, this death rate is unacceptable to the public. The U.S. Environmental Protection Agency (EPA) uses numbers in the range of 0.01% (10^{-4}) to 0.0001% (10^{-6}) as acceptable lifetime risks. Even with careful and clever study designs using internal controls and looking at rare cancers and searching for a dose-response gradient, the power of epidemiology will never be adequate to prove or disprove the linear no-threshold dose response hypothesis at doses that may nonetheless be worth protecting people from.

5.4.5 Risk Management in the Face of Uncertainty

We're left with a difficult public policy choice: what do we do in the face of this uncertainty? Overprotecting is obstructive and wastes money. Under-protecting is unacceptable to the public. Currently, risk managers have chosen to use the linear, no-threshold model.

6 Recent Reviews

There have been a number of recent reviews by both "establishment" groups and individuals.

6.1 NCRP

The NCRP recently issued a report on collective dose (NCRP 1995). Since the concept of collective dose is invalid without an assumption of a linear, no-threshold model, or at least a model with a threshold below background, NCRP Report 121 provides an in-depth review of the LNT model for cancer.

It concludes, "Taken as a whole, the body of evidence from both laboratory animals and human studies allows a presumption of a linear no threshold response at low doses and lo-dose rates, for both mutations and carcinogenesis. Therefore, from the point of view of the scientific bases of collective doses for radiation protection purposes, it is prudent to assume the effect per unit dose in the low-dose region following single acute exposures of low-dose fractions is a linear response. There are exceptions to this general rule of no threshold, including the induction of bone tumors in both laboratory animals and in some human studies due to incorporated radionuclides, where there is clearly evidence for an apparent threshold.

"However, few experimental studies, and essentially no human data, can be said to prove or even to provide direct support for the concept of collective dose with its implicit uncertainties of nonthreshold, linearity and dose-rate independence with respect to risk. The best that can be said is that most studies do not provide quantitative data that, with statistical significance, contradict the concept of collective dose.

"Ultimately, confidence in the linear no threshold dose-response relationship at low doses is based on our understanding of the basic mechanisms involved. Genetic effects may result from a gene mutation, or a chromosome aberration. The activation of a dominant acting oncogene is frequently associated with leukemias and lymphomas, while the loss of suppressor genes appears to be more frequently associated with solid tumors. It is conceptually possible, but with a vanishingly small probability, that any of these effects could result from the passage of a single charged particle, causing damage that could be expressed as a mutation or small deletion. It is a result of this type of reasoning that a linear nonthreshold dose-response relationship cannot be excluded. It is this presumption, based on biophysical concepts, which provides a basis for the use of collective dose in radiation protection activities... (NCRP 1995)"

6.2 NRPB

The National Radiological Protection Board (NRPB) reviewed the current state of knowledge in some of the major fields relevant to the assessment of the risk of radiation-induced cancer at low doses and low dose rates for radiation protection purposes (Cox et al. 1995). The review considered the results of epidemiological investigations and fundamental studies on the cellular and molecular mechanisms involved in radiation damage and response, supplemented by studies with experimental animals which provide further guidance on the form of the dose-response relationship for cancer induction, as well as the effect of dose rate on tumor yield. They conclude that "the data relating to the role of gene mutations in tumorigenesis, the monoclonal origin of tumors, and the relationship between DNA damage repair, gene/chromosomal mutation and neoplasia are well established and broadly consistent with the thesis that, at low doses and low dose rates, the risk of induced neoplasia rises as a simple function of dose and does not have a DNA damage or DNA repair related threshold-like component. Whilst adaptive responses or other protective mechanisms may influence the risk of tumor development, they do not provide a sound basis for judgement that tumorigenic response at low doses and low dose rates of radiation is likely to have a non-linear component which might result in a dose threshold below which the risk may approach zero. These mechanistic studies, in addition to the epidemiological information, indicate that for radiation protection purposes there is little basis for arguing that low radiation doses (about 10 mGy) would have no associated cancer risk and that, in the present state of knowledge, it is appropriate to assume an increasing risk with increasing dose."

6.3 ACRP

Canada's Advisory Committee on Radiological Protection (ACRP) recently completed and published a report entitled "Biological Effects of Low Doses of Radiation at Low Dose Rate"(Advisory Committee on Radiological Protection 1996). "The purpose of this report was to examine available scientific data and models relevant to the hypothesis that induction of genetic changes and cancers by low doses of ionizing radiation at low dose rate is a stochastic process with no threshold or apparent threshold. Assessment of the effects of low doses of radiation is based on a wealth of data from both humans and other organisms.

"The best evidence to support the linear non-threshold hypothesis stems from studies on radiation-induced genetic changes in lower organisms such as bacterial, yeast and spiderwort plants (Tradescantia). At low dose rate, the yield of genetic mutations in these organisms is strictly proportional to dose down to very low doses in the region of a few mSv of sparsely ionizing radiation. Studies on specific locus mutations

in the offspring of irradiated male mice represent a less sensitive endpoint but the results are compatible with the linear non-threshold hypothesis and demonstrate that the effects of radiation delivered either at low dose rates or in fractionated doses are additive.

"The data on radiation-induced cancer are less clear. This may be due to the fact that the development of cancer, in contrast to genetic changes, involves several different steps. It may therefore be unwise to extrapolate directly from the data on radiation-induced genetic changes to radiation-induced cancers in some cases. Not all available data on radiation-induced cancers fit the linear non-threshold hypothesis.

"In humans, epidemiologcal data suggest a practical threshold for induction of bone cancer by long-lived radium-226 and for induction of liver cancer by thorotrast (an insoluble form of long-lived thorium-232). The concept of a practical threshold for induction of bone cancer by long-lived radionuclides has been confirmed in experimental animals with a variety of internally deposited alpha and beta emitters. Similar evidence of a practical threshold appears for induction of lung cancer in (non-smoking) dogs by long-lived alpha emitters, in (non-smoking) rats after prolonged exposure to low levels of radon, and possibly in non-smoking humans where lung cancer incidence is relatively low. However, the data on induction of lung cancer by radon in miners who smoke cigarettes, and who already demonstrate a high incidence of lung cancer due to smoking, is compatible with the linear non-threshold hypothesis. The concept of a practical threshold implies an accumulated dose below which no excess cancers are likely to appear within the normal life span of humans or other animals (even if excess cancers might appear within the normal life span of humans or other animals (even if excess cancers might appear below this threshold if the animals were to live forever). This concept is most likely to apply to those types of cancers which are relatively rare in humans when the radiation dose is accumulated over a large portion of the human life span.

"Other human data which do not appear to fit the linear non-threshold hypothesis include some, but certainly not all, of the results on excess cancers after exposure to x-rays. For example, the data suggest a marked threshold in the dose-response relationship for induction of lung cancer in fluoroscopy patients both in Massachusetts and Canada. The data on excess cancers other than leukemia induced in the Japanese bomb survivors at Hiroshima and Nagasaki are clearly compatible with the linear non-threshold dose response hypothesis, but the data on excess leukemias in the same bomb survivors are possibly compatible with a threshold in the region of 200 mSv even for brief radiation exposures at high dose rates.

"The dose response relationship for induction of different types of tumors in experimental animals are complex. In general, there is roughly an equal chance of observing linear and non-linear dose response relationships for induction of different types of tumors. However, life shortening due to induction of all types of tumors in two strains of mice followed accurately a linear non-threshold dose response relationship for lifetime gamma-ray exposures at dose rates from about 3 up to 200 mSv per day. There is some evidence that highly fractionated doses of sparsely ionizing radiation may actually increase the life span of animals, especially in the presence of other environmental stresses such as unusual ambient temperatures. It is highly probable that any potential increases in average life span are associated with other physiological factors necessary for the maintenance of a healthy state, not with a decrease in cancer incidence.

"Adaptive responses to radiation doses as low as 5 mSv are known to occur and were reviewed in this report. However, it currently seems improbable that these adaptive responses would have any influence on the shape of the dose response relationships at low dose rates equivalent to 50 mSv per year received at a relatively uniform rate over the course of a year."

Among the recommendations of the ACRP is "the assumption of linearity may be quite appropriate for practical purposes in radiological protection even though it may not always be the best model for the relationship between dose and any particular effect." Limitations on collective dose are prescribed: > 200 mSv to an individual, it's fine; for individual exposures between 10 μSv/y and 200 mSv in a short time, predictions should be referred to as hypothetical or potential health effects only; below 10 μSv/y, "the potential individual risks are considered to be negligible even if the linear non-threshold hypothesis is assumed to be correct."

6.4 The Latest (July 1996) from the Radiation Effects Research Foundation (RERF)

The next five years cancer data from RERF have just been published (Pierce et al. 1996). The addition of 10,500 new persons for whom dose estimates are available brings the cohort to 86,572 persons, over 60% of whom have dose estimates of at least 0.005 Sv. In the group with doses > 5 mSv, there have been 4741 cancer deaths, approximately 420 of those being attributable to radiation, comprised of about 335 solid tumors and about 85 leukemias. Doses are based on DS86 Version 3, using a "quality factor" of 10 for neutrons. "Excess risks for solid cancer appear quite linear up to about 3 Sv, but for leukemia apparent nonlinearity in dose results in risks at 0.1 Sv estimated at about 1/20 of those for 1.0 Sv" (a DDREF of 2). The authors state "excess relative risk (ERR) depends

markedly on sex and age at exposure," underlining the point that a "dose-response" relationship is a simplistic concept. "These data do not suggest the existence of a threshold below which there is no excess risk. In fact, it should be pointed out that the estimated ERR per Sv, and standard errors, in the first few dose categories are:

Dose Category	ERR	ERR per Sv
0.005-0.02	0.03	2.6 ± 2.1
0.02-0.05	0.05	1.6 ± 0.90
0.05-0.10	0.04	0.60 ± 0.40
0.10-0.20	0.06	0.43 ± 0.25
0.20-0.50	0.12	0.38 ± 0.13

in comparison to the slope of about 0.37 obtained from a linear fit for the dose range 0-3 Sv" adjusted for age and sex. "Although the standard errors are large, this pattern taken at face value does reflect a nonlinearity -- with greater slope at low dose -- of marginal statistical significance..."

6.5 Others

A very interesting collection of papers constitute the entire June, 1996 issue of *Health Physics*. Kathren has published a historical review of the adoption of the LNT paradigm (Kathren 1996). Brodsky, Muckerheide, and Tschaeche have published reviews critical of LNT (Brodsky 1995; Muckerheide 1995; Tschaeche 1996; Pretre and Stoll 1995; Cox et al. 1995; NCRP 1995; Sagan 1989; Wolff 1989; Dennis 1996; Clarke 1996), and there were numerous articles in the June, 1995, *Health Physics Society Newsletter* with a response by Strom (Strom 1995) with concurrence by Meinhold.

7 Recent Controversies

7.1 Health Physics Society Position Statement

The HPS Position Statement that appeared in the March, 1996 Newsletter triggered a storm of criticism in the May Newsletter. Among other weaknesses, it uses the "epidemiology can't see it" argument.

7.2 Goldman's *Science* Editorial

Goldman (Goldman 1996) and his critics (Puskin and Nelson 1996; Nussbaum 1996; Pierce and Preston 1996) have brought the challenge to the pages of *Science* (29 Mar and 3 May 1996; the 2 Aug 1996 response by Goldman is in press).

Goldman argues, "We should review the molecular biology, the newer models, the available human data, and other pertinent scientific information and decide whether to develop new paradigms for risk that better relate low levels of exposures to scientifically based determinations of potential harm." Goldman uses the "one ionization" argument and criticizes the use of collective dose calculations, and provides an argument that raising the heels of our shoes one inch will increase the collective dose by enough to kill 1500 people over the next 50 years. He claims that our inferences about radiation and cancer are derived from"cohorts exposed to very high levels of insult." He cites ecological studies of background exposures, claims that the bomb survivors do not reveal anything about low doses, and discusses age dependence and individual susceptibility. He states that the multi-stage nature of carcinogenesis should lead to an S-shaped dose-response curve.

Puskin and Nelson of EPA disagree with several of Goldman's points (Puskin and Nelson 1996). They cogently present the molecular science basis for linearity in a multistage process: "It is widely accepted that carcinogenesis is a multistage process in which a single cell gives rise to a tumor, with mutation of cellular DNA required in one or more of the steps leading to malignancy. Since cancer is a common disease, obviously the background rate for each of these steps is not zero, and any filtration mechanism for removing precancerous cells is imperfect. Therefore, any exposure that increases the rate of somatic mutations would be expected to increase the risk of cancer. Radiation is believed to be mutagenic down to the lowest doses, as ionization clusters generated by a single track can produce DNA damage that is not always faithfully repaired. Consequently, a threshold for radiation carcinogenesis seems unlikely." They point out the inconsistency of the dose-rate effects between human and animal experiments, and challenge his assertion that there is a practical threshold for bone cancer. They dismiss Goldman's reference to background radiation epidemiologic studies by stating that "most epidemiologists consider such 'ecologic' studies to be noninformative because of statistical limitations and potential confounding." They project that the one-inch heels would add 1.2, not 1500, additional fatal cancers to the world population over 50 years.

Nussbaum criticizes Goldman for not citing the "large body of scientific evidence ... of the many inconsistencies and open questions in this highly politicized and controversial field of health science" (Nussbaum 1996).

Pierce and Preston of the Radiation Effects Research Foundation (RERF) point out that the bomb survivor studies are not exclusively low dose studies, and that they statistical analysis does not group people in dose categories such as 0.2-0.49 Sv, but rather use each

datum individually (Pierce and Preston 1996) They flatly state, "The data for solid cancers, including tumor registry incidence data as well as cancer mortality data, are inconsistent with the notion of a threshold for radiation effects. However, epidemiological studies have inherent limitations in assessing such issues, and it is important to also consider basic radiobiology results.

7.3 Alternatives to LNT: The Industrial Hygiene Model

If a threshold for cancer and genetic ill-health can be established, it would presumably have the form of an amount of dose delivered in an amount of time that causes no adverse health effects. Such a threshold would have to incorporate a safety factor. If all one wanted to do was protect humankind and the environment from the harmful effects of radiation, then one needs to keep exposures below such a limit. Unlike protection from chemicals, which often includes instantaneous thresholds, short-term exposure limits (STELs), or 8-hour time-weighted average (TWA) concentrations, the radiation limits would likely apply to periods of a year with no restriction on instantaneous dose rate. The challenge would be to provide reasonable assurance that exposures from all sources will not add up to more than the threshold dose in a year. Meeting this challenge this would result in limits on both dose and dose rate from any single source that may not be much different from radiation protection today.

8 Science and Risk Management

Managing projected risk before radiation exposure involves science policy choices and setting standards (National Research Council 1994; National Research Council 1983). Scientific findings, their uncertainties, and scientific unknowns are combined with societal values in a political and regulatory framework to set risk management policy and law. In contrast, predicting the risk of a given radiation exposure in an individual after the fact may be reduced to a matter of science and dosimetry, with little input from social values or risk management. There, science and dosimetry should prevail. In the risk management case, it is not that simple.

Dose and Dose-Rate Effectiveness Factors (DDREFs) are used to adjust the linear model for dose rate effects to account for repair (NCRP 1980; ICRP 1991). The theory of dual radiation action (Kellerer and Rossi 1972) has a linear term at low doses. While a universal DDREF cannot possibly be consistent with all the data, a universal DDREF must be adopted for purposes of risk management: we distinguish between science and what we must do for radiation protection. RBE is the outcome of a biology experiment with a given dose/dose-rate/dose fractionation regime, in a given species, for a given biological endpoint. That RBE is a function of dose, dose rate, and dose fractionation is no surprise. For purposes of managing radiation risks, however, we have "universal" 1) quality/radiation-weighting ($Q/w_{R)\ factors}$ for diverse groups such as "fast" neutrons; 2) tissue weighting factors (w_T); and 3) DDREF's that allow us to combine exposures, respectively, 1) to various kinds of radiation; 2) for non-uniform irradiation; and 3) at doses and dose-rates where we have no direct data. These are summaries of radiation biology experiments for risk management purposes. ICRP Publication 26 provides an explanation of the use and limitations of quality factors (ICRP 1977).

We don't have direct evidence of effects at very low doses, but must nonetheless make risk management policy choices in the face of uncertainties and unknowns. What should we use in place of the LNT model for protecting the public and the worker? Should we tell them, "We don't know, so we assume a low dose carries no risk?" Can we prove the existence of a threshold? In the absence of that proof, is it prudent to assume one exists? What are the consequences if we're wrong?

Whether we can detect an effect with epidemiology is not the point. The point is that there may well be real risks at low doses that aren't detectable by epidemiology. In radiation protection, we use the LNT hypothesis prospectively in order to manage radiation risks. Did anyone ever say that we should use it to assess risks after exposure? Even the probability of causation approach uses a linear-quadratic for leukemia, sex- and age-dependence of exposures, and time-since-exposure methods, a far cry from LNT in the retrospective case (Wagner et al. 1989).

9 Top Ten Reasons (Well, Actually 14 Reasons)

	Top Ten Reasons for Believing in LNT as the Basis for Radiation Protection	Top Ten Reasons for NOT Believing in LNT as the Basis for Radiation Protection
14	Given uncertain and conflicting scientific results, you believe that risk management policy must be simple and coherent and err on the side of safety.	Given uncertain and conflicting scientific results, you believe that risk management policy must be simple and coherent and err on the side of economic development.
13	You let establishment groups of "experts" do your thinking for you	You let anti-establishment groups of "experts" do your thinking for you
12	In the face of uncertainty, you assume the worst.	In the face of uncertainty, you assume the best.
11	You cherish family values.	You cherish family values.
10	You're outraged at ignorant people making exaggerated and unfounded claims about the safety of radiation.	You're outraged at ignorant people making exaggerated and unfounded claims about the danger of radiation.
9	You are basically a "Chicken Little" at heart, and you think the world is really a dangerous place that shouldn't be left in care of the "Rambos."	You are basically a "Rambo" at heart, and you think that the world is really a safe place that shouldn't be left in care of the "Chicken Littles."
8	You believe that "Better safe than sorry" is wiser than "Waste not, want not."	You believe that "Waste not, want not" is wiser than "Better safe than sorry."
7	You believe that we can afford LNT	You believe that we can't afford LNT.
6	You're a conservative "old stick in the mud" who refuses to shift his paradigm from "ALARA" back to "tolerance dose."	You're a conservative "old stick in the mud" who refuses to believe that the paradigm should have been shifted 50 years ago from "tolerance dose" to "ALARA."
5	You're blind to the evidence.	You're blind to the evidence.
4	Since you studied science with the Sierra Club, Greenpeace, the NRDC, and the Union of Concerned Scientists, you quote only those theories and studies that support your belief.	Since you studied science with the Tobacco Institute, the National Rifle Association, and the Ferengi Academy of Sciences, you quote only those theories and studies that support your belief.
3	You put your faith in epidemiologic studies of the cohort and case-control designs.	You put your faith in epidemiologic studies of the ecologic design.
2	You believe that what you can't see can hurt you.	You believe that what you can't see can't hurt you
1	You are conspiring with a diabolical group of desperados who will stop at nothing to keep their health physics jobs.	You are conspiring with a diabolical group of desperados who will stop at nothing to enhance the value of their nuclear power stock.

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