The Linear No-Threshold Theory of Radiation Carcinogenesis Should Be Rejected

Bernard L. Cohen, Ph.D.

It is commonly stated that "any radiation dose, no matter how small, can cause cancer." The basis for that statement is the linear-no threshold theory (LNT)–which might more appropriately be called "linear-no threshold hypothesis"—of radiation carcinogenesis. According to LNT, if a 1 Gy (100 rad) dose gives a cancer risk R, the risk from a dose of 0.01 Gy (1 rad) is R/100, the risk from 0.00001 Gy (1 millirad) is R/100,000, and so on. Thus the cancer risk is not zero regardless of how small the dose.

However, over the past several years, many radiation health scientists have come to regard risk estimates in the low-dose region based on LNT as exaggerated or completely negligible. For example, the 6,000-member Health Physics Society, the principal organization for radiation protection scientists, issued a position paper[1] stating: "Below 10 rad…risks of health effects are either too small to be observed or are nonexistent." A similar position statement was issued by the American Nuclear Society. When the *Health Physics Society Newsletter* asked for submission of comments on validity of LNT, there were about 20 negative comments submitted and only a single comment supportive of LNT. In a worldwide poll conducted by the principal on-line discussion group of radiation protection professionals (RADSAFE), the vote was 118 to 12 against LNT. A 2001 Report by the French Academy of Medicine concluded that LNT is "without any scientific validity," and an elaborate joint study by the French Academy of Medicine and the French Academy of Sciences[2] strongly condemned the use of LNT.

While U.S. official agencies have been slower to accept this position, the U.S. National Council on Radiation Protection and Measurements (NCRP) stated in NCRP Publication No. 121:[3] "Few experimental studies and essentially no human data can be said to prove or even provide direct support for the [LNT] concept," and in NCRP Publication No. 136[4] stated: "It is important to note that the rates of cancer in most populations exposed to low-level radiation have not been found to be detectably increased, and in most cases the rates appear to be decreased." A group of scientists opposing use of LNT (Radiation Science and Health) submitted several hundred papers supporting their position to the National Research Council.

Beyond failure of LNT, there is substantial evidence that low-level radiation may be *protective* against cancer; a view known as "radiation hormesis." There is a society, formerly called the International Hormesis Society, now known as the International Dose-Response Society, which sponsors an annual international scientific conference and publishes a peer-reviewed scientific journal and a regular newsletter, *BELLE: Biological Effects of Low Level Exposures*.

Previous reviews[5-7] with somewhat different approaches to similar objectives, have also reviewed the basis for LNT and information that has caused a shift in views.

Foundation for the Linear-No Threshold Hypothesis Challenged

The original basis for LNT, as it emerged in the mid-20th century, was theoretical and very simple. A single particle of radiation hitting a single DNA molecule in a single cell nucleus of the human body can initiate a cancer. The probability of such a cancer initiation is therefore assumed to be proportional to the number of such hits, which is proportional to the number of particles of radiation, which is proportional to the dose. Thus the risk is proportional to the dose—this is the LNT.

An important problem with this simple argument is that factors other than initiating events affect the cancer risk. Human bodies have biological defense mechanisms that prevent the vast majority of initiating events from developing into a fatal cancer.[8] Some of the most important examples, as summarized by Feinendegen, include: induction of DNA repair enzymes; apoptosis,[9] a process by which damaged cells "commit suicide"; immune system stimulation; and delaying mitosis and thus extending the time before it occurs, during which damage repair is most effective. Low-level and high-level radiation have opposite effects on these processes.

By far the most important cause of DNA damage is reactive oxygen species (ROS). Elevation of ROS stimulates the scavenging processes that remove them by initiating biochemical reactions that are stress responses. Thus, "the best protection against stress is stress itself."[10] These scavenging processes are enhanced by low-level radiation.

Altered cell timing affects DNA repair in many ways.[11] Other effects of low-level radiation on cell survival have been observed and are referred to as "low-dose hypersensitivity," "increased radiation radioresistance," and "death-inducing effects."[12]

It is now recognized that development of cancer is a much more complex process than was originally envisioned. The role of "bystander effects," signaling between neighboring cells relevant to their radiation experiences,[9] is now recognized to be an important, albeit poorly understood factor. In fact it seems that tissue response, and even whole organ response, rather than just cellular response, must be considered.[2]

There is also apparently obvious evidence for failure of the original simple model. For example, the number of initiating events is roughly proportional to the mass of the animal—more DNA targets mean more hits. Thus the simple theory predicts that the cancer risk should be approximately proportional to the mass of the animal. But the cancer risk in a given radiation field is similar for a 30 g mouse and a 70,000 g human. As another example, our very definition of dose, based on the energy absorbed per unit mass of tissue, which is proportional to the number of radiation hits per unit target mass, would be misleading if only the total number of hits (which is proportional to the number of initiating events) were relevant regardless of the target mass.

A detailed theoretical approach to evaluating the validity of LNT is based on the commonly accepted idea that double-strand

breaks (DSB) in DNA molecules are the principal initiating event in causing cancer. But DSB are also caused by endogenous ROS. (In fact the main mechanism for radiation-induced DNA damage is the production of ROS by the ionizing effects of the radiation on omnipresent water.) It is estimated that endogenous ROS cause about 0.1 DSB per cell per day, whereas 100 mSv (10 rem) of radiation, which is close to the upper limit of what is normally called low-level radiation, causes about 4 DSB per cell.[5] Assuming that the number of cancers is proportional to the number of DSB, a 100 mSv dose of radiation would increase the lifetime (28,000 days x 0.1 DSB/day) risk of cancer by only about 4/2,800 (0.14%), whereas LNT predicts an increase of 1%.

Direct Experimental Challenges to the LNT

A direct demonstration of the failure of the basis for LNT derives from microarray studies determining what genes are up-regulated and down-regulated by radiation. It is found that different sets of genes are affected by low-level radiation than by a high-level dose. For example, in one study of mouse brain,[13] 191 genes were affected by a dose of 0.1 Sv but not by a dose of 2.0 Sv, 213 genes were affected by 2.0 Sv but not by 0.1 Sv, while 299 genes were affected by both doses. The 0.1 Sv dose induced expression of genes involved in protective and repair functions, while down-modulating genes involved in unrelated processes.

A similar study with even lower doses on human fibroblast cells[14] found that a dose of 0.02 Sv caused more than 100 genes to change their expression, and these were generally different from the genes affected by 0.5 Sv. The former group was heavily weighted by stress response genes.

Several other microarray studies have shown that high radiation doses that serve as the calibration for application of LNT are not equivalent to an accumulation of low radiation doses.[7]

Sophisticated experimental techniques have been developed for observing the effects of a single alpha particle hitting a single cell. It was found[15] that the probability for transformation to malignancy from N particle hits on a cell is much greater than N times the probability for transformation to malignancy from a single hit. This is a direct violation of LNT, indicating that estimated effects based on extrapolating the risk from high exposure, represented by N hits, greatly exaggerates the risk from low-level exposure as represented by a single hit.

A very clear demonstration of a threshold response, in contrast to LNT, was found in tumor induction by irradiation throughout life of mouse skin.[16] For irradiation rates of 1.5 Gy/wk, 2.2 Gy/wk, and 3 Gy/wk, the percentage of mice that developed tumors was 0%, 35%, and 100%, respectively.

The Adaptive Response

According to the biological defense mechanism called the "adaptive response," which was described by UNSCEAR,[17] exposing a cell to a stress such as radiation stimulates natural defense and thereby protects against subsequent further stresses. Experimentally, this is most easily studied by exposing cells to a low dose to prime the adaptive response, followed by a "challenge dose," and comparing the response to that of the challenge dose alone.

Radiation exposure increases the number of chromosome aberrations, the simplest tool for detecting genetic damage. Table 1 shows how a priming low dose decreases radiation-induced aberrations in human lymphocyte cells in vitro.[18] An in vivo experiment in mice found that the chromosome aberrations induced by 65 cGy (65 rad) fell from 38% to 19.5% in bone marrow cells and from 12.6% to 8.4% of spermatocytes when a priming dose of 0.2 cGy was administered 3 hours earlier.[19]

Table 1. Chromosome Aberrations. Two types of chromosome aberrations in human lymphocytes induced by 400 cGy of X-rays, either alone or 6 hr after pre-exposure to 5 cGy.[18]

	Dicentrics & Rings		Deletions	
DONOR	400 cGy	(5 + 400) cGy	400 cGy	(5+400)cGy
#1	136	92	52	51
#2	178	120	62	46
#3	79	50	39	15
#4	172	42	46	34
#5	134	106	58	41

Many other such experiments have been reported,[17] and the results are usually explained as production of repair enzymes by the priming dose.

The effects of human exposure were studied in lymphocytes taken from residents of a high background radiation area (1 cGy/y) and those of a normal background radiation area (0.1 cGy/y) in Iran. After exposure to 1.5 Gy (150 rad), the mean frequency of chromosome aberrations was 0.098 ± 0.012 for cells from the high-background group compared to 0.176 ± 0.017 for cells from the normal-background group, a difference of 4 standard deviations.[20]

In a microarray study on human lymphoblastoid cells,[21] in which a 0.05 Sv priming dose was followed by a 2.0 Sv challenge dose, 145 genes were affected by the priming dose. Generally, genes affecting protein synthesis were up-regulated, and those involved in metabolic processes and signal transduction were down-regulated, perhaps as a means of conserving resources needed for DNA repair. The specifics were quite complex and sometimes pointed in different directions; for example, the TP53 gene plays an important role both as a tumor promoter and suppressor.

One in vitro study of genetic mutations[22] found that the frequency of mutations at the *hprt* locus in human lymphocytes was reduced from 15.5×10^{-6} to 5.2×10^{-6} when an X-ray exposure of 300 cGy was preceded 16 hours earlier by an exposure to 1 cGy. Other examples of adaptive response have been reported from studies of genetic mutations.

A priming dose of 2 cGy before a pre-mating dose of 200 cGy of X-rays consistently reduced dominant lethal mutations in *Drosophila* by half.[23]

In addition to protecting against a large challenge dose, low-dose radiation protects against spontaneous malignant transformation in predisposed cells. Spontaneous neoplastic transformation was reduced by 78% in C3H 10T1/2 mouse cells,[24] and by 55% in human HeLa x skin fibroblast cells.[25] The effect is statistically significant even at very low doses, below 1 cGy.

This adaptive response protection against spontaneous cancers probably results from reducing ROS and increasing the antioxidants that remove them. In a study of rat cells,[26] 50 cGy of X-ray exposure decreased the amount of the oxidant lipid peroxide by

about 20%, and increased the amount of the antioxidant enzyme superoxide dismutase (SOD) by about 25%. These beneficial effects were appreciable over the entire dose range up to above 100 cGy. Many other studies with similar results have been summarized by Yukawa.[27]

Stimulation of the Immune System

The immune system destroys cells with persistent DNA damage and is thus important in protecting against the development of cancer. The effects of low-level radiation on several different measures of the immune response[28] are listed in Table 2. We see that by each of these measures, the immune response is increased by low-level radiation, and increasingly so at least up to 7.5 cSv. Responses over a wide range of radiation doses[29,30] show that the stimulatory effects at low levels are reversed at high doses of radiation.

Table 2. Effects of Radiation on Immune Response. Percent response to various tests in mice exposed to indicated dose compared to response of unexposed mice.[28]

Test	2.5 cGy	5 cGy	7.5cGy
PFC Reaction	110	143	174
MLC Reaction	109	133	122
Reaction to Con A 191	155	530	
NK activity	112	109	119
ADCC Activity	109	128	132

PFC = plaque forming cell; MLC = mixed lymphocyte culture, used as test of T-cell function; Con A = concanavalin-A, lectin that stimulates T-lymphocytes; NK = natural killer cells which recognize and kill tumor cells; ADCC = antibody-dependent cell-mediated cytotoxicity, which assists NK activity.

The Effect of Dose Rate

Contrary to expectations from the basic assumption of LNT that the cancer risk depends only on total dose, effects on the immune system are very different for the same total dose given at low dose rate vs. high dose rate. In a study of effects on various indicators of immune response in several wild-type mouse strains,[31] continuous whole-body irradiation at 1.2 mGy/hr stimulated immune response, but the same doses given at a high rate had the opposite effect.

In a study of thymic lymphomas in mice,[32] acute challenge doses totaling 7.2 Gy induced tumors in 90% of the mice, but if the mice were previously exposed at a rate of 1.2 mGy per hour for 258 days (a total of 7.2 Gy), only 43% developed such tumors. Note that the total priming dose is equal to the challenge dose. The difference is in the low dose rate. Even extending the low-dose-rate exposure to 450 days for a total exposure of 12.6 Gy resulted in no tumors without a challenging dose. Various indicators of immune response were significantly increased by the continuous whole-body radiation, and the authors attribute their results to this stimulation of the immune system.

Several studies have shown that the immune system provides resistance to metastasis of tumors. For example, when tumor cells are transplanted into the groins of mice, the rate of their metastasis into the lung is cut about in half by total-body irradiation with 15–30 cGy 12 days after the transplantation.[33] Doses above 50 cGy, on the other hand, reduce the immune response, leading to increased rates of metastasis. A study in rats[34] showed that total-body irradiation—but not tumor irradiation—with low-level radiation reduces the rate of metastasis and increases infiltration into the tumor of immune-system agents.[35]

Studies on naturally cancer-prone mice[36] found that, while low-level radiation exposure does not prevent eventual development of cancer, it delays the process substantially. Total-body irradiation with low-level radiation has also been shown to reduce tumor size.[29, 37] The only reasonable explanation for such effects of total-body low-level radiation would seem to be stimulation of the body's immune system.

Experimental and Observational Studies of Cancer Risk vs. Dose

Animal Studies

There have been numerous direct studies of cancer risk vs. dose in animals, testing the validity of LNT. Nearly all of these studies indicate, with high statistical significance, that LNT overestimates the cancer risk from low-level radiation, generally suggesting a threshold. In a study at Oak Ridge National Laboratory, the LNT not only failed in the low-dose region, but animals exposed to low doses lived up to 40% longer than controls. A review of more than 100 such experiments[38] involved a total of 85,000 exposed animals with their 45,000 corresponding controls, with a total of 60,000 and 12,000 cancers in exposed and control animals respectively. In cases where cancers were observed in control animals, either no effect or an apparent reduction in cancer risk was observed in 40% of the data sets for neutron exposure, 50% of the data sets for X-rays, 53% of the data sets for gamma rays, and 61% of the data sets for alpha particles.

Atomic Bomb Survivors

The principal human data cited by those in influential positions to support LNT are those for solid tumors (all cancers except leukemia) among the Japanese A-bomb survivors. The data do indeed suggest a linear relationship with the intercept near zero dose. But when error bars are considered, they give no statistically significant indication of excess cancers for doses below about 25 cSv. This conclusion applies to the incidence data as well as to the mortality data.[39] In fact, it was shown[40] that considering the three lowest dose points alone (i.e. up to 20 cSv), the slope of the dose-response curve has a 20% probability of being negative (risk decreasing with increasing dose). A later update[41] of the data on A-bomb survivors has been published, but with insufficient detail to repeat the above analysis. A crude preliminary analysis indicates that the above conclusions will not be appreciably changed.

The data on leukemia among A-bomb survivors[42] strongly suggest a threshold above 20 cSv, and this difference from LNT expectations is recognized by the authors and by all widely recognized reviews.

Studies of Monitored Radiation Workers

The principal other evidence that has been widely cited as supporting LNT is the IARC (International Association for Research

on Cancer) studies of monitored radiation workers. The first and most fully reported[43] was a study of 95,673 monitored radiation workers in the United States, United Kingdom, and Canada. For all cancers except leukemia, there were 3,830 deaths but no excess over the number expected. The risk is reported as -0.07/Sv (90% confidence limits. -0.04 , +0.3). There is surely no support for LNT here.

However, for the 146 leukemia deaths, a positive risk-vs.-dose relationship was reported and was vociferously claimed to support LNT. The data are listed in Table 3. It is obvious from those data that there is no indication of any excess risk below 40 cSv; even the excess for >40 cSv is by only 1.4 standard deviations. The conclusion by the authors that this supports LNT is based on an analysis that arbitrarily discards the data in Table 3 for which O/E (observed/expected) is less than unity! That means that three of the seven data points are arbitrarily discarded.

Table 3. Leukemia deaths from IARC Study.[43] The final column is the ratio of observed to expected, O/E.

Dose (cSv)	Observed	Expected	O/E
0-1	72	75.7	0.95
1-2	23	21.2	1.08
2-5	20	21.8	0.92
5-10	12	11.3	1.06
10-20	9	7.8	1.15
20-40	4	5.5	0.73
>40	6	2.6	2.3

For a follow-up study by the same group, involving 407,000 monitored workers in 154 facilities spread through 15 countries, results were reported only as excess risk per Sv, assuming LNT. Thus a data display similar to that in Table 3 cannot be given here, but since the lead author is the same, it seems reasonable to assume that similar questionable procedures were used. No information on smoking status, an important risk factor for cancer, was collected. No consideration was given to nonoccupational exposure; the average occupational exposure was 2 cSv, and 90% were below 5 cSv, whereas the average person is exposed throughout life to about 25 cSv of nonoccupational radiation with large variations, typically at least 10 cSv, depending on geography and medical treatment. Thus the "signal" is very much smaller than the noise, making any conclusions about validity of LNT highly debatable. Another weakness is that most of the data were derived from photographic film badges, which are sensitive to humidity and temperature. The films were handled differently in the 15 different countries (and also frequently by different organizations in the same country), reducing the reliability of the results. There are other inherent problems in combining data from many different sources, such as differences in ethnicity and socioeconomic status. If the data from just one of the 15 countries, Canada, are excluded, the excess risk is no longer statistically different from zero.

Many other studies have been reported on cancer risk vs. dose for normal occupational exposures. In response to heavy media coverage of some nonscientific reporting, a $10 million study[44] was carried out by the U.S. Centers for Disease Control and Prevention (CDC) of workers in eight U.S. Navy shipyards involved in servicing nuclear-propelled ships. The study included 28,000 exposed workers and 33,000 age- and job-matched controls who worked on non-nuclear ships. The former group all had exposures above 0.5 cSv and average exposures of 5 cSv. The cancer mortality rate for the exposed was only 85% of that for the unexposed, a difference of nearly two standard deviations. Hiring procedures, medical surveillance, job type, and other factors were the same for both groups; the study was specifically designed to eliminate the "healthy worker effect," which is often used to explain such results. The issue of nonoccupational exposure was not addressed, but there was a high degree of homogeneity among the different worker groups being compared.

When mortality rates for employed workers are compared with those for the general population, it is invariably found that employed workers have lower mortality. This is widely understood to result from the fact that unemployed persons may be unemployed because of health problems that may cause their earlier demise. However, the healthy worker effect should not apply to cancers occurring long after their initial employment, because health problems leading to such cancers would not be apparent in a pre-employment medical examination.[45] A direct test of this in Sweden,[46] comparing 545,000 employed women with 1,600,000 unemployed women found that the standardized cancer incidence rate for employed women was 1.05 (95% confidence interval [CI], 1.03-1.07) times higher than for the unemployed women. This would certainly seem to eliminate healthy worker effects for cancer.

Several other studies of cancer rates among people whose employment involves radiation exposure have been published:

British radiologists who began work in earlier years, when exposure standards were much more lax than today, had excess cancers compared to other medical practitioners. But among the most recent cohort, radiologists who began work between 1955 and 1979, cancer mortality was only 0.71 (95% CI, 0.49–1.00) times that of other medical practitioners, who presumably had considerably lower radiation exposures.[47]

A study of Chinese medical workers, comparing those exposed with those not exposed to X-rays, showed a relative risk of cancer incidence of 2.4 for leukemias and 1.2 for solid tumors in earlier workers whose average exposure was 55 cGy. For more recent workers, with average exposures of 8.2 cGy, the RR was not significantly different from 1.0.[48]

A U.S. study of 146,000 radiologic technologists[49] reported a standardized mortality ratio (SMR) of 0.82 for all cancers, compared with the total U.S. population, but there was a statistically significant increase among those first employed before 1940, compared with those who began work after 1960.

A review of studies of eight cohorts of radiologists and radiological technologists in various countries, comprising 270,000 monitored radiation workers,[50] concluded that there was good evidence for excess cancers among the early workers, but no such evidence among more recent workers.

Among 22,000 monitored workers in the French nuclear power industry,[51] the cancer mortality rate was only 0.58 (90% CI, 0.49–0.68) times that for the general population of France. The authors attribute this to the healthy worker effect, but this seems to be an unlikely explanation for such a large effect. There was no evidence for increased cancer as a function of increasing radiation exposure.

Perhaps the most reasonable conclusion from studies of normally exposed radiation workers is that they give no conclusive information on effects of low-level radiation. There is as much information suggesting zero or negative risk as information indicating the increased risk claimed by the IARC study. In any case, the fact that the monitored radiation received by the subjects was much lower than their nonoccupational unmonitored exposures, make these data inherently of marginal significance.

Other Human Data

There is a substantial, statistically robust collection of human data contradictory to LNT. These are some examples:

Canadian women exposed to frequent fluoroscopic examinations in a tuberculosis sanatorium seemed to have a decreased risk of breast cancer with increasing doses up to at least 25 cSv, although statistical uncertainties are substantial.[52]

Lung cancer data from these same Canadian women, and also from a study of 10,000 individuals in Massachusetts,[53] suggest a decreasing risk with increasing dose in the low-dose region, in this case extending at least up to 100 cSv, and no statistically significant increased risk up to 350 cSv. This is drastically inconsistent with the data for Japanese A-bomb survivors for whom the risk seems to increase linearly with dose up to 300 cSv, where it is three times the zero-dose risk. There are many factors to be considered in the bomb survivors,[54] one being the high dose rate from the bomb compared with the protracted fluoroscopic examinations extending over many weeks.

In 1957, an explosion in a mismanaged radioactive waste storage facility at the U.S.S.R. Mayak nuclear weapons complex in the Eastern Urals of Siberia caused large radiation exposures to people in nearby villages. A follow-up on 7,852 of these villagers[55] found that the rate of subsequent cancer mortality was much lower among these than among unexposed villagers in the same area. The ratio ± one standard deviation for exposed to unexposed was 0.73 ± 0.07 for 4 cGy, 0.61 ± 0.07 for 12 cGy, and 0.72 ± 0.12 for 50 cGy.

Studies are underway on the workers at this Mayak complex,[56] among whom there have been many excess cancers, but exposures were generally quite high and the data reported give little information on the dose-response relationship in the low-dose region.

Stimulation of the immune system by low-level radiation is being used on an experimental basis for medical treatment of non-Hodgkin's lymphoma with total-body and half-body (trunk only) irradiation. This radiation was administered to one group of patients ("irradiated" group), but not to an otherwise similar "control" group, before both groups were given similar other standard treatments such as chemotherapy with or without accompanying high radiation doses to tumors. In one such study,[33] 50% of the control group, but only 16% of the irradiated group had died after 9 years. In a much earlier study[57] with different standard treatment, 4-year survival was 70% for the irradiated group versus 40% for the controls. In another study in that time period[58] with a more advanced chemotherapy, 4-year survival was 74% for the irradiated group versus 52% for the control group. Despite information supportive of using whole-body or half-body low-level radiation to stimulate the immune system, U.S. physicians have not utilized it. Further applications, however, are underway in Japan.

Further work is needed on the effects of radiation-contaminated buildings in Taiwan,[59] where 10,000 occupants were exposed for up to 20 years to an average of 40 cSv total. Among these, 232 cancer deaths would be expected from natural causes plus 70 additional deaths expected from LNT, but only seven cancer deaths have occurred. Differences in the age distribution of the affected people as compared with the general population have not been carefully investigated, but preliminary estimates are that this might reduce the expected number of cancers by about 20%, a change that would not affect the conclusions. It would seem to be very important to conduct a full epidemiological study of this situation, but the funding agencies have not been cooperative despite heavy pressures from segments of the scientific community.

Alpha Exposures

In addition to the data described above for X-rays, gamma rays, and some neutrons for bomb survivors, there are also impressive relevant data from radiation with alpha particles. One such study is of bone and head cancers among dial painters, chemists, and others occupationally exposed to ingested radium.[60] There were no tumors among those with exposures below 1,000 cGy; however, 25% to 38% in each category developed cancers for dose ranges centered about 1,800 cGy; 3,500 cGy; 7,500 cGy; and 20,000 cGy. Elaborate analyses of these data shows that an LNT fit is statistically unsupportable and a threshold behavior is strongly suggested.

Several studies have reported that workers who inhaled plutonium, resulting in sizable radiation exposures to their lungs, have lung cancer mortality rates equal to or lower than those not thus exposed.[61-63]

A study of lung cancer mortality rate as a function of average indoor radon exposure showed a clear, statistically indisputable[64] tendency for lung cancer mortality to *decrease* with increasing radon exposure, with or without correction for smoking prevalence. These data have been analyzed for more than 500 possible confounding factors, including socioeconomic, geographic, environmental, and ethnic associations,[65] and the possible effects of an unrecognized confounding factor were investigated,[66] but the conclusion remains firm that LNT fails decisively by grossly over-estimating the cancer risk from low-level radiation.

A pooled analysis of seven case-control studies[67] has been interpreted as being in conflict with the above results. Its data are listed in Table 4. Note that none of the data points show a statistically significant excess lung cancer risk. The pattern

Table 4. Odds Ratios for Lung Cancer vs. Residential Radon Exposure from Seven Pooled Case-control Studies[67]

Radon level (Bq/m3)	Odds ratio (95% C.I.)
<25	1.00
25-49	1.13 (0.95-1.35)
50-74	1.09 (0.89-1.34)
75-99	1.16 (0.91-1.48)
100-149	1.24 (0.96-1.60)
150-199	1.22 (0.87-1.71)
>199	1.37 (0.98-1.92)

suggests an excess risk from radon exposures, although it does not necessarily increase with dose, at least for the four lowest points that comprise the region of significance in the Cohen study. A pooled study includes many complicated adjustments for differences among the various studies in the pool, and potential confounding factors with the adjustments for the few of them that are recognized might be a problem. In any case, the results in Table 4 cannot be interpreted as a test of LNT.

Dependence of Latent Period on Dose

A substantial body of data, both on animals and on humans, indicates that the time delay between radiation exposure and cancer death increases with decreasing exposure.[68, 69] These observations lead to the obvious conclusion that for low enough exposures, this time delay exceeds the normal life span, so no actual cancers develop. Thus, there is an effective threshold.

This effect alone, even in the absence of all considerations discussed previously in this paper, would invalidate LNT as applied to low-level radiation.

Conclusion

The conclusion from the evidence reviewed in this paper and more extensively elsewhere[70] is that the linear-no threshold theory (LNT) fails very badly in the low-dose region, grossly over-estimating the risk from low-level radiation. This means that the cancer risk from the vast majority of normally encountered radiation exposures is much lower than given by usual estimates, and may well be zero or even negative.

Bernard L. Cohen, Ph.D., is a professor of physics and of environmental and occupational health, University of Pittsburgh. Contact: blc@pitt.edu.

Acknowledgement: The author acknowledges a great debt to Myron Pollycove and James Muckerheide for help in pointing out references involved in this paper, and to Jane Orient for help in its preparation.

This paper is adapted from a chapter by B.L. Cohen, "The cancer risk from low-level radiation" in Tack D, Gevenois PA, eds. *Medical Radiology Radiation Dose from Pediatric and Adult Multidetector Computed Tomography.* Berlin: Springer-Verlag; 2007, with the kind permission of Springer Science and Business Media.

REFERENCES

1 Health Physics Society (HPS). Radiation Risk in Perspective: Position Statement of the Health Physics Society (adopted January 1996). *Health Physics Society Directory and Handbook, 1998-1999*: p 238.

2 Aurengo A, Averbeck D, Bonnin A, et al. Dose-effect relationship and estimation of the carcinogenic effects of low dose ionizing radiation. Académie des Sciences—Académie national de Médicine; Mar 30, 2005. Available at: http://www.radscihealth.org/rsh/Papers/FrenchAcadsFinal07_04_05.pdf. Accessed Jun 23, 2008.

3 NCRP (National Council on Radiation Protection and Measurements). Principles and application of collective dose to radiation protection. NCRP Publication 121. Bethesda, Md.; 1995.

4 NCRP. Evaluation of the linear nonthreshold dose-response model for ionizing radiation. NCRP Publication 136. Bethesda, Md.; 2001.

5 Feinendegen LE. Evidence for beneficial low level radiation effects and radiation hormesis, *Brit J Radiol* 2005;78:3-7.

6 Feinendegen LE. Low doses of ionizing radiation: relationship between biological benefit and damage induction, a synopsis. *World J Nuc Med* 2005;4:21-34.

7 Tubiana M, Aurengo A. Dose effect relationship and estimation of the carcinogenic effects of low doses of ionizing radiation. *Int J Low Radiat* 2005;2:1-19.

8 Pollycove M, Feinendegen L. Biologic responses to low doses of ionizing radiation: detriment vs hormesis; Part 1. *J Nucl Med* 2001;42:17N-27N.

9 Portess DI, Bauer G, Hill MA, O'Neill P. Low dose irradiation of non-transformed cells stimulates the removal of precancerous cells via intercellular induction of apoptosis. *Cancer Res* 2007;67:1246-1253.

10 Finkel T, Holbrook NJ. Oxidants, oxidative stress, and the biology of aging. *Nature* 2000;408:239-247.

11 Boothman DA, Meyers M, Odegaard E, Wang M. Altered G1 checkpoint control determines adaptive survival responses to ionizing radiation, *Mutation Res* 1996;358:143-153.

12 Bonner WN. Phenomena leading to cell survival values which deviate from linear-quadratic models. *Mutation Res* 2004;568:33-39.

13 Yin E, Nelson DO, Coleman MA, Peterson LE, Wyrobek AJ. Gene expression changes in mouse brain after exposure to low-dose ionizing radiation. *Int J Radiat Biol* 2005;79:759-775.

14 Golder-Novoselsky E, Ding LH, Chen F, Chen, DJ. Radiation response in HSF cDNA microarray analysis. DOE Low Dose Radiation Research Program Workshop III, U.S. Dept. of Energy, Washington, D.C.; 2002.

15 Miller RC, Randers-Pehrson G, Geard CR, Hall EJ, Brenner DJ. The oncogenic transforming potential of the passage of single alpha particles through mammalian cell nuclei. *Proc Natl Acad Sci U S A* 1999;96:19-22.

16 Tanooka H. Threshold dose-response in radiation carcinogenesis: an approach from chronic beta-irradiation experiments and a review of non-tumor doses. *Int J Radiat Biol* 2001;77:541-551.

17 UNSCEAR (United Nations Scientific Committee on Effects of Atomic Radiation). Report to the General Assembly. *Annex B: Adaptive Response*. United Nations, N.Y.; 1994.

18 Shadley JD, Dai GQ. Cytogenic and survival adaptive responses in G-1 phase human lymphocytes. *Mutat Res* 1992;265:273-281.

19 Cai L, Liu SZ. Induction of cytogenic adaptive response of somatic and germ cells in vivo and in vitro by low dose X-irradiation. *Int J Radiat Biol* 1990;58:187-194.

20 Ghiassi-nejad M, Mortazavi SMJ, Beitollahi M, et al. Very high background radiation areas of Ramsar, Iran: preliminary biological studies and possible implications. *Health Phys* 2002;82:87-93.

21 Coleman MA, Lin E, Peterson LE, et al. Low dose irradiation alters the transcript profiles of human lymphoblastoid cells including genes associated with cytogenic radioadaptive response, *Radiat Res* 2005;164:369-382.

22 Kelsey KT, Memisoglu A, Frenkel A, Liber HL. Human lymphocytes exposed to low doses of X-rays are less susceptible to radiation induced mutagenesis. *Mutat Res* 1991;263:197-201.

23 Fritz-Niggli H, Schaeppi-Buechi C. Adaptive response to dominant lethality of mature and immature oocytes of D. Melanogaster to low doses of ionizing radiation: effects in repair-proficient and repair deficient strains. *Int J Radiat Biol* 1991;59:175-184.

24 Azzam EI, de Toledo SM, Raaphorst GP, Mitchel REJ. Low dose ionizing radiation decreases the frequency of neoplastic transformation to a level below spontaneous rate in C3H 10T1/2 cells. *Radiat Res* 1996;146:369-373.

25 Redpath JL, Antoniono RJ. Induction of a rapid response against spontaneous neoplastic transformation in vitro by low dose gamma radiation. *Radiat Res* 1998;149:517-520.

26 Yamaoka K. Increased SOD activities and decreased lipid peroxide in rat organs induced by low X-irradiation. *Free Radic Biol Med* 1991;11:3-7.

[27] Yukawa O, Nakajima T, Miura Y, Ueda J, Ozawa T. Induction of radical scavenging ability and suppression of lipid peroxidation in rat liver microsomes following whole body low dose X-irradiation. *J Radiat Biol* 2005;81:681-688.
[28] Liu SJ. Multilevel mechanisms of stimulatory effect of low dose radiation on immunity. In: Sugahara T, Sagan LA, Aoyama T, eds. *Low Dose Irradiation and Biological Defense Mechanisms*. Amsterdam: Elsevier Science; 1992:225-232.
[29] Makinodan T. Cellular and sub-cellular alteration in immune cells induced by chronic intermittent exposure in vivo to very low dose of ionizing radiation and its ameliorating effects on progression of autoimmune disease and mammary tumor growth. In: Sugahara T, Sagan LA, Aoyama T, eds. *Low Dose Irradiation and Biological Defense Mechanisms*. Amsterdam: Elsevier Science; 1992:233-237.
[30] Liu SZ. Non-linear dose-response relationship in the immune system following exposure to ionizing radiation: mechanisms and implications. *Nonlinearity Biol, Toxicol Med* 1992;1:71-92.
[31] Ina Y, Sakai K. Activation of immunological network by chronic low dose rate irradiation in wild type mouse strains: analysis of immune cell populations and surface molecules. *Int J Radiat Biol* 2005;81:721-729.
[32] Ina Y, Tanooka H, Yamada T, Sakai K. Suppression of thymic lymphoma induction by life-long low dose rate irradiation accompanied by immune activation of C57BL/6 mice. *Radiat Res* 2005;163:153-158.
[33] Sakamoto K, Myogin M, Hosoi Y, et al. Fundamental and clinical studied on cancer control with total and upper half body irradiation. *J Jpn Soc Ther Radiol Oncol* 1997;9:161-175.
[34] Hashimoto S, Shirato H, Hosokawa M, et al. The suppression of metastases and the change in host immune response after low-dose total body irradiation in tumor bearing rats. *Radiat Res* 1999;151:717-724.
[35] Makinodan T, James SJ. T cell potentiation by low dose ionizing radiation: possible mechanisms. *Health Phys* 1990;59:29-34.
[36] Mitchel REJ, Jackson JS, Morrison DP, Carlisle SM. Low doses of radiation increase the latency of spontaneous lymphomas and spinal osteosarcomas in cancer prone, radiation sensitive Trp53 heterozygous mice. *Radiat Res* 2003;159:320-327.
[37] Anderson RE. Effects of low dose radiation on the immune response. In: Calabrese EJ, ed. *Biological Effects of Low Level Exposures to Chemicals and Radiation.* Chelsea, Mich.: Lewis; 1992:95-112.
[38] Duport P. A data base of cancer induction by low-dose radiation in mammals: overview and initial observations. Second Conference of the World Council of Nuclear Workers (WUNOC), Dublin; 2001.
[39] Heidenreich WF, Paretzke HG, Jacob B. No evidence for increased tumor risk below 200 mSv in the atomic bomb survivor data. *Radiat Environ Biophys* 1997;36:205-207.
[40] Cohen BL. The cancer risk from low level radiation. *Radiat Res* 1998;149:525-526.
[41] Preston DL, Pierce DA, Shimizu Y, et al. Effect of recent changes in atomic bomb survivor dosimetry on cancer mortality risk estimates. *Radiat Res* 2004;162:377-389.
[42] Pierce DA, Shimizu Y, Preston DL, Vaeth M, Mabuchi K. Studies of the mortality of atomic bomb survivors, Report 12, Part 1, Cancer: 1950-1990. *Radiat Res* 1996;146:1-27.
[43] Cardis E, Gilbert ES, Carpenter L, et al. Effects of low dose and low dose rates of external ionizing radiation: Cancer mortality among nuclear industry workers in three countries. *Radiat Res* 1995;142:117-132.
[44] Matanoski GM. Health effect of low level radiation in shipyard workers, Final report. Report No. DOE DEAC02-79 EV10095; U.S. Dept of Energy; 1991. See Tables 3.6B and 3.6D.
[45] Monson RR. Observations on the healthy worker effect. *J Occup Med* 1986;28:425-433.
[46] Gridley G, Nyren O, Dosemeci M, et al. Is there a healthy worker effect for cancer incidence among women in Sweden? *Am J Ind Med* 1999;36:193-199.
[47] Berrington A, Darby SC, Weiss HA, Doll R. 100 years of observation on British radiologists; mortality from cancer and other causes, 1897-1997, *Br J Radiol* 2001;74:507-519.
[48] Wang JX, Zhang LA, Li BX, et al. Cancer incidence and risk estimation among medical X-ray workers in China, 1950-1995. *Health Phys* 2002;82:455-466.
[49] Mohan AK, Hauptmann M, Freedman DM, et al. Cancer and other causes of mortality among radiologic technicians in the United States. *Int J Cancer* 2003;103:259-267.
[50] Yoshinaga S, Mabuchi K, Sigurdson AJ, Doody MM, Ron E. Cancer risks among radiologists and radiologic technologists: review of epidemiologic studies. *Radiology* 2004;233:313-321.
[51] Rogel A, Carre N, Amoros E, et al. Mortality of workers exposed to ionizing radiation at the French National Electricity company. *Am J Ind Med* 2005;47:72-82.
[52] Miller AB, Howe GR, Sherman GJ, et al. Mortality from breast cancer after irradiation during fluoroscopic examinations in patients being treated for tuberculosis. *N Engl J Med* 1989;321:1285-1289.
[53] Davis HG, Boice JD, Hrubec Z, Monson RR. Cancer mortality in a radiation-exposed cohort of Massachusetts tuberculosis patients. *Cancer Res* 1989;49:6130-6136.
[54] Scott BR, Sanders CL, Mitchel REJ, Boreham DR. CT scans may reduce rather than increase the risk of cancer. *J Am Phys Surg* 2008;13:8-11.
[55] Kostyuchenko VA, Krestina LY. Long term irradiation effects in the population evacuated from the East-Urals radioactive trace area. *Science of the Total Environment* 1994;142:119-125.
[56] Koshurnikova NA, Gilbert ES, Shilnikova NS, et al. Studies of the Mayak nuclear workers: health effects. *Radiat Environ Biophys* 2002;41:29-31.
[57] Chaffey JT, Rosenthal DS, Moloney WC, Hellman S. Total body radiation as treatment for lymphosarcoma. *Int J Radiat Oncol Biol Phys* 1976;1:399-405.
[58] Choi NC, Timothy AR, Kaufman SD, Carey RW, Aisenberg AC. Low dose fractionated whole body irradiation in the treatment of advanced non-Hodgkin's lymphoma. *Cancer* 1979;143:1636-1642.
[59] Chen WL, Luan YC, Shieh MC, et al. Is chronic radiation an effective prophylaxis against cancer? *J Am Phys Surg* 2004;9:6-10.
[60] Evans RD. Radium in man. *Health Phys* 1974;27:497-510.
[61] Tokarskaya ZB, Okladlnikova ND, Belyaeva ZD, Drozhko EG. Multifactorial analysis of lung cancer dose-response relationships for workers at the Mayak Nuclear Enterprise. *Health Phys* 1997;73:899-905.
[62] Voelz GL, Wilkinson CS, Acquavelle JF. An update of epidemiologic studies of plutonium workers. *Health Phys* 1983;44(Supplement 1):493-503.
[63] Gilbert ES, Petersen GR, Buchanan JA. Mortality of workers at the Hanford site: 1945-1981. *Health Phys* 1989;56:11-25.
[65] Cohen BL. Updates and extensions to tests of the linear-no threshold theory. *Technology* 2000;7:657-672.
[66] Cohen BL. Test of the linear-no threshold theory; rationale for procedures. *Nonlinearity Biol Toxicol Med* 2005;3:261-282.
[67] Krewski D, Lubin JH, Zielinski JM, et al. Residential radon and risk of lung cancer: a combined analysis of 7 North American case-control studies. *Epidemiology* 2005;16:137-145.
[68] Raabe OG. Three dimensional models of risk from internally deposited radionuclides. In: *Internal Radiation Dosimetry.* Raabe OG, ed, Madison, Wis.: Medical Physics; 1994:633-656.
[69] Cohen BL. The cancer risk from low level radiation. *Health Phys* 1980;39:659-678.
[70] Cohen BL. The cancer risk from low level radiation. In: Tack D, Gevenois PA, eds. *Medical Radiology: Radiation Dose from Pediatric and Adult Multidetector Computed Tomography.* Berlin: Springer-Verlag; 2007.