AN EVALUATION OF THEORIES CONCERNING THE HEALTH EFFECTS OF LOW-DOSE RADIATION EXPOSURES

By

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SUBMITTED TO THE DEPARTMENT OF NUCLEAR SCIENCE AND ENGINEERING
IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF

BACHELOR OF SCIENCE IN NUCLEAR SCIENCE AND ENGINEERING
AT THE
MASSACHUSETTS INSTITUTE OF TECHNOLOGY

JUNE 2012

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ABSTRACT

The danger of high, acute doses of radiation is well documented, but the effects of low-dose radiation below 100 mSv is still heavily debated. Four theories concerning the effects of low-dose radiation are presented here: supra-linearity, linear-no-threshold (LNT), threshold, and hormesis. The available evidence for and against these theories, which falls into the categories of either epidemiological studies, *in vitro* cell experiments, or *in vivo* animal experiments, includes studies which support each of the four theories.

Currently, all radiation risk estimates are based on an LNT interpretation of the life span study (LSS) of atomic bomb survivors in Japan. However, while this pattern is undisputed at high doses, this linear extrapolation of risk to low doses is challenged by many recent experiments involving cell mechanisms and animal models, and there is also high uncertainty involved in estimating risk using only epidemiological studies.. Variations have also been observed depending on dose-rate, the organ at risk, and other factors for which the current data cannot adequately account. While the evidence is still inconclusive, the existence of a threshold in human responses to low-dose radiation would drastically alter current guidelines, such as those currently restricting many people from returning to their hometowns in Fukushima, Japan. Thus, it is important to further investigate these low dose responses in order to more fully describe the risks and to create more accurate radiation guidelines.

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I. Introduction

1. Motivating Reasons for Research: the Fukushima Accident

On March 9, 2011 the country of Japan was struck by a 9.0 earthquake and, shortly after, by a series of tsunamis. The combination of these natural disasters led to the losses of many lives, destruction of infrastructure, and also to a nontrivial release of radiation from the Fukushima Daiichi nuclear power plant on the northeast coast of Japan. According to the INPO Special Report on the accident, an estimated 6.3x10^17 Bq of radioactive material was released from the power plant between March 11 and April 5 [1]. As a result of this release, the government of Japan ultimately ordered a 30km evacuation zone around the Fukushima Daiichi power plant. The government also took other protective measures including a restriction on drinking water, monitoring and restriction of foodstuffs, and monitoring of dose-rate in each Japanese prefecture.

As of February 14, 2012, the environmental radioactivity level found in every Japanese prefecture except for Fukushima have been within normal variation. According to MEXT, the Japanese Ministry of Education, Culture, Sports, and Science, and Technology, the average radioactivity for Fukushima between February 10-14 has remained between 0.90-0.91 μSv/hr at 2.5m from the ground, which is higher than Fukushima prefecture's normal value band of 0.036-0.056 μSv/hr [2]. A a survey of schools in the Fukushima prefecture measured doses of 0 to 0.7 μSv/hr, while a sampling of sites within Fukushima on have found radioactivity levels of a maximum of 3.6 μSv/hr in the village of Iitate [3]. Individual reading points, such as one taken at the Namie monitoring posts in Futaba County on Feb 15, 2012 have also reported dose-rates of up to 23 μSv/hr [4]. These dose-rate readings all presumably include natural background radiation in their measurements, since there is no indication that background levels have been subtracted from the reports. In general, then, the measured dose-rates in affected areas of Japan might be said to range from 0-30 μSv/hr, or 0-262.8 mSv/year (background radiation included) for someone who lived at the spot of highest contamination for 24 hours a day, 365 days a year.

According to MEXT, the upper limit of radiation dose permitted by the Japanese government is 250 mSv/year above background dose for people who engage in emergency work, 50 mSv/ year above background for radiation workers, police, and firefighters who engage in disaster prevention, and 1 mSv/year above background for the general public [5]. These standards are in close agreement with those of the United States NRC, or Nuclear Regulatory Commission, which sets an upper bound of total effective dose equivalent of 50 mSv/year for occupational workers [6] and 1 mSv/year for the general public [7].

The radiation emitted from a normally-functioning nuclear power plant is far below these standards, reaching at most 0.05 mSv/year above background. However, following the

Fukushima incident, the Japanese people must now commence extensive cleanup operations in order to lower the radiation around them to something near the 1 mSv/year above background standard. Since these cleanup operations are expensive, time-consuming, and labor-intensive [8-11], it seems reasonable to question whether the health benefits of soil decontamination are worth the resources being expended to clean up these low levels of radioactivity. Put another way, exactly what are the long-term health effects of chronic, low level radiation exposure?

2. Background on Ionizing Radiation

Ionizing radiation is defined as energy that can separate an electron from its atom, and has been described in detail in sources such as the NRC, WHO, and BEIR VII report [12-14]. Briefly, the main types of ionizing radiation are alpha particles, beta particles, neutrons, and photons (X-rays and gamma rays). Alpha and beta particles have electrical charge while neutrons and photons are electrically neutral. Additionally, alpha particles and neutrons are both "high linear energy transfer (high LET)" forms of radiation, while beta particles and photons, having comparatively smaller masses, are referred to as "low LET" radiation. High energy particles transfer more energy and thus create more damage per unit length as they travel through a cell. Each form of radiation interacts differently with matter, but they can all be described using the same units of dose (usually referring to absorbed dose) and effective dose.

Radiation can be measured in units of decay, exposure, absorbed dose, and effective dose. The number of decays per second is measured in Curies or Bequerels (Bq), which literally describe the number of atoms which undergo radioactive decay in a certain amount of time. The quantity of charge in the air is measured in Roentgens (R) or Coulombs per kilogram (C/kg), while the absorbed dose to the human body is measured in rads or Grays (Gy). Finally, the effective dose to the human body, also known as the equivalent dose or weighted dose, is measured in rems or Sieverts (Sv). 1 Gy is equal to 100 rad and 1 Sv equals 100 rem. A Gray and a Sievert are also both defined in units of a joule per kilogram, and for low-LET radiation, 1 Gy generally equals 1 Sv. However, the distinction remains because in situations of high-LET radiation, a weighting factor is applied to account for the higher quantity of cellular damage. Thus, 1 Gy of alpha radiation equals 20 Sv of effective dose. Radiation experiments and radiotherapy doses are generally reported in terms of absorbed dose (Gy), while risk assessments and radiation protection measures tend to use effective dose (Sv). For consistency throughout this thesis, the SI units of Bq, Gy, and Sv will be used instead of the Curie, rad, and rem. Additionally, low-LET human doses will generally be converted from Gy to Sv since 1 Gy of low-LET radiation is equivalent to 1 Sv.

Although radiation is often associated with large exposures from sources such as nuclear weapons, all humans encounter a measurable amount of ionizing radiation in their everyday lives. Globally, the average person receives a natural background dose of 2.4 mSv of ionizing radiation per year, though this number can be as high as 10 mSv/year in high natural background regions (HNBR) of the world, like Guarapai, Brazil [5]. Natural sources of background radiation include the radioactive decay of uranium into airborne radon, the cosmic radiation that ionizes

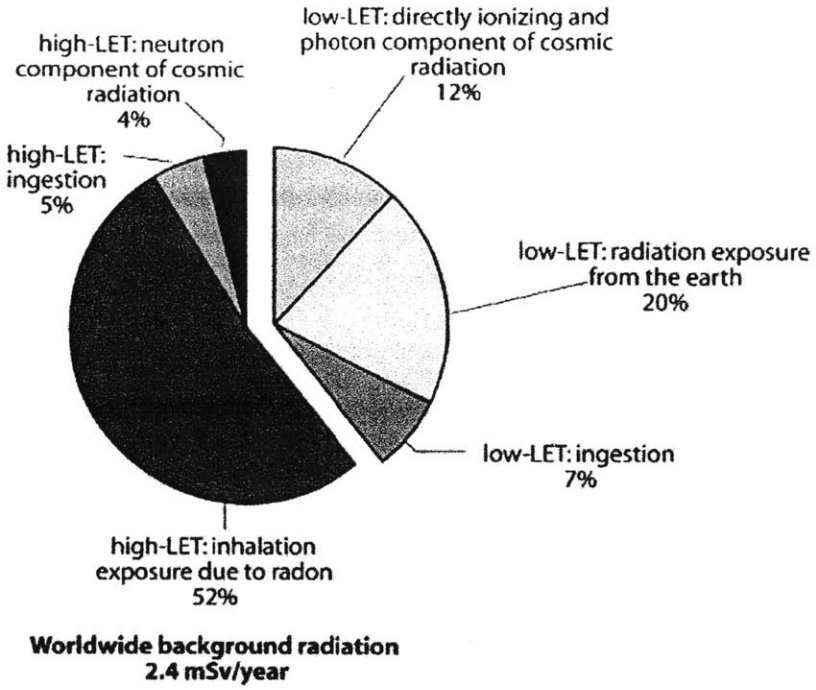

Figure 1. Origins of Global Background Radiation. The average sources of natural background radiation worldwide, sorted by high and low LET. Source: UNSCEAR 2000 [15]

air molecules, and radioactive isotopes of potassium found in food, just to name a few. The graph in Figure 1 summarizes the average amount and sources of natural background radiation encountered worldwide [14].

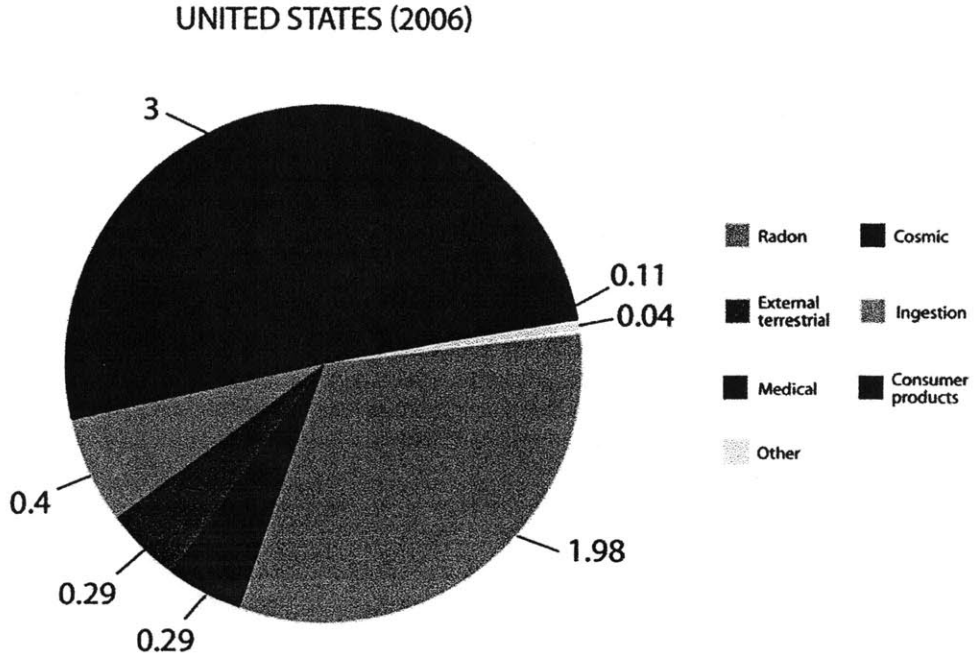

Figure 2. Origins of Background Radiation in the United States. The average sources of natural and man-made background radiation in the U.S. The largest source is medical exposures, followed by radon. Source: UNSCEAR 2008 [16]

In addition to natural sources, man-made sources also contribute to background radiation levels, making the average background radiation in the U.S. now 6.2 mSv/year, as shown in Figure 2. The highest man made sources of radiation in the U.S. are medical exposures such as X-ray and CT scans, followed by indoor radon exposure from living and breathing in houses. Smaller amounts of radiation come from various other sources [16]. For example, a single chest CT scan delivers about 6.9 mSv, while a round trip flight from Tokyo to New York delivers 0.2 mSv of cosmic radiation. NRC limits on radiation exposure and average doses associated with some common scenarios are shown in Table 1.

Table 1. Common Radiation Sources and Prescribed Limits

Dose	Radiation Sources or Limits	References
0.000009 mSv/year	Dose from a nuclear power plant	NRC [12]
0.00008 mSv/year	Dose from a smoke detector	NRC
0.0003	Dose from a coal plant	NRC
0.02 mSv/hour	Maximum permitted dose to the public	NRC Regulations [7]
0.05 mSv/scan	Chest X-ray	MEXT [5]
0.07 mSv/year	Dose from living inside a building	NRC
0.2 mSv/trip	Round trip flight from Tokyo to New York	MEXT
0.4 mSv/year	Maximum difference between background levels of two Japanese prefectures	MEXT
0.6 mSv/scan	Gastrointestinal X-ray	MEXT
0.89 mSv/year	Dose received by dental practitioner	UNSCEAR 2008 [16]
1 mSv/year	Maximum permitted dose to the public	NRC Regulations
1.7 mSv/year	Dose from air in Denver, CO or Campania, Italy	UNSCEAR 2008
1-2 mSv/year	Dose received by aircrew or nuclear industry workers	UNSCEAR 2008
1.9-2.2 mSv/year	Dose received by PET physician	UNSCEAR 2008
2.25	Average medical exposure in Japan	MEXT
2.4 mSv/year	Average natural background dose worldwide	MEXT
5 mSv/year	Permitted dose to the public under special circumstances; permitted whole body dose for occupational worker minors; permitted dose to a fetus/pregnant woman	NRC Occupational Regulations [6]
6.2 mSv/year	Average dose in the U.S. from natural and human sources	UNSCEAR 2008
6.7 mSv/year	Background dose in Ramsar, Iran	UNSCEAR 2008
6.9 mSv/scan	Chest CT scan	MEXT
4.6-8 mSv/year	Dose received by PET technologists	UNSCEAR 2008
10 mSv/year	Background dose in Guarapari, Brazil	MEXT
13.14 mSv/year	Background dose in Kerala, India	UNSCEAR 2008

Table 1. Common Radiation Sources and Prescribed Limits

Dose	Radiation Sources or Limits	References
24.5 mSv/year	Background dose in Araxa, Brazil	UNSCEAR 2008
30 mSv/year	Dose received by interventional cardiologist	UNSCEAR 2008
50 mSv/year	Permitted whole body dose for occupational workers such as firefighters, police, and radiation workers	NRC Occupational Regulations
120 mSv/year	Maximum dose received by interventional cardiologist to hand and shoulder	UNSCEAR 2008
150 mSv/year	Permitted dose to the lens of the eye for occupational workers	NRC Occupational Regulations
170 mSv/year	Dose received on the international space station	Brenner [17]
200 mSv/year	Average dose of A-bomb survivors in the LSS cohort	Brenner
250 mSv/year	Permitted dose for emergency workers	MEXT
500 mSv/year	Permitted dose to a single organ or to skin for occupational workers	NRC Occupational Regulations

3. Low Dose Radiation Theories

The lethal effects of large radiation doses are well known, but the health benefits or risks of low-dose background radiation are heavily debated. Acute, whole-body doses greater than 1 Sv of ionizing radiation result in various stages of "acute radiation syndrome," which increases in severity with dose and results in almost certain death above 5 Sv [12]. Even at lower, acute doses

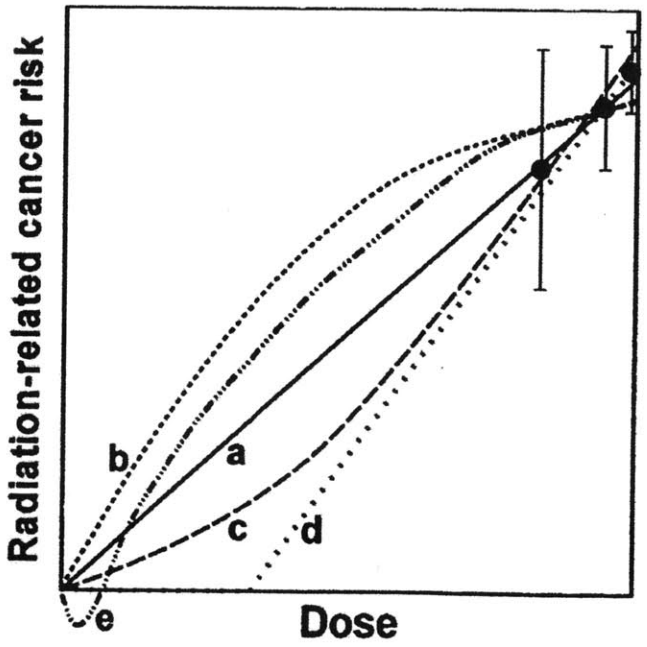

Figure 3. Schematic Representation of Various Low-Dose Radiation Risk Patterns. All of these relations are, in principle, consistent with high-dose epidemiological data. Curve a is LNT, curve b is supra-linear, curve c is linear-quadratic (treated with LNT), curve d is threshold, and curve e is hormesis. Source: Brenner [17]

of about 0.2-1 Gy, a linear relationship has generally been observed between total dose and severity of induced health effects. However, when doses in the "low-dose" range of less than 100 mGy are brought into the picture, the scientific literature becomes unclear [14].

The range of beliefs concerning low levels of radiation can be roughly divided into four categories: supra-linearity, linear-no-threshold, threshold, and hormesis, each with their passionate defenders. These four hypotheses are illustrated in the graph in Figure 3. The supra-linearity hypothesis, which is considered by Brenner [17], Prasad [18], and Gofman [19], says that small doses of radiation are even more harmful that what is accounted for by linear extrapolation. If supra-linearity is true, then even the accumulation of small doses, such as the natural background radiation of 2.4 mSv/yr, may have detrimental effects on the body. The second theory is the linear-no-threshold (LNT) hypothesis, which is defended by the BEIR Report [14], Pierce and Preston [20], and other Life Span Study (LSS) reports [21-24] of the atomic bomb survivors. LNT says that every dose of radiation is associated with some non-negligible amount of risk, leading to claims such as the NRC's statement that every exposure to 0.01 mSv of radiation is equivalent to 1.2 minutes of life lost - and every smaller dose, whether 0.001 or 0.0001 mSv of radiation, results in some smaller amount of life-shortening. Third, the threshold hypothesis, which is examined by Feinendegen [25], Tubiana [26], and Tanooka [27], says that low doses of radiation below a certain threshold amount have no significant effect on human health. This threshold is believed to exist where the literature begins to be inconsistent, that is around 100 mSv of acute dose and probably higher for fractionated or chronic doses. The final belief is the hormesis hypothesis, which is presented by Feinendegen [25] and Cohen [28] and says that chronic, low doses of radiation actually have a beneficial effect on human health. There is no consensus among the scientific community concerning these hypotheses, but the truth of the matter has strong implications for nuclear industry regulations and government procedures after an accident, as the cleanup after Fukushima has demonstrated.

Currently, the radiation protection guidelines set by the ICRP, NRC, and other regulatory bodies are all based on the LNT hypothesis, since almost all risk calculations assume that there is no threshold dose. The fitted equations describing risk of solid tumor incidence and risk are generally linear, with modifications for age at exposure, a dose and dose-rate effectiveness factor (DDREF) at low dose ranges, and adjustments for risks to specific organs. Although there is much evidence that could support supra-linearity or hormesis, few quantitative risk estimates have been made using these models. The threshold model generally accepts the LNT-based risks for higher doses, but would argue that those numbers should not be extrapolated downwards for lower doses. Possible thresholds have been calculated by Tanooka using a "non-tumor-inducing dose"[27], but the calculations are not as extensive as the risk estimates based on LNT.

4. Objective

The objective of this thesis is to evaluate the scientific basis for saying that the radiation in areas affected by the Fukushima Daiichi power plant is dangerous. Each of the four major hypothesis concerning chronic, low-dose radiation (supralinearity, LNT, threshold, and hormesis)

will be evaluated based on past research studies. The focus be will be on studies involving low dose-rates similar to what is being observed at Fukushima, and can be broadly divided into three categories: epidemiological studies, *in vivo* animal studies, and *in vitro* cell studies. Each type of study has its own pros and cons, which will be discussed before presenting the results, and the conclusions of each study will be examined. After the presentation of data, the strengths and then weaknesses of each low dose model will be critiqued, and readers are invited to judge for themselves which arguments are the most persuasive. Finally, a perspective on the radiation risks to human health will also be presented.

II. Epidemiological Studies

1. Introduction to Epidemiological Studies

The most straightforward way to examine the effects of radiation on humans is through epidemiology, by studying the health of populations who have been exposed to radiation. Epidemiological studies are popular because they seem easy to understand: look at a group of people who have been exposed to higher amounts of radiation than average, and count the number of cancer or leukemia incidences in that population compared to an average expected level. The excess cancers should then reflect the excess dose of radiation which was received. Risks can be expressed as excess relative risk (ERR), which describes the percentage of incidence or mortality above baseline levels, excess absolute risk (EAR), which describes the number of cases above baseline, or lifetime absolute risk (LAR), which describes the excess percentage of the population that will develop incidence or mortality during their lifetime. In general, findings of significant ERR or EAR are usually taken to support the LNT hypothesis, although an extremely high excess risk might also point to supralinearity. Alternatively, the absence of an ERR or EAR is usually taken to support a threshold model or, in extreme cases, hormesis.

Although epidemiological evidence is abundant and seemingly easy to decipher, there are many possible confounding factors which can never be completely eliminated. For example, smoking is known to cause lung cancer and must somehow be accounted for when studying the effects of chest X-rays or radon inhalation on lung cancer. Additionally, extremely large cohorts of subjects are needed to prove statistical significance of small risks. Over 10,000 people are needed to detect a significant cancer risk at 100 mGy, for example, and the risks get harder to see as dose rates get lower. At 10 mSv, as many as 62,000 similar cases would be needed to have an 80% chance of finding an effect with 5% significance [17]. Similarly, in studies of very low background doses, a large sample of 100,000 people, such as in Yanjiang, may yield only 500 cancers. Once these cancers are separated by cancer type, sex and age of subject, and radiation dose received, there is barely enough information to draw a linear or threshold dose-response graph with any significance [29]. Even in the 22,000 men who participated in U.K. weapons testing, the difference in rate of chronic myeloid leukemia was only 12 cases in the exposed group versus 4 cases in the controls [32-33].

It is also difficult to choose unbiased controls and statistics which accurately describe a population. In ecological studies, where the statistic of interest is rate of cancer incidences or mortalities, the controls are usually the rate for a larger area, such as a whole country or even continent. Background incidence rates are difficult to ascertain, so more often morality rates are used - but mortality can be a function of available medical care and not just incidence level, and participants of a study often receive more thorough medical attention than average. Cancer registries are nonexistent or incomplete for many parts of the world, so background levels also tend to be underestimated within a cohort. In case-control studies, which are more statistically meaningful but also more time consuming, a cohort of individuals, such as A-bomb survivors of

the Life Span Study (LSS), cases of childhood cancer in a specific area, or workers at a nuclear power plant during a set time period, are compared to a group of non-exposed controls. The controls are usually matched to the exposed cohort in some way, such as children who were born in the same year, or workers at the plant who were exposed to high levels vs. low levels of radiation.

Then, many of the studies are ecological studies, which study the number of cancers recorded in a region compared to that region's population. These broad-reaching studies involved large numbers of subjects, but often fail to take into account details of age, body mass, genetics, and length of time that the subjects lived in an area. Radiation doses are usually estimated in hindsight, since many human radiation exposures are unplanned, which makes exact doses subject to uncertainties and recall bias. In the Chernobyl studies, for example, while the elevated amount of childhood thyroid cancer is a relatively undisputed fact, many doses were estimated based on the broad region where subjects lived and the approximate amount of milk that they drank. It is impossible to control for all confounding factors, which further include "environment, diet, and lifestyle related factors that contribute mutagens, carcinogens, and tumor promoters as well as cancer-protective substances" [18].

The epidemiological studies presented here include acute exposures such as Hiroshima and Nagasaki, atomic weapons testing fallout, the Chernobyl accident, and radioactive discharges from plutonium production facilities; as well as protracted exposures from medical and dental procedures, elevated home radon levels, high natural background regions (HNBR), occupational exposures to radiation, and the discovery of so-called "leukemia clusters" near some nuclear power plants. It will be seen that epidemiological studies have been used to argue for every possible type of low dose response, for the conclusions drawn from these studies are strongly influenced by the interpretations of their researchers, and sometimes studies are even used to support two opposing viewpoints. The purpose of this section is not to provide an exhaustive review of every low-dose radiation study which has ever been published, but to show the few undisputed results and to highlight the areas of controversy using some representative papers.

2. Atomic Bomb Survivors' Life Span Study

The first study that should be mentioned in any review of radiation effects on human health is the Life Span Study (LSS) of atomic bomb survivors from Hiroshima and Nagasaki. The LSS cohort contains over 86,000 survivors who were within 10 km of the bomb epicenters, have individual dose estimates based on their location at the time of the explosions, and have been studied since 1950 with less than 2% of the subjects lost during follow-up. In other words, the LSS is a large set of acute exposure subjects with known individual doses and a very long follow up time. Because the LSS study is is so large and includes all ages and both sexes, it has provided the starting point for most radiation risk estimates in use today, and is possibly the "single most important source of data for evaluating risks of low-linear energy transfer radiation at low and moderate doses" [14, p. 141].

It is rather unfortunate, however, that the LSS tends to be the only study used in constructing risk estimates, because study is not always consistent with other epidemiological studies. For instance, the LSS has detected an excess risk in cardiovascular disease that is associated with doses of less than 1-2 Sv to the heart, but which has not been observed in any other radiation exposure study. Also, Japanese baseline rates for many cancers have changed over the past 60 years and the baseline cancer rates for many cancers in the U.S. differ significantly from those for Japan, making excess risks hard to quantify [14, p. 268]. Such inconsistencies suggest that the excess risks observed in the LSS are not necessarily representative of all radiation exposures.

A common criticism of the LSS studies is that since the survivors were exposed to such high doses of radiation, the results cannot be extrapolated to low dose ranges. However, this is not the most significant worry, since most LSS survivors did receive less than 500 mSv of radiation, as shown in Figure 4 [23]. The survivors who received less than 5 mSv of radiation are usually

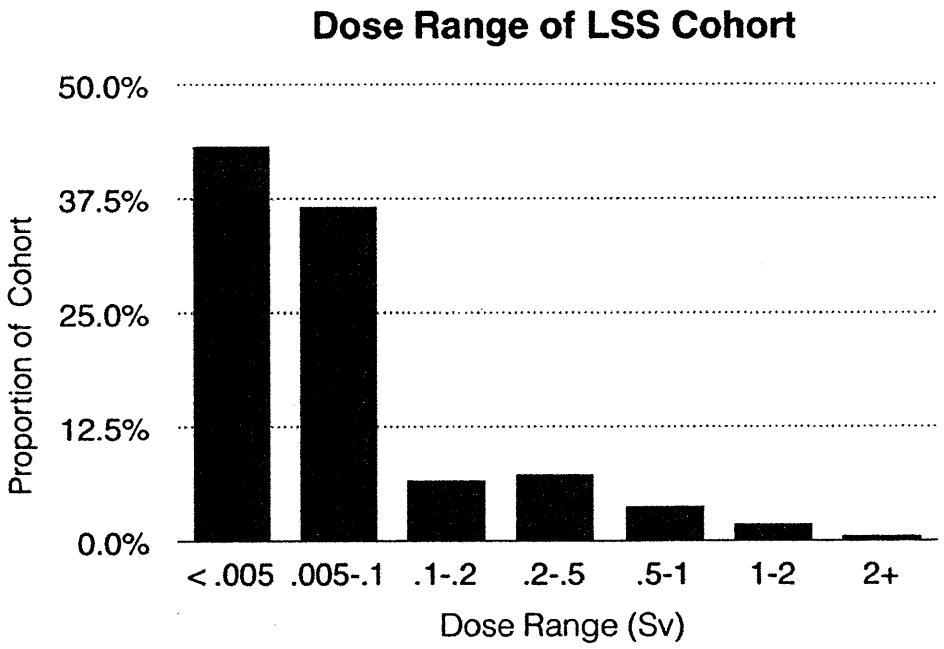

Figure 4. Distribution of Radiation Doses for the 86,572 A-bomb Survivors in the Life Span Study. Source of data: Pierce and Preston [20]

taken as the control group (which, interestingly, assumes a radiation threshold of 5 mSv), and the majority of the remaining subjects have low-dose exposures between 5-100 mSv, so it is fair to use the LSS to look for dose response relations at low doses. If people who were more than 3km away are not used, as is often the case, the total number of those have doses between 5-200 mSv is about 35,0000 [20], which, according to Brenner, should still be enough to detect an increased risk at 100 mSv.

On the other hand, the A-bomb survivors are only one group of people with a specific genetic background. At the time of exposure, they had been living under war-time conditions with possible malnourishment and other challenges. The survivor cohort is also the group that survived the war and the acute effects of the bombs, so both the exposed and control groups may be more resilient to other non-cancer diseases or be otherwise different from other populations. Additionally, the A-bomb exposure was an acute, external exposure while most radiation limits involve protracted exposures such as annual occupational dose or maximum permitted radon dose inside a house. Most epidemiological studies do not distinguish clearly between different dose rates, but there is a physical difference between receiving 200 mSv in the space of a few seconds compared to received it over a few years. For all these reasons, care should be taken to not depend solely on the LSS for estimating the health effects of radiation, especially in areas where other studies disagree with the LSS conclusions.

The official LSS studies have found the LSS to support a no-threshold model for both solid cancers and leukemia. Solid cancer incidence is believed to follow a linear no-threshold (LNT) model as shown in the graph from the BEIR report reproduced in Figure 5, while leukemia

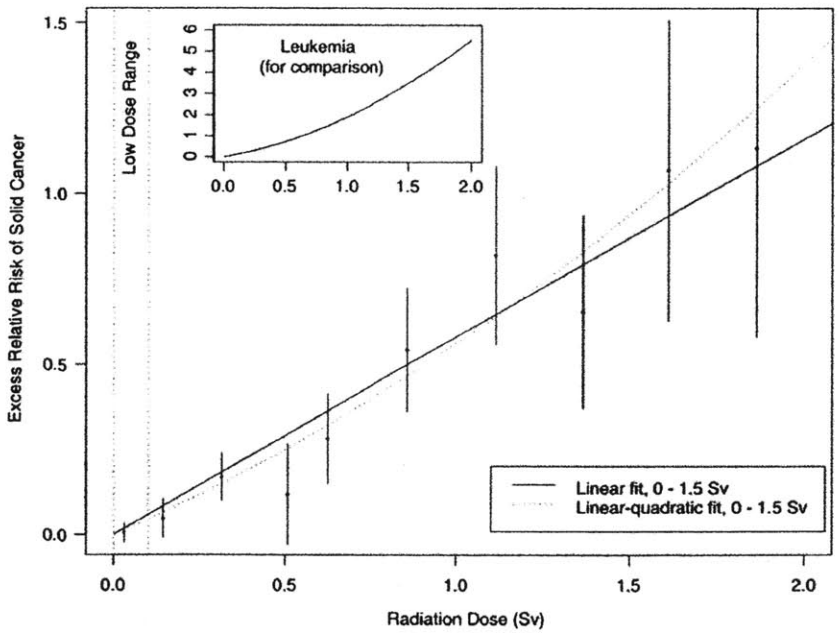

Figure 5. Excess Relative Risks of Solid Cancer for Japanese Atomic Bomb Survivors. Plotted points are estimated relative risks of solid cancer incidence a caged over sex and standardized to represent individuals with exposed age 30 and attained age 60. Vertical lines represent 95% confidence intervals. Source: BEIR VII [14]

incidence follows a linear quadratic model which also has no threshold. Notice, though, that only one point is plotted in the low dose region, so the risk pattern for that region could easily follow a different model if the low dose region data were displayed differently. The difference in interpretations of the same data can be seen in a comparison of two papers by Brenner and Cohen, which are shown in Table 2, as well as in the juxtaposed graphs of Figures 6 and 7.

Table 2. Epidemiology Studies for Acute Exposure of A-bomb Survivors (Life Span Study)

Study Description	Doses Involved	Number of Subjects	Findings	Hypothesis Supported	Sources
Solid Cancer Mortality	5-125 mSv (mean 34 mSv)	30,000+	Significantly increased risk in solid cancer mortality for 5-125 mSv, not for 5-100 or 5-50 mSv	LNT	Brenner 2003 [17]
Solid Cancer Incidence	5-100 mSv (mean 29 mAv)	30,000+	Significantly increased risk in solid cancer incidence for 5-100 mSv	LNT	Brenner 2003, Pierce Preston 2004 [20]
Solid Tumor Mortality	0-700 mSv	40,000+	No significantly increased solid tumor mortality from 0-250 mSv when error bars taken into account	threshold	Cohen 2002 [28]
Leukemia Mortality	0-700 mSv	40,000+	No significantly increased leukemia mortality from 0-200 mSv when error bars taken into account	threshold	Cohen 2002
Leukemia Mortality	10+ mSv; average 295 mSv	30,000+	Non-tumor-inducing dose of 200 mSv for leukemia	threshold	Tanooka 2001 [27]

In Figures 6 and 7, Cohen and Brenner both cite results from the Life Span Studies to plot the ERR against dose, but they end up with very different conclusions. Figure 6, from the Brenner paper, shows the ERR for solid cancer mortality using groups of increasingly larger dose ranges and traces out an LNT dose response dotted line, which goes through the origin. Figure 7, on the

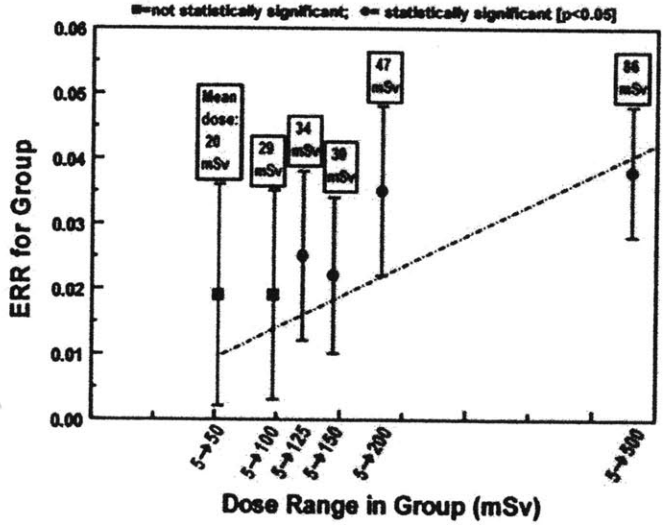

Figure 6. Excess Relative Risks of Solid Cancer Mortality for Japanese Atomic Bomb Survivors. Mean dose for each group is indicated in the box above each data point. The dashed line represent a linear fit to all of the data from 5 to 4,000 mSv, including dose points that are not shown. Source: Brenner [17]

other hand, takes similar data and emphasizes how the mortality from solid cancers stays near zero below doses of 20 cSv or 200 mSv. Both plots use ERR, since 1 excess death per 100 expected would translate to an excess relative risk of 0.01, but the range of ERR is actually higher in the figure arguing for a threshold. Figure 6 only reaches 0.06 because it includes the 5-50 mSv group in every data point, while the range in Figure 7 reaches the equivalent of almost

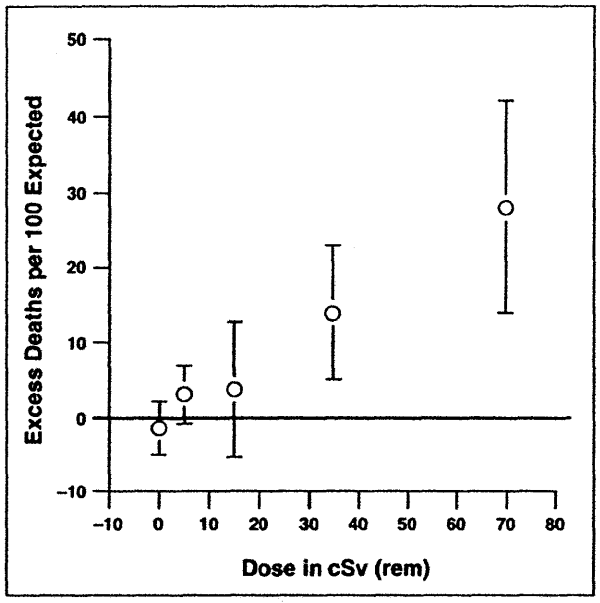

Figure 7. Excess Absolute Risks of Solid Cancer for Japanese Atomic Bomb Survivors. Error bars represent 95% confidence intervals. Source: Cohen [28]

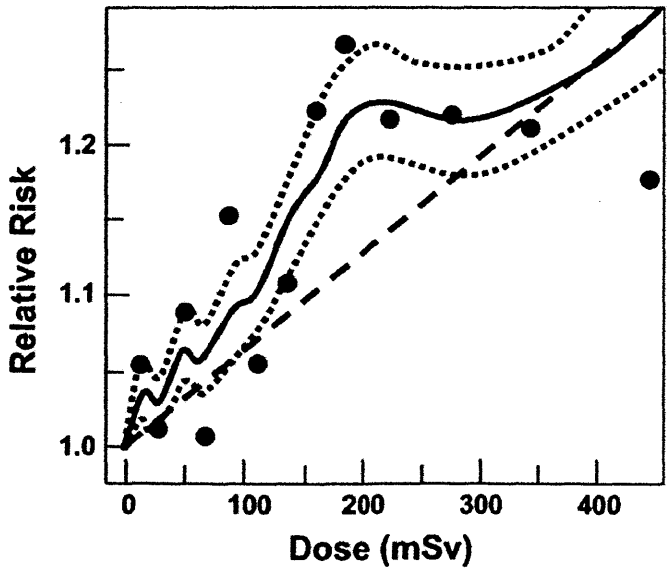

Figure 8. Excess Relative Risks of Solid Cancer for Japanese Atomic Bomb Survivors. Plotted points indicate the mean dose in each category. The solid curve is a weighted moving average of the points shown, the dotted curve represents one standard error, and the dashed straight line is a linear fit to the data from 5-2,000 mSv, including points not shown. Source: Brenner [17]

0.30. Additionally, ignoring the discrepancies in ERR, a horizontal threshold line could easily be drawn within the error bars of the first few doses in Figure 6, and a LNT model could be drawn just as easily within the error bars of Figure 7.

Brenner also used LSS data to explore the possibility of supra-linearity, or increased risk at low doses, as shown in Figure 8. This time, information from 0-450 mSv is plotted as ERR for each dose category, and the points seem to form a graph of decreasing slope, which would support the supra-linearity hypothesis. The straight, dotted line shows the LNT model uses data from 0-2000 mSv for comparison.

While graphs give a good visual, the equations that are fitted to the data and risk estimates that are drawn from the LSS data also need to be confirmed by tests of significance. And statistical tests, like graphs, are heavily influenced by how data are grouped, what data should be excluded, and what tests are chosen. Without going into too many details, it seems sufficient to mention that the LSS data has been tested for a threshold by many parties. Little and Muirhead claim that a significant threshold exists around 160 mSv [30], while Preston and Pierce claim that the test for a threshold, which should be at most 60 mSv, is not significant [20].

As this selected amount of data demonstrates, despite all efforts to be quantitative and objective when evaluating the LSS data, many results are affected by the authors' choices of mathematical models. Even if everyone uses the same data, decisions of how to group the data, what equations to fit to the data, and which statistical tests to apply can strongly influence the conclusions that are drawn. The LSS tends to be most often cited by proponents of LNT, as it does provide the basis for almost all (LNT-based) risk estimates, but its data could also support either a threshold or supralinearity hypothesis, depending on which arguments one finds most convincing.

3. Radiation Fallout from Atomic Bomb Testing

Another source of low dose, acute radiation exposure is fallout from atomic bombs. Less data is available for these populations than for the LSS A-bomb survivors, but still the results are intriguing. The main countries which conducted atomic weapons testing were the U.S., U.K., and U.S.S.R, so the studies of radiation fallout from weapons testing comes from people affected by these three countries. A summary of some studies is provided in Table 3.

Table 3. Epidemiology Studies For Acute Exposures from Fallout of Atomic Bomb Tests

Study Description	Doses Involved	Number of Subjects	Findings	Hypothesis Supported	Sources
U.K. military A-bomb test participants	"total collective γ dose was about 17 mSv"	21,000 exposed participants, 22,000 controls (both groups all males)	No significant difference in overall mortality, cancer risk, or multiple myeloma risk; slightly more myeloid leukemias in exposed group	threshold	Darby 1993 [32], Muirhead 2003 [33]

Table 3. Epidemiology Studies For Acute Exposures from Fallout of Atomic Bomb Tests

Study Description	Doses Involved	Number of Subjects	Findings	Hypothesis Supported	Sources
U.S. military A-bomb test participants	mean 78 mSv exposures, <2.5 mSv in controls	1000 personnel who received over 50 mSv doses, 2800 Navy low-dose participants as controls	Greater RR for overall mortality and lymphopoietic cancer mortality; no increased RR for all cancers, respiratory cancers, leukemia, and others	LNT or threshold	Dalager 2000 [34]
Utah residents <20 years old near the Nevada nuclear test site	6-30 mSv	1200 leukemia deaths, 5300 other deaths (controls)	significant risk for leukemia in the high dose group	LNT	Stevens 1990 [35], cited in Brenner 2003 [17]
USSR residents near Semipalatinsk, Kazakhstan	Exposed group avg 634 mSv, controls avg 20 mSv	9800 residents of exposed villages, 9600 residents of non-exposed villages	Differences in all solid angers, lung cancer, stomach cancer, female breast cancer, esophagus cancer; no dose response for overall mortality	Mostly LNT, threshold for mortality	Bauer 2005 [36]
Residents of Marshall Islands during the Castle BRAVO test	average thyroid dose 0-6.76 Sv	3,700 residents born before the BRAVO test, 1000 residents born after the BRAVO test	More thyroid cancers in exposed population than in controls, but not a significant dose response	threshold	Takahashi 2003 [37]

Overall, the atomic weapons fallout studies in Table 3 seem to indicate a threshold or no risk for US and UK military personnel who were mostly exposed to less than 100 mSv of radiation. Although the US study by Dalager did show significant increases in overall mortality and lymphopoietic cancer mortality, there was no significant increase in leukemia or other radiogenic cancer mortality, which suggests that the detected increases were not caused by the fallout radiation. Also, the numbers involved in the US study are still extremely small by epidemiological standards, and the detected excess of lymphopoietic cancer mortality was based on only 11 cases [14, p. 213]. Even in the UK study, the greatest difference between the exposed and control personnel was 12 cases of chronic myeloid leukemia in the exposed personnel and 4 cases in the non-exposed. At numbers so small, there are many other sources besides radiation which might have caused the cancers, and really, the best that can be concluded might be that there is no supralinear radiation response occurring in here.

An interesting question to ask is why did the Utah residents study detect an increased risk for leukemia mortality while the US and UK personnel studies did not? One could argue that the US military and Utah studies were both too small to detect any pattern at all, but if we follow that line of reasoning, most of the epidemiological studies ever published will have to be discarded. Notice instead that the Utah study focused only on childhood leukemia, that is, the population studied was less than 20 years old. Children are known to be more sensitive to radiation than adults, so doses that do not affect adults (especially healthy, working adults employed by the military) might still induce leukemia in children.

It is even more difficult to draw conclusions from the USSR and Marshall Islands studies. In the USSR fallout region, the control group had doses that were almost equal to that of the exposed group doses from the military studies, while the exposed group had doses many times higher than 100 mSv. In the Marshall Islands, the doses also spanned a wide range from 0 to over 6 Sv, and thyroid cancer was exceptionally high in both exposed and control subjects. No one questions that 6 Gy of acute, whole body dose can kill a person, and that even 0.6 Gy is much more dangerous than 0.1 Gy, so perhaps it is most surprising that the last two studies in Table 3 did not show a clearer dose-risk relation. Altogether, these A-bomb fallout studies do not provide conclusive evidence for any one hypothesis.

4. Exposures From the Chernobyl Accident

Another heavily studied population is the residents of Ukraine, Russia, and Belarus who were affected by radiation fallout from the Chernobyl power station explosion in Ukraine in 1986. The radioisotopes released were mostly I-131 and Cs-137, and the most commonly studied outcomes are childhood thyroid cancer and leukemia. Three major populations have been scrutinized: residents of contaminated areas who were not evacuated, residents who were evacuated, and cleanup workers (commonly called liquidators). Table 4 shows only shows a few of the dozens of studies carried out in response to the Chernobyl accident, but it is enough to show that the incidence of childhood thyroid cancer has been greatly elevated in this region and follows a clear linear response. Even though the sample sizes of each study are rather small, a significant excess risk is hard to dispute because so many studies have been performed on children this region with the same linear results. 5000 cases (15 fatalities) of childhood thyroid cancer have been reported between 1986-2002 [38-39].

However, a number of factors may cause the calculated ERR to be higher than the actual ERR. First, the children in the Chernobyl studies received more thorough healthcare scrutiny than the rest of Russia and Ukraine, so there were probably more thyroid cancers diagnosed for this population relative to the baseline rates for the rest of the country. Secondly, if the children were suffering from iodine deficiency at the time of the accident, they would have been more vulnerable to thyroid cancer [38]. It is also hard to prove whether the thyroid dose response has a threshold, because many of the doses involved were much higher than 100 mSv, and in addition, most of the doses are only rough estimates based on where the children lived and whether or not they drank contaminated milk. Thus, while the studies do show that the primarily I-131 Chernobyl fallout did increase the risk in childhood thyroid cancer, there is not information to give a quantitative relationship at low doses, or even to say whether the observed response holds at doses below 100 mSv.

Table 4. Epidemiology Studies For Acute Exposures from the Chernobyl Accident

Study Description	Doses Involved	Number of Subjects	Findings	Hypothesis Supported	Sources
Children in Belarus	mean 535 mSv, median 848 mSv	107 cases, 214 controls	Significant dose response for childhood thyroid cancer	LNT	Astakhova 1998 [40], cited in Cardis 2006
Children in Bryansk, Russia	median exposed 555 mSv, median control 120 mSv	26 cases, 52 controls	Significant dose response for childhood thyroid cancer	LNT	Davis 2004a [41], cited in BEIR VII & Cardis 2006
Children from Belarus and Russia	median 365 mSv in Belarus, 40 mSv in Russia	276 cases, 1300 controls	Significant dose response for childhood thyroid cancer at doses > 1 Gy, ERR 4.5-7.4/Gy	LNT	Cardis 2005 [39], cited in Cardis 2006
Children in Belarus and the Ukraine	95% intervals Belarus: 25-1110 mSv; Ukraine: 14-330 mSv	1000 cases, population 1.6 million children	Significant dose response for childhood thyroid cancer, ERR 18.9/Gy	LNT	Jacob 2006 [42], cited in Cardis 2006
Adults in Bryansk, Russia	26 mGy (based on Cardis 2006)	1051 cases from a population of about 1 million	Excess of thyroid cancers but no association with dose	threshold	Ivanov 2003 [43], cited in BEIR VII, Cardis 2006
Estonian and Latvian liquidators	mean 109 mSv, median 96 mSv	10,000 male workers	7 thyroid cancers and 7 leukemia cases; no association of dose to any cancer type	threshold	Rahu 2006 [44], cited in Cardis 2006
Russian liquidators	approx mean 100 mSv (from Cardis 2006)	99,000 male workers	Significant excess of thyroid cancers but no association to dose	inconclusive	Ivanov 2002 [45], cited in Cardis 2006
Children in the Ukraine	mean 4.5 mSv, max 101 mSv	98 cases, 151 controls	Significant leukemia risk and radiation dose response in males	LNT	Noshchenko 2002 [46], cited in Cardis 2006

In contrast to the ERR seen for childhood thyroid cancer, the impact of Chernobyl on childhood leukemia, other childhood cancers, and on adult cancers is less certain. One of the only useful studies is the one of children in Ukraine by Noshchenko, which involves doses of less than 100 mSv and shows a linear relation between childhood leukemia and dose. The fact that it is a case-control study makes it more reliable, but there are only 98 cases in the study, and the relation has not been supported by other case-control studies [38]. Thus, the connection between Chernobyl and childhood leukemia is weaker than the observed connection between the atomic bombs and leukemia in Japan.

Finally, very few studies have been performed on adult populations, and, like the three studies listed in Table 4 demonstrate, most of them have not found any significant dose response or increase in cancers. Whether for adult thyroid cancer, adult leukemia, or any other adult cancers,

the studies conducted around Chernobyl are inconclusive. In conclusion, the data from Chernobyl points to a linear dose relation for childhood thyroid cancer, but only at doses generally higher than 100 mSv, and does not offer strong support for increased risk of any other types of cancer incidence or mortality.

5. Exposures from Plutonium Production Facilities

Two other nuclear facility exposures which have received some scrutiny are releases from the Mayak plutonium production facility, which is along the Techa River in the southern Ural Mountains of Russia, and a release from the Hanford production facility in Washington state in the U.S. In the Mayak case, over 25,000 residents were exposed to external γ-radiation as well as radionuclides discharged into the Techa River from the Mayak plutonium production facility in the 1950s. The Hanford site had similar doses. As seen in Table 5, the cohort near the Mayak facility showed mixed dose responses for thyroid and other cancers, with the strongest effect being a 3-4 times increased risk in thyroid cancer, but also a study that supports hormesis. Conversely, a study around a plutonium production plant in the U.S. found no excess of thyroid cancer, benign thyroid nodules, total neoplasia, any thyroid nodules, autoimmune thyroiditis, and hypothyroidism. Thus, the Hanford study supports a model of little to no risk for thyroid diseases from low doses of radiation, which the authors suggest might result from the lessened effects of protracted exposure to low doses. [14, p. 213] [49].

Table 5. Epidemiology Studies For Acute Exposures from Plutonium Production Plants

Study Description	Doses Involved	Number of Subjects	Findings	Hypothesis Supported	Sources
Residents exposed to radioactive discharges from the Mayak facility	median 7 mSv soft tissue, 253 mSv bone marrow	25,000 residents	Excess risks for thyroid cancer (ERR 3-4), leukemia, cancer mortality, solid tumors; lung, stomach, and esophagus cancers	LNT	Kossenko 1996 [47]
Residents exposed to radioactive discharges from the Mayak facility	mean 155 mSv, range 5-496 mSv	7800 residents	cancer mortality lower in exposed than unexposed residents at <500 mSv	Threshold or hormesis	Kostyuchenko 1994 [48]
Residents exposed to radioactive discharges from the Hanford facility	median 97 mSv, mean 174 mSv	3,400 people born in the region	no increase in thyroid cancer or other thyroid diseases	threshold	Davis 2004b [49]

6. Medical Exposure Studies

Medical procedures now account for about half of a U.S. resident's annual exposure to ionizing radiation, so it is becomingly increasingly important to be able to quantify the risks associated with basic X-rays, CT scans, PET scans, and radiotherapy. As shown in Table 6, studies like the prenatal X-ray study supports an LNT or even superlinearity cancer risk for *in utero* exposures, but others such as the fluoroscopy and Thorotrast studies show no dose-related increase in cancers, and therefore support a threshold-type model for low levels of radiation. Some of the

Table 6. Epidemiology Studies For Medical Radiation Exposures

Study Description	Doses Involved	Number of Subjects	Findings	Hypothesis Supported	Sources
Children in Britain exposed to prenatal X-rays	mean 2-4.6 mSv per film, 6 mSv per fetus	7,600 children exposed *in utero*, 7,600 controls	Increased risk of cancer mortality with prenatal X-ray exposure	LNT	Mole 1990 [50]
Fluoroscopy-treated tuberculosis patients in Canada	mean dose to lung: 1.02 mSv	64,000 patients: 39% exposed, rest were controls	No excess lung cancer mortality in exposed vs. Canadian general population	threshold	Howe 1995 [51]
Fluoroscopy-treated female tuberculosis patients in Canada	0-690 mSv	32,000 patients	No excess breast cancer mortality in exposed vs. Canadian general population, decreased risk from 100-290 mSv	threshold / hormesis	Miller 1989 [53], cited in Kauffman 2003 [52]
Fluoroscopy-treated tuberculosis patients in Massachusetts	840 mSv	6,200 exposed, 7,100 patients treated without radiation	No dose response for lung cancer, total cancer, or leukemia deaths; cancer deaths less in exposed group	threshold or hormesis	Davis F 1989 [54]
Female fluoroscopy-treated tuberculosis patients in Massachusetts	mean breast dose 790 mSv, range 1-6400 mSv	2,500 exposed women	Excess cancers observed; linear dose-response for breast cancer	LNT	Boise 1991 [55]
U.S. scoliosis females <20 years old who had many diagnostic X-rays	mean 108 mSv for 25 exposures	5,400 patients	Significantly increased risk of breast cancer, 77 cases where 46 expected, RR 1.6	LNT	Doody 2000 [56]
Children who received fractionated irradiation of the scalp	mean 62 mSv, range 40-70 mSv	10,000 patients, 15,000 controls	Significant increase in thyroid cancer risk	LNT	Ron 1989 [57]
Patients treated for non-Hodgkin's lymphoma using radiation	unknown	unknown	9 year survival of irradiated group much higher (84%) than of non-irradiated control group (50%)	hormesis but inconclusive	Sakamoto 1997 [58]

studies even found a lower morality rate among the exposed subjects compared to their control groups, which may support a hormesis effect at low, fractionated exposures.

Care should be taken in interpreting the data from medical exposures, since the subjects who are being treated have some sort of pre existing health conditions, so their responses may not always parallel that of the normal population. In particular, it is known that radiation therapy can increase the lifespan of cancer patients. This should not be taken to suggest that irradiation of a person without cancer would necessarily increase their lifespan as well. Also, dose estimates are often uncertain since records were not always kept for patients before the 1980's, and were often reconstructed based on interviews or questionnaires. Finally, the strongest LNT-supporting studies were generally for breast cancer or children, two groups which seem to be more sensitive to irradiation, while adult lung cancer and other health endpoints show no significant increases over the control populations. Since medical irradiation procedures (with the exception of total-body irradiation treatment for lymphoma in the Sakamoto study) tend to focus on specific parts

of the body, these results also highlight the variations in responses from different organs and the need for caution in generalizing from a specific cancer to whole-body effects.

7. Chronic, Elevated Background Studies

Protracted, elevated exposure to radiation can also come from living in homes with unusually high levels of radon or from living in HNBR areas. Increased background radiation can also come from proximity to nuclear power plants, even though the radiation released from these plants to their surroundings under normal circumstances is less than 0.00001 mSv/year, many thousands of times less than the natural background dose of 2.4 mSv [5]. However, since leukemia clusters in the vicinity of nuclear facilities tend to receive a lot of media coverage, they will also be examined here.

First, the correlation between radon exposure in homes and lung cancer was first studied in a controversial study by Cohen, who found a negative correlation between lung cancer mortality and radon level. The doses involved in these studies are difficult to pinpoint because radon levels vary greatly from house to house and also by season and location within a house, but a yearly average can be found by leaving detectors inside each home for extended periods of time [59]. Effective doses can then be estimated based on the ICRP's association of one year of breathing air at 300 Bq/m3 with 5 mSv of internal dose [60].

Table 7. Risk from Elevated Radon Exposure in Houses

Population Studied	Doses Involved	# of Subjects	Findings	Hypothesis Supported	Sources
Children in Great Britain homes with high indoor radon	unknown	6091 children	No association of home radon levels with childhood leukemia	threshold	Richardson 1995 [61], cited in BEIR VII
Homes in 1729 U.S. counties	18-110 Bq/m3	not listed	Negative correlation between lung cancer and radon exposure	hormesis	Cohen 2002 [28], cited in Kauffman 2003
Residents of Taipei apartments with elevated radon doses	4.8 mSv in first year, 330 mSv in 16 years	10,000 occupants	Fewer cancers and leukemias than Taiwan national average	hormesis	Luan 1999 [62]
Pooled 7 studies of U.S. and Canada residents	25-131 Bq/m3	3600 cases; 5000 controls	RR for lung cancer was 1.11 per 100 Bq/m3	LNT	Krewski 2005 [63]
Europe	weighted mean 97 Bq/m3	7000 cases; 14000 controls	RR for lung cancer was 1.08 per 100 Bq/m3	LNT	Darby 2006 [59]

As seen in Table 7, Cohen's study of radon exposure in U.S. homes supports a hormesis hypothesis while pooled studies of North American and European homes support LNT. The EPA and WHO accept the pooled studies from North America and Europe as conclusive evidence that indoor radon levels will cause lung cancer. But although efforts have been made to account for

smoking, the lung cancer risk from smoking is much higher than than the risk from radon inhalation, making low dose trends difficult to distinguish. Also, epidemiology standards are inconsistent across studies. The doses associated with lung cancers are all less than 5 mSv on average, while "exposed" survivors in the LSS and many other studies all experienced more than 5 mSv of whole-body dose and survivors receiving less than 5 mSv were used as controls. Why should the subjects in Table 7 now be treated as the exposed group instead of contributing to a baseline estimate? Finally, aside from lung cancer, no consistent risk has been detected between elevated radon concentration and any other cancers. [60] so everyone at least agrees that if indoor radon is harmful, it contributes only to the risk of lung cancer and no other solid cancers.

Studies have also been conducted on areas of the world with high natural background radiation (HNBR) levels. The highest known radiation levels are found in Ramsar, Iran; Guarapari, Brazil; Kerala, India; and Yangjiang, China. In the region of Ramsar, Iran, doses reach up to 260 mSv/ year, about the same as what is being detected in some regions of Fukushima. Not many studies have been conducted in the HNBR regions, and they are difficult to conduct in part because cancer registries are nonexistent or very recently started, but a sample of ones that have been published are summarized in Table 8. [60]. As this table shows, no excess cases have been detected in any of these four regions compared to the lower background regions nearby, except possibly for women in the region of Ramsar, Iran.

Table 8. Risk in High Natural Background Radiation (HNBR) Areas

Population Studied	Doses Involved	# of Subjects	Findings	Hypothesis Supported	Sources
Residents of Pocos de Caldas, Araxa, and Guarapari in Brazil	< 7 mSv	6000, 1300, and 12000 in HNBR area	increased cancer mortality for Pocos and Araxa cities compared to the rest of their state, but HNBR regions alone not studied	inconclusive	Hendry 2009 [60]
Residents of Yangjiang, China	average 6.4 mSv/ year	100,000 people followed over 19 years	557 cancer deaths, no increased relative risk	threshold	Tao [29]
Residents of Kerala, India	average 6.9 mSv/ year	360,000 residents, cancer registry from 1990-2001	no significant relation between total cancer mortality and dose	threshold	Nair 1999 [64]
Residents of Kerala, India	average 6.9 mSv/ year	205 lung cancer cases, 615 controls	increased risk only above 10 mSv external dose (internal doses unknown)	threshold	Hendry 2009 [60]
Residents of Ramsar, Iran	average 6 mSv external, 2.5-72 internal	3000 high dose subjects, 7000 low dose subjects	increased risk compared to national rates for women only (lack of cancer registry & only 4 year follow up)	LNT / inconclusive	Hendry 2009 [60]

A third source of background radiation is nuclear power plants. There have been several "leukemia clusters" observed near specific nuclear power plant or processing sites in Europe. These sites include the village of Seascale near the Sellafield nuclear reprocessing plant in Great

Britain, the 25km vicinity around the Dounreay nuclear reprocessing plant in Scotland, near the Krummel nuclear power station in Germany, and near the La Hague reprocessing plant in France, as summarized in Table 9. These leukemia clusters are sometimes cited as proof that very low level radiation is even more dangerous than what the LNT model predicts. However, as seen in Table 9, further studies on leukemia clusters, usually involving larger populations, have found no patterns of increased risk near nuclear facilities as a whole, and some clusters have also been found in regions which have no nuclear facility nearby. Many other studies, which are referenced in chapter nine of the BEIR VII report and in Laurier 2001, also indicate that while leukemia clusters do exist, they seem to have to correlation to radiation dose [65].

Table 9. Risk Near Nuclear Facilities

Study Description	Doses Involved	Number of Subjects	Findings	Hypothesis Supported	Sources
Children living near Sellafield, England	<0.001 mSv/year	411	4 lymphoid incidences, 4 leukemia mortalities	supralinearity	Black 1983 [66], cited in Rubery 1985 [67]
Children living near Sellafield, England	<0.001 mSv/year	52 cases of childhood leukemia, 1001 controls	Possible childhood leukemia risk connected to fathers' exposures of >100 mSv prior to conception	supralinearity	Laurier 2001[65]
Children in England and Wales	<0.001 mSv/year	11,000 cases of leukemia and non-Hodgkin's lymphoma	No relation between leukemia or NHL incidence and proximity to nuclear facilities except at Sellafield	inconclusive	Bithell 1994 [68]
Children living near Dounreay, Scotland	<0.001 mSv/year	estimated population 3500	9 cases of lymphoma or leukemia where 4.5 were expected	supralinearity	Sharp 1996 [69]
Children living near 7 nuclear facility locations in Scotland	<0.001 mSv/year	estimated population 355,000	Incidence of lymphoma and leukemia not higher than expected	threshold	Sharp 1996 [69]
Children living near Krummel, Germany	<0.001 mSv/year	population not given; equaled 29,000 person years	6 cases of childhood leukemia within 5km	supralinearity	Hoffman 1997 [70]
Children living near La Hague, France	<0.001 mSv/year	1.3 million children in the region	38 cases of leukemia within 10 km	supralinearity	Guizard 2001 [71]

Thus, studies of populations living in high background areas have been used to argue for hormesis, threshold, LNT, or even supra-linearity relations between cancer rates and low doses of radiation. At the same time, all of the above studies have also been criticized by opponents of these views for being ecological studies, meaning that the population of a region is studied as a whole without accounting for individual variations like migration in and out of the area of study, that individual doses were often not estimated, and that there was no control population with which to compare the data. As Tables 7-9 show, the sample sizes also tend to be small and

follow-up times for the HNBR areas have been short. More importantly, studies of similar sizes and follow-up times have reached differ conclusions, so no one model stands out above the others.

8. Radiation Worker Studies

Workers who are exposed to radiation in their occupations are another popular group for radiation health studies, but again most studies conducted so far have been limited in scope. Occupations where workers are routinely exposed to radiation include radium dial painters, nuclear power plant workers, uranium miners, U.S. Navy shipyard workers, radiologists and dentists, and airline attendants and pilots. The studies, summarized in Table 10, point to everything from beneficial effects to extreme danger, making them once again difficult to interpret.

Table 10. Epidemiology Studies For Occupational Nuclear Exposures

Study Description	Doses Involved	Number of Subjects	Findings	Hypothesis Supported	Sources
3 country study of nuclear workers in the U.S., Canada, and U.K.	mean 40 mSv	95,000 radiation workers	Significantly increased risk for leukemia mortality	LNT	cited in Brenner 2003 [17]
3 country study of nuclear workers in the U.S., Canada, and U.K.	mean 40 mSv	95,000 radiation workers	No increased risk for overall mortality or solid cancer mortality; dose rate relationship for leukemia mortality at > 400 mGy	threshold	cited in Cohen 2002 [28]
UK radiation workers	mean 30 mSv	120,000 radiation workers	significantly increased risk for leukemia, not for solid cancers	LNT for leukemia, threshold for solid cancers	Gilbert 2001 [72]
Canadian radiation workers	mean 6.6 mSv	190,000 radiation workers	Excess solid cancer incidence and leukemia incidence	LNT	Sont 2000 [73]; cited in Brenner 2003, Gilbert 2001
Canadian radiation workers	mean 6.3 mSv	200,000 radiation workers	Excess solid cancer mortality, not for leukemia mortality	LNT for solid cancers, threshold for leukemia	Ashmore 1998 [74]; cited in Brenner 2003, Gilbert 2001
U.S. Navy Shipyard Workers	high dose >0.5 mSv	28,000 high dose (9000 >5 mGy, 19,000 0.5-5 mGy), 10,000 low dose, and 32,000 unexposed workers	Cancer and overall mortality in high dose workers less than in low dose or unexposed	hormesis	Sponsler 1995 [75]
Radium dial workers	0-300 mSv	820 female workers	No excess bone cancers above 10 Gy, linearly increased risk above 20 Gy	threshold	Carnes 1997 [76]

Table 10. Epidemiology Studies For Occupational Nuclear Exposures

Study Description	Doses Involved	Number of Subjects	Findings	Hypothesis Supported	Sources
Accidental plutonium inhalation	unknown	14,000 workers	Lung cancer mortality lower than non-exposed workers	Threshold/ hormesis	Omar 1998 [77]
British radiologists since 1954	5-50 mSv/year	2,700 radiologists who registered with a radiological society from 1897-1979	Lower cancer and overall mortality rates than other male medical practitioners	hormesis	Berrington 2001 [78], cited in Kauffman 2003 [52], Duport 2003 [79]
Uranium miners	unknown	64,000 miners	Excess of lung cancers in miners, but no excess of other cancers	LNT in lung only	cited in Duport 2003 [79]

One caveat that is specific to occupational exposures is the "healthy worker effect," where workers who are able to hold the jobs involving radiation exposures are probably healthier than the regional average, so their mortality and cancer rates are expected to be somewhat lower than non-workers. In most of the studies listed above, therefore, control groups were drawn from the same group of workers - for instance, navy shipyard workers exposed to high doses were compared to other shipyard workers who received zero or very low doses; and male British radiologists were compared to male British physicians in other specialties. Some studies involved smaller cohorts than others, but at least a few involved over 10,000 or even over 62,000 people, adding to their statistical power.

9. Conclusions from Epidemiology

In conclusion, epidemiological studies have been claimed to support everything from supralinearity to hormesis at low doses. The largest and most studied cohort, the LSS, forms the basis for most LNT-based risk estimates for solid cancers and leukemia. However, even the LSS itself has sometimes been claimed to support threshold and supra-linearity models at low doses. Other studies of acute exposures, such as from atomic bomb testing, show no relationships between dose and cancer risk, supporting a threshold model, while the exposures from the Mayak and Hanford plants support LNT and a threshold, respectively. The studies following Chernobyl point towards an increased risk for childhood thyroid cancer with large doses of radiation but not for adult cancers. Medical exposure studies are controversial, some arguing for LNT and others for a threshold. There is also no doubt that radiation therapy can extend the lifetime of cancer patients, but whether this supports a hormesis response for the general population is less obvious. Chronic, elevated home radon studies indicate either LNT or hormesis for lung cancer; high natural background areas suggest a threshold; and leukemia clusters near power plants are cited to support supralinearity. Finally, the host of occupational radiation exposures is just as inconclusive, with some studies proving LNT "with significance" while others deny the linear response with equal significance. Unfortunately, the contradictory conclusions of present studies suggests that epidemiology by itself will never be able to resolve

the low-dose response models with certainty. No matter what new data emerges or which hypothesis it supports, opponents of that hypothesis will immediately cite past studies that disagree with its conclusions.

Everyone on earth is exposed to an average dose of 2.4 mSv a year, so trying to find effects below that dose using epidemiological studies is very difficult. In case-control studies, since it is impossible to find subjects who have not been exposed to any radiation, the subjects used as controls are usually those with doses below a certain level. The LSS, for example, uses survivors who received less than 5 mSv acute dose as its controls, while the study of U.S. Shipyard workers used 0.5 mSv of occupational exposure (that is, 0.5 mSv above background) for controls. In almost every epidemiological study except those specifically studying HNBR areas, background doses are virtually ignored because they are too variable and difficult to account for. However, since the exposure dose is often not much higher than background, it is difficult to know how much of the observed trends actually come from the "excess" radiation doses - or even where the cutoff for background radiation should be.

Epidemiological studies have had their uses. The follow up from the LSS, Chernobyl, and other acute exposures have shown that radiation has deleterious effects at high doses, and that cancer induction seems to follow linear and linear quadratic relationships at high doses. However, in regards to low doses, the data is contradictory. Certain cancers, such as lung cancer after radon exposure or childhood thyroid cancer after I-131 exposure, seem to be more sensitive to low dose radiation, but the data for adult leukemia, for instance, are still unclear. The best that the epidemiological data have been able to do is really to define where the low dose region exists: 0-100 mSv for whole-body at acute doses, and perhaps higher at protracted doses. As seen in the studies above, there is extensive support both for and against LNT. But because epidemiological studies are limited in their sensitivity to such low risk rates, the answer to these responses should probably be sought using more sensitive methods, such as laboratory studies.

III. *In Vitro* Cellular Studies

1. Introduction to Cellular Studies

In vitro studies allow cellular responses to be observed in a controlled environment with minimal confounding factors. However, cells grown in single layer cultures differ from cells found *in vivo* because they are usually flatter, belong to immortal cells lines, and divide while most body cells do not. There is also a lot of confusion over what endpoint an experiment should measure: micronuclei, cessation of cell division, cell death, formation of cell repair centers, chromosome translocations, double strand breaks, chromosome dicentrics, chromosome translocations, HPRT mutations, and malignant transformations. Of these, the endpoints most important in tumor formation are believed to be DNA double strand breaks (DSBs), which can be produced by ionizing radiation, by exposure to other carcinogens, or just by mistakes in normal cell replication, and if they are not repaired properly, may result in carcinogenesis [80].

Do any of these effects correspond proportionally to tumor formation? It is hard to know. The BEIR report claims that a linear dose-response relationship exists from 20-200 mGy, and that a threshold, if any exists, must be below 20 mGy. Furthermore, if neighboring cells do not influence each others' responses, then at low doses any cell affected by radiation would probably receive only one electron track. As doses get lower, the number of cells experiencing a track gets less, but the likelihood of a DSB arising from each track remains the same. If each damaged cell is equally likely to lead to a tumor, then risk of cell damage decreases proportionally with dose.

However, the emerging picture of cell responses is not so simple. In place of the LNT single-track single-damage theory, in which every ionized particle has a chance of developing into its own tumor, the current model for cancer induction is a two-stage clonal model where damaged cells must survive and then replicate in order to develop into a tumor [81]. Because of cell repair and regulatory processes, 1 mGy dose of low LET radiation is associated with about 10-2 double strand breaks but only about 10-13 or 10-14 chance of developing into a lethal cancer [Feinendegen 2004]. Other phenomena that affect the growth of a cell into a tumor, include the adaptive response, hypersensitivity, induced radioresistance, dose-rate responses, fractionation, the bystander effect, genomic instability, and clastogenic factors. Each of these effects has been documented on its own and adds to the complexity of cell responses to radiation. As research continues to examine how these effects work together and which effects dominate in which situations, it is less and less obvious that a linear, no-threshold response gives the best description for the health effects of low-dose radiation.

The main effects which have been documented *in vitro* at low doses are listed in Table 11 and are discussed further in this section. Notice that they are all fairly recent discoveries: only in the past decade has technology allowed such detailed observations about cell behavior.

Table 11. Summary of Cellular Responses Observed at Low Radiation Doses

Effect	Definition	Hypothesis Supported	Representative Papers
Linear Damage	Observed DNA damage is proportional to dose	LNT	BEIR Table 2-1 [14]
Bystander Effect	Neighbors of unirradiated cells display radiation responses like translocations and death	Supralinearity - small doses cause more damage through bystander effect than LNT predicts	Schettino 2003 [82]; Morgan 2003 [83-84]
Adaptive Response	After a "priming dose," cells are more resistant to later trauma	Hormesis - small priming doses make cells more resistant to non-radiation-induced damage	Joiner 2001 [85]; Feinendegen 2004 [25]
HRS (Low dose hypersensitivity) & IRR (induced radioresistance)	U-shaped reactions to small acute doses: more cell death from 100-500 mGy, more resistance at 500-1000 mGy	Unclear, but challenges LNT assumption of constant risks at all doses	Schettino 2003; Joiner 2001; Rothkamm and Lobrich 2003 [86]
Dose rate & Inverse dose rate	U-shaped reactions to protracted, varying dose rate exposures	Unclear, but challenges LNT assumption of constant risks at all doses	Vilenchik Knudson 2000 [87]; Mitchell 2002 [88]
Dose Fractionation	Spreading out the dose delivery time by decreasing dose rate decreases accumulated damaged	Threshold, if the decrease in dose rate and thus risk gets low enough.	Yuhas 1974 [89], BEIR p. 76
Genomic Instability	Low doses cause latent effects where DNA is now more prone to mutation later	LNT or supralinearity - when small doses cause seemingly undetectable responses, latent cell damage is present	Morgan 2003; Prasad 2004 [18]

2. The Bystander Effect

The bystander effect refers to the way that neighbors of irradiated cells seem to display radiation responses even though they were not directly traversed by an ion. The effect is observed even at low doses, low LET doses. A review of the bystander effect by Morgan suggests that the radiation damaged cell can send a signal to its neighbors either via cell-to-cell junctions or secreted cytotoxic factors, causing DNA damage or cell death [83].

In one experiment, Schettino irradiated single cells on a plate using a microbeam and found that 10% of the cells on the plate died when 50 mGy was delivered. Clusters of damaged cells were found even where no radiation had passed through. Even when 2 Gy dose was delivered to a single cell, the cell mortality still remained at 10%. Then, when the entire plate was irradiated, a similar percentage of about 10% cell death was observed below 200 mGy. Above 200 mGy, the cell survival curves for whole-plate irradiation showed typical dose-dependent mortality rates. The results of the bystander phenomena have been interpreted to mean that a single radiation track can harm more than just the cell it traverses, thus providing support for a supralinearity response to low doses of radiation. Notice, however, that the bystander effect seems limited to cases of single cell irradiation and does not play a role when whole plate (or perhaps whole body) irradiation is involved.

3. The Adaptive Response

In opposition to the bystander response, the adaptive response seems to play a positive role in cell survival at low doses. This response takes hours to develop and can last for weeks or even months. For example, human lymphocytes and tissue culture cells were protected again induced chromosomal aberrations and micronuclei formation from about 4 hours to 3 days after being exposed to a low-LET priming dose [25]. In another case, a dose-rate of 20 mGy/hr was shown to change intracellular signaling and activate cellular defense against radiation without causing any DNA damage [27]. Adaptive response mechanisms include increased damage protection, increased damage repairs, damage removal by apoptosis, stimulation of the immune response, premature differentiation out of the cell cycle, decreased spontaneous cancers, and changes in gene expression. All these changes are prompted by exposure to 5-200 mGy of X- or γ-rays, with the peak response at 100 mGy, and they act to reduce the proportion of damaged DNA [25].

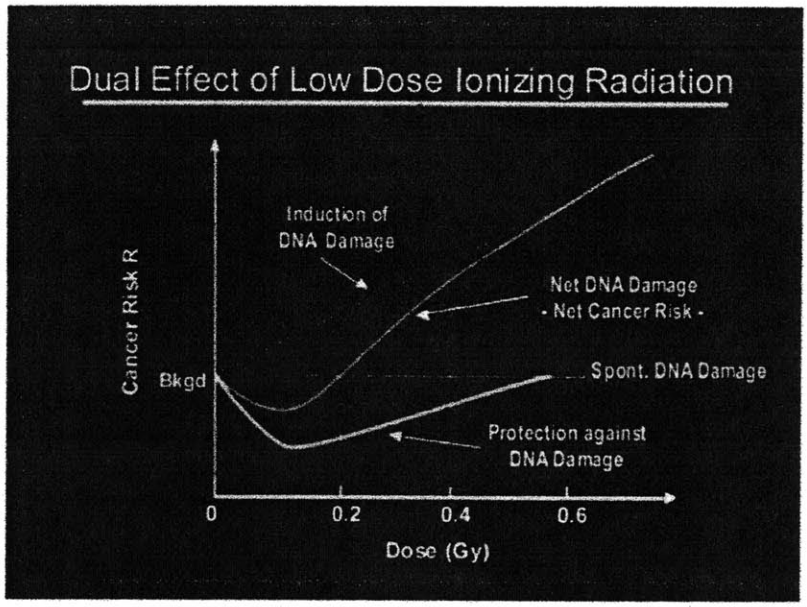

Figure 9. Model of Hormesis from the Adaptive Response. The dual effects of acute, low-dose radiation. Net cancer risk is the sum of the induced DNA damage and protective responses. Additional protection against damage through apoptosis not shown. Source: Feinendegen [25]

If the stimulation of DNA protection and repair after some amount of radiation damage is greater than the damage induced by the radiation, then the adaptive response may be able to not only counteract the induced damage, but even repair other endogenous DNA damage. As illustrated in Figure 9, the adaptive response may mean that a hormesis effect can be associated with low doses. However, there are also arguments that injuries like acute trauma and hyperthermia can also induce an "adaptive effect," and just because the body has such coping mechanisms does not mean that the initial trauma was a good thing [18].

4. Interaction Between Adaptive and Bystander Responses

The adaptive and bystander responses have each been studied separately. Adaptive responses are observed as protection from high doses of radiation after a 5-200 mGy priming dose of low-LET radiation, while bystander responses are seen in DNA damage of neighboring cells following single cell microbeam irradiation. An interesting question is how the two conflicting phenomena interact together. The BEIR report believes that dose-response from 20-100 mGy "is most likely to be linear and not affected significantly by either an adaptive or a bystander effect," but more recent evidence suggests that these phenomena can no longer be ignored when studying low dose responses. Perhaps the beneficial effects of the adaptive response are exactly cancelled out by the exacerbation caused by the bystander effect, but it seems unlikely that the two responses would negate each other so perfectly.

In one experiment designed to study the interaction of these effect, Zhou (2003) discovered that nonirradiated cells acquired mutations after being in direct contact with irradiated ones. However, if the cells were primed with 20 or 100 mGy of X-rays beforehand, the bystander effect was significantly decreased - in other words, the adaptive response here protected the cells from a bystander effect [90]. However, Prasad that some bystander cells showed increased radiosensitivity after exposure to X-rays [18], so the adaptive response seems to be absent there. While the literature once again presents conflicting results, it is perhaps worthwhile to note that the bystander effect is only observed when less than a small percentage of cells or only a single cell on a plate is irradiated, while the adaptive response is characteristic of whole-plate irradiation. Most radiation exposures involve doses to whole organs or the whole body, so perhaps in everyday encounters the adaptive response has a more dominant role.

5. Hyperradiosensitivity and Increased Radioresistance

Another pattern observed at low doses of radiation is low dose hyper-radiosensitivity and induced radioresistance (HRS and IRR). Hyper-radiosensitivity, or HRS, is demonstrated by the 10% cell death after whole plate irradiation in the same Schettino experiment which demonstrated the bystander response, but it is distinct from both the bystander and adaptive responses [85]. As illustrated using human glioma cells in Figure 10, the surviving fraction decreases rapidly with dose in the HRS region below 300-500 mGy. Then, in the IRR region from about 500-1000 mGy, the surviving fraction barely decreases at all before resuming a linear or linear-quadratic dose response above 1 Gy [85].

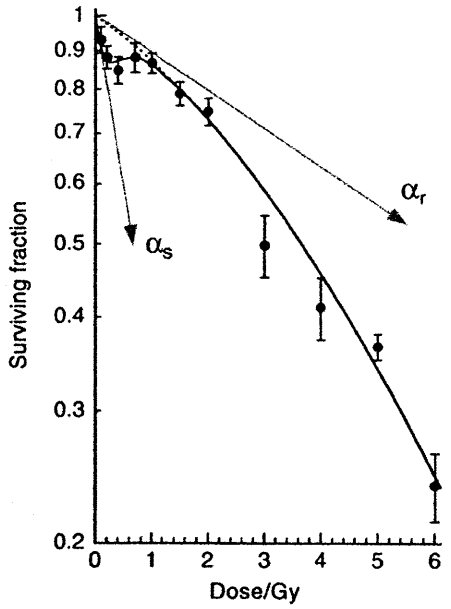

Figure 10. Example of Hyper-Radiosensitivity and Induced Radioresistance. Survival of asynchronous T98G human gloomy cells irradiated with 240 kVp X-rays. Each point is the mean of 10-12 measurements. Source: Joiner [85]

The HRS increase in cell death might indicate supralinearity, but then the IRR region following it could similarly be used to indicate a threshold response to increasing dose. Actually, a number of papers suggest that the HRS phenomenon works to prevent carcinogenesis by removing cells which have been irradiated and thus are likely to contain DSBs or other mutations. At higher doses, it is not sensible for the body to cause too many cell deaths, because then the overall mortality would be too high, but at lower doses, perhaps the number of damaged cells is low enough that the body prefers to induce cell deaths rather than potentially misrepair the damage and leave tumor cells alive. Meanwhile, the IRR region shows that cells are able to increase their repair rate up to a certain dose. Other caveats are that the HRS/IRR phenomenon is only seen for low-LET exposures, is not observed for every cell line, and may be related to the arrest of laboratory cells in the sensitive G2 phase, which does not occur for most quiescent body cells [14, p. 76]. Even a conservative interpretation of the HRS/IRR effect, though, points to variable resistance and cancer risks, not the straight line dose-response that is predicted by LNT theory.

6. Dose-Rate, Inverse-Dose-Rate, and Fractionation Responses

Cell responses have been shown to change with dose-rate as well as dose. As seen in Figure 11, the number of induced mutations per dose follows a U-shaped pattern as the dose rate increases. The increase of mutations per dose with increasing dose rate that is seen above 1 cGy (10 mGy) per minute is known as the dose-rate response, while the downward leading slope below 10 mGy/min is the "inverse dose-rate response". Minimum damage occurs from about 0.1 to 1.0

cGy/min, in a minimal mutability region [87]. Although the mechanisms for the dose-rate and

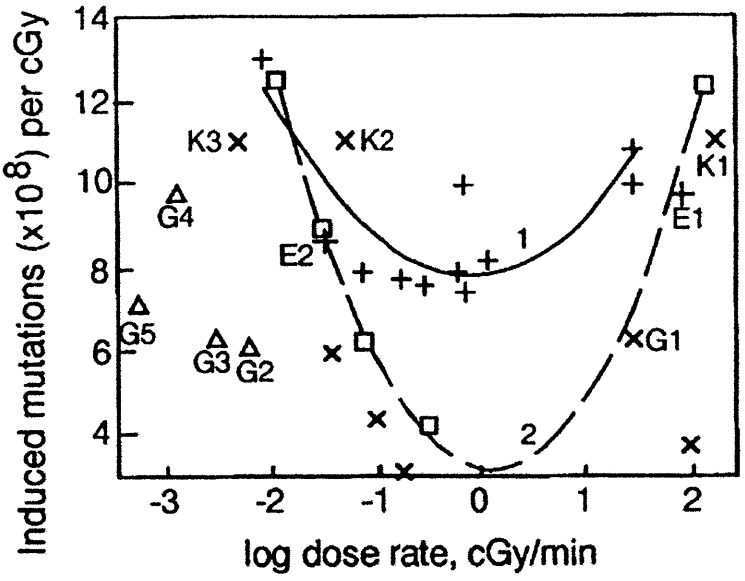

Figure 11. Example of U-Shaped Dose-Rate and Inverse Dose-Rate Effects. The points are compiled from many cell studies that measured the number of HPRT mutations induced at each dose-rate. The upper curve follows mouse L5178Y cells and the lower curve, Chinese hamster V-79 cells. Source: Vilenchik and Knudson [87]

inverse-dose-rate effects are not completely understood, they seem to be connected to cell cycle regulating genes. In the big picture, dose-rate effects have been observed for both mutations and cell killing [91], questioning the LNT assumption that carcinogenic risk is proportional to dose.

A related effect to dose-rate responses is fractionation kinetics. If a single dose of 2 Gy, for example, is split into two 1 Gy doses separated by a long period of time, will the overall effect on the cell be the same? Intuitively, the answer should be no: just as the heat from a radiator over many months will not hurt, but the same amount of heat concentrated into a single explosion can be deadly, radiation is more harmful in acute doses than protracted ones. Judging from the results of cell studies (without worrying about epidemiological evidence for the moment), repair seems to occur on the time scale of less than 24 hours [14]. This suggests that protracted doses which are accumulated over more than 1-2 days can be counted as separate doses in the effect they have on the body, and that risk estimates from accumulated background doses should be very different from the risk estimates for acute exposures.

7. Radiation-Induced Genomic Instability

Genomic instability refers to everything which contributes to the accumulation of mutations in cells, most notably chromosomal rearrangements. This instability can be measured in terms of chromosome aberrations, changes in ploidy, micronuclei formation, gene mutations and

amplifications, microsatellite instabilities, and decreased plating efficiency [83]. Whichever endpoint is used, the overall effect is that cells amass latent genetic problems, which might not be immediately obvious from just measuring double strand breaks or tumor formation, but which make them more sensitive to other carcinogens. As Prasad notes, X-ray irradiation in a cell enhances the amount of transformation caused by chemical carcinogens, UV radiation, ozone, viruses, and even caffeine [18]. This increases the indirect health risk from radiation, since exposure may cause humans to be more vulnerable to other cancer-causing sources.

Genomic instability also persists many generations after the original radiation exposure - even for up to 400 days! This suggests that its mechanisms might involve deficiencies in DNA repair, changes in gene expression, increase in reactive oxygen species, or perturbations to homeostasis within a cell. Furthermore, there is also a bystander component where signals from irradiated cells can cause genomic instability in cells not directly exposed [83]. All of these observations suggest some sort of supralinearity effect, where the actual risk incurred by a cell is not completely predicted by the LNT model, and they urge caution in assuming a threshold or hormesis response too easily.

8. Conclusions from *in vitro studies*

Unfortunately, there is no consensus on the low dose data from cellular studies, but our knowledge of cell damage and repair mechanisms is constantly growing. Some effects suggest increased danger above what LNT predicts at low doses: the bystander effect, genomic instability, and effects of carcinogens on irradiated cells fall into that category. On the other hand, the adaptive response and fractionation point to a decreased risk for low doses or low dose rates, while the HRS/IRR and dose-rate/inverse-dose-rate effects are less clear on what they support. Adding to the complexity are studies which demonstrate that effects vary depending on the cell line involved, and that seemingly deleterious mechanisms, such as cell killing, may actually act as protection against future cancer growth. Setting up experiments where multiple effects have the chance to come into play will allow further insight into how mechanisms all interact at low doses. In any case, it seems clear that the way to incorporate these effects into the preset risk models is not to discard them or assume that they cancel each other out.

IV. *In Vivo* Animal Studies

1. Introduction to Animal Studies

A intermediate step between epidemiological studies and mammalian cell studies is performing studies on animals, usually mice or rats, *in vivo*. These types of experiments have the advantage of being able to assign a control group and experimental group, and to perform experiments involving whole body or organ specific irradiation while controlling much more carefully for confounding variables. Animal studies also have an advantage over strictly *in vitro* cell studies because the cells are not all plated in a single layer culture, but organized into tissues and organs which interact with each other as they do in human bodies.

Cautions that should be taken in animal studies, on the other hand, are that their responses are not identical to human responses and are influenced by the animal's genetics, gender, and a whole-body response to the radiation. For example, thymic lymphoma is often studied in mice, but its induction process is complex and lacks a counterpart disease in humans [14]. Also, thymic lymphoma is studied in female RFM mice because they are more sensitive to induction of this lymphoma, while myeloid leukemia is studied in male CBA mice, and the observed responses vary widely depending on their genetics [84]. And of course, *in vivo* irradiated cells are now more difficult to image and are affected by responses of the immune system as well as other differentiated cells, making the outcomes much more complicated to detect.

2. Two Perspectives on the Same Data

Two thorough reviews of animal irradiation experiments can be found in BEIR VII [14] and the paper by Tanooka [27]. Interestingly, the papers cite many of the same studies and draw opposing conclusions from them, highlighting the the low-dose response debate's dependence on interpretation and perspective. BEIR tends to focus on the shape of the responses regardless of what radiation doses are involved, while Tanooka looks for a "non-tumor-inducing dose," which is defined as the "highest dose at which no statistically significant tumor increase was observed above the control level." Some representative studies are listed in Table 12.

Table 12. Comparison of Animal Studies on Radiation Dose Responses

Study Description	Study Author	BEIR VII Discussion	Tanooka 2002 Discussion
Myeloid leukemia in RFM mice induced by 250-3000 mGy γ rays	Uptown 1970	A quadratic, linear-quadratic, or simple linear dose-response all equally supported	Non-inducing tumor dose of 1.5 Gy for male mice, 2.5 Gy for females
Thymic lymphoma in RFM mice induced by 100-3000 mGy γ rays	Ullrich and Storer 1979c	Complicated dose-response with a large threshold	Non-inducing tumor dose of 0.1 Gy for acute exposure, 0.5 Gy for protracted

Table 12. Comparison of Animal Studies on Radiation Dose Responses

Study Description	Study Author	BEIR VII Discussion	Tanooka 2002 Discussion
Pituitary tumor in RFM mice induced by γ rays	Ullrich and Storer 1979b	Linear or linear-quadratic response	Non-inducing tumor dose of 0.1 Gy for acute exposure, 0.5 Gy for protracted
Harderian tumor in RFM mice induced by γ rays	Ullrich and Storer 1979b (or 1976 - Tanooka)	Linear or linear-quadratic response	Non-inducing tumor dose of 0.1 Gy
Lung adenocarcinoma in BALB/c mice induced by γ rays	Ullrich 1983	Linear response at low doses independent of exposure time	Non-inducing tumor dose of 0.1 Gy
Ovarian tumor in RFM mice induced by γ rays	Ullrich and Storer 1979b, 1979c	High sensitivity to low doses, but also threshold dose-response	Non-inducing tumor dose of 0.1 Gy for acute exposure, 0.5 Gy for protracted
Skin cancer in Sprague-Dawley CD rats induced by electrons or protons	Burns 1975, 1978	Clear threshold for tumorigenesis	Non-inducing tumor dose of 10 or 20 Gy for electrons, 0.75 Gy for protons
Latent effects of skin irradiation after exposure to a single 30 Gy dose of β rays	Hoshino and Tanooka 1975	supralinearity	Promotion with 4NQO 400 days after initial exposure resulted in 15% skin tumor incidence
Bone sarcomas in CF1 mice induced by Sr-90 β rays (injected)	Finkle 1959	threshold	Non-inducing tumor dose of 20 Gy

From these mice studies, it can be seen that the hypothesis which is supported depends on the way the data is interpreted. For some studies, such as thymic lymphoma and ovarian cancer, both BEIR and Tanooka agree that a threshold response is present. However, Tanooka interprets the thresholds to suggest a similar response for tumors in humans, while the BEIR report suggests that these two cancers are not appropriate models for understanding dose-response in humans because they are only indirectly caused by radiation and because cell killing plays a large part in the tumor formation. In other studies, the BEIR report focuses in the linearity of the dose-responses to support LNT, while Tanooka points out that these responses are only significant above a certain non-tumor-inducing dose. These two interpretations are not necessarily contradictory, but if the reasoning of both authors is logically sound, the data would ultimately support the threshold hypothesis.

Finally, both papers also acknowledge the latent effects of skin irradiation after a 30 Gy dose of β rays, but it is unclear what the implication would be for humans. On the one hand, latent carcinogenic effects add to the warning of the supralinearity or LNT models - even if low-dose radiation damage isn't immediately visible, they would say, cells have still been harmed. On the other hand, 30 Gy of acute exposure hardly qualifies as low dose! And since the active debate is over whether or not the linear relations observed at high doses can be extrapolated down to low doses, it is not immediately obvious that the observed latent effects can add much to the discussion.

3. Other Studies Challenging LNT

Besides the non-tumor-inducing doses calculated by Tanooka, two other reviews also challenge the LNT hypothesis for low doses. A review of the database of the International Centre for Low-Dose Radiation Research by Duport [79] and a second one on Radiation-Induced Genomic Instability and Bystander Effect *In Vivo,* Clastogenic Factors and Transgenerational Effects by [84] also present experimental evidence that is inconsistent with an LNT model. Some of the data is presented in Table 13. The doses involved here were higher than 100 mSv, suggesting that in mice, at least, a threshold for radiation damage may exist above 100 mSv. This threshold may be at a different dose range for humans, but if there is any parallel between murine cancers and the humans they are supposed to model, then all these evidences for a threshold in mice is strong evidence that a threshold may exist in humans as well. The evidences for hormesis should be taken with a grain of salt, though, because they involve irradiation of mice that are already prone to cancer. This is analogous to treating a cancer patient with radiotherapy - we know that the radiation treatment will help the patient live longer than they would live without treatment, but that does not mean the radiation would prevent or reduce the rate of oncogenesis.

Table 13. Animal Studies Challenging the LNT Hypothesis

Study Description	Findings	Hypothesis Supported	Sources
Review of ICLDRR; looked at 748 low dose experiment data sets	apparent reduction in cancer rate for mice exposed to 100-250 mGy γ	hormesis	Duport 2003 [79]
Review of ICLDRR; looked at 748 low dose experiment data sets	Lifespan of exposed animals exceeded lifespan of controls in 30-46% of cases	hormesis	Duport 2003
Review of ICLDRR; looked at 748 low dose experiment data sets	Mice with alveolar carcinoma exposed to 250 mGy neutron dose: exposed mice had greater mean survival than controls 41% of the time	hormesis	Maisin 1996 [92], cited in Duport 2003
Genomic Instability in Mice	No instability observed in CBA/H, C57BL/6 mice, or Swiss mice exposed to 3 Gy of X-rays.	threshold	Morgan 2003 [84]
Bystander Effects in Mice	*In vivo* bystander effects may be organ specific in scope, but literature support is weak	inconclusive	Morgan 2003
Abscopal Effects in Mice, Rats, Earthworms, and White Leghorn Cockerels.	Not enough information	inconclusive	Morgan 2003
Induction of Latent Clastogenic Factors in Mice	Not enough information	inconclusive	Morgan 2003

As Table 13 further shows, the field of animal irradiation studies has a lot of room to grow. Little is known about the cellular responses of *in vivo* irradiation on bystander effects, abscopal effects (responses in tissues definitely separate from the irradiated tissue) and latent effects from

clastogenic factors. Although these phenomena have been well documented *in vitro*, there is currently not enough evidence to judge whether animal models will display the same responses. Evidence for *in vivo* cellular effects would be an important middle step to bridge the gap between test tube observations and carcinogenesis in humans.

Many cell response patterns, such as the adaptive response, HRS/IRR, and genetic instability, have been observed in animal models as well. For instance, a single low dose irradiation of mice who were genetically predisposed to develop lymphoma and spinal osteosarcoma significantly delayed the onset of these cancers, similar to how the adaptive response increases the latent period of radiogenic cancers [Feinendegen]. The HRS/IRR effect was observed in rat thymocytes, where apoptosis was rare at low doses and then increased in frequency with dose. [Feinendegen] In support of genetic instability, Hoshino and Tanooka found that if mice were exposed to the tumor promoter 4NQO between 11 to 400 days after irradiation, the mice would develop skin tumors, although they would not have developed the tumors from radiation exposure alone. Through examples like these, the observations of varying dose responses made *in vitro* were confirmed in mice models.

4. Conclusions from *in vivo* Studies

A survey of animal data shows many studies which do not follow the LNT pattern, and more studies which follow a linear dose-response, but only at high doses. It may be that a threshold only appears to exist because many studies were not conducted for long enough for solid tumors to form, but there are also cases where the lifetimes of the irradiated animals exceed the lifetimes of the controls. The BEIR VII report argues that cancers exhibiting threshold responses, like thymic lyphoma, should not be extrapolated to humans because cell killing plays a role in their development, but that seems strange considering that cell killing also occurs in the human body and is thought to be involved in DNA damage protection. Mice are not people, but the existence of so many threshold responses in most animal studies gives good reason to question the use of no-threshold models for every type of cancer.

V. Analysis of Low Dose Rate Hypotheses

To be objective in a survey of low dose rate hypotheses, each perspective should be allowed to present its strongest possible cases based on the available scientific evidence, and then critiqued and allowed to respond to the raised objections. Unfortunately, a full review of each hypothesis would probably come to resemble the BEIR VII report in length and labor, so only a partial defense will be possible here, but every effort will be made to present each case in the best possible light.

1. Arguments for Supralinearity

The low dose supralinearity hypothesis says that small doses of radiation cause more damage per dose than larger doses, and therefore each additional dose of radiation is less harmful than the lower dose [19]. If supralinearity is true, then every radiation track is dangerous, the present risk requirements are not nearly stringent enough, and our daily radiation exposures should be reduced to as low as is humanly achievable.

The cellular basis for supra-linearity is primarily based on HRS, bystander response, and genetic instability, including interactions with carcinogens. For example, Rothkamm and Lobrich found HRS for cell mortality and cell repair from 500-1000 mSv. One cause might be that many cell repair responses need a certain threshold of radiation to be triggered, so low-dose-induced mutations tend to persist unnoticed by the cell. Also, the bystander effect and genetic instability tend to multiply the damage incurred from a small dose of radiation. Of these effects, the newest and most compelling reason to take supra-linearity seriously is the synergistic effects of radiation followed by exposure to other carcinogens. These genetic instability studies suggest that even though low dose radiation might not initiate cancer on its own, the induced radiation damage makes an organism more vulnerable to other tumor promoters. Also, the multiplicative effect of other carcinogens has been observed up to 400 days after irradiation [14, p. 76]. If these instabilities can last over a year, they are unlikely to be spontaneously repaired anytime afterwards, making them to some extent irreversible risks.

The supralinear relationship has also been seen in epidemiological studies, such as the concave downward trend in LSS data, the unexplainable leukemia clusters near some nuclear power plants, and the *in utero* irradiation studies connecting childhood cancer to diagnostic X-rays. The latter two studies involve extremely small doses of radiation: less than 0.001 mSv in the leukemia clusters [65] and less than 2.5 mSv for one *in utero* exposure [18]. If the leukemia clusters and childhood cancer mortalities do stem from these elevated radiation levels, then based on the number of deaths relative to exposure, the relative risk per dose of radiation is much greater than what would be predicted by LNT, and "no radiation doses can be considered completely safe" [18].

2. Cautions against Supralinearity

Although hyper-radiosensitivity is used in many papers as an argument for supralinearity, these arguments should be treated with caution because while HRS does entail increased cell killing, and the overall effect on the body is not necessarily harmful. After all, the death of damaged cells removes them from the cell cycle and assures that any mutations will not be passed on to future generations. The bystander response and genetic instability, on the other hand, do seem like worrisome patterns, and they should be further investigated to see if the *in vitro* observations are replicated in living organisms.

Although the LSS, leukemia clusters, and *in utero* exposures do seem to exhibit supralinear relationships, many other epidemiological studies do not. Regarding adult populations, leukemia clusters and *in utero* exposures are not very informative because both studied populations under 20 years old. There are many indications that children are more vulnerable to radiation harm than older populations [81] so it is possible that even their pattern of dose-response differs from that of the general population. Additionally, the LSS data is controversial in shape, as discussed earlier, and can appear linear or to have a threshold depending on how it is analyzed.

Even for childhood risks, leukemia clusters have not been observed around every nuclear plant, and they have also been observed in areas without power plants, suggesting that the clusters are caused by another factor. Also, the clusters tend to consist of very small groups - generally less than 10 cases - and larger, multi-site studies have not detected a trend of excess cases around power plants. The *in utero* studies have been criticized for relying on mothers' memories and using rough estimates for received doses, but the bigger problem is that they are not supported by a similar study of children exposed to radiation from Hiroshima either *in utero* or at very young ages [28]. In general, epidemiological studies are easy to criticize and difficult to defend, and the existence of studies that support every hypothesis (and other papers criticizing each of those studies) simply points to the unreliability of using only population studies to look at low dose risks. The hypotheses proposed by studies such as leukemia clusters or even the LSS are only informative as starting points for examining mechanisms on a cellular and mammalian model scale.

3. Arguments for Hormesis

The other extreme from supralinearity is hormesis, the hypothesis that low amounts of radiation have beneficial health effects. Arguments for hormesis center around some large-scale epidemiological studies and the evidence from animal irradiation experiments, but most notably the recent advances in knowledge of the adaptive response.

At a cellular level, the adaptive response makes a convincing case in support of hormesis. As discussed earlier, exposure to very low "priming" doses of radiation makes cells more resistant to higher doses later on. The priming triggers stimulation of immune responses and increase in DNA repair efficacy. These responses, in turn, more than compensate for the DNA damage

induced by the radiation dose, and thus lead to additional repair of endogenous DNA damage caused by reactive oxygen species or other non-radioactive carcinogens. [25] Adaptive responses have also been shown to increase the latent time between radiation exposure and carcinogenesis. If this latent period becomes longer than the human lifespan, then the risk of developing radiation-induced cancer effectively becomes zero.

Many animal and epidemiological studies also lend support to the hormesis argument. In 30-40% of animal experiments, for example, exposed animals had longer lifespans compared to unirradiated controls [79]. Since animal studies are very controlled for confounding variables - all the animals generally come from the same genetic strain - the high prevalence of increased lifetime cannot be easily attributed to factors other than the radiation. Hormesis was also observed in the large-scale epidemiological studies of lung cancer incidence compared to home radon levels; in residents of naturally high background areas in the U.S.; in residents of Taipei apartments with elevated radon levels; in Canadian fluoroscopy patients; in British radiologists; uranium miners; and in U.S. shipyard workers. [28, 52, 79]. In every one of these cases, which are presented in more detail in the previous section, the exposed population had a lower rate of cancer incidence or overall mortality than the control population did. Thus, the hormesis effect has been observed in both laboratory and epidemiological settings.

4. Cautions on Hormesis

Taken alone, the adaptive effect provides good *in vitro* evidence for a hormesis response. However, tissue insults like acute trauma and hyperthermia can also induce an adaptive effect, even though these injuries are not beneficial to humans. Rather, the adaptive responses here "simply reflect that cells have been exposed to injurious agents and that attempts are being made to repair some of the damage." [18]

Regarding animal data in support of hormesis, the increased lifespans have mostly been a result of fewer infectious diseases and lower non-cancer mortality, suggesting that low dose radiation stimulated the immune response in general rather than increased cell repair of DNA damage. However, even if there is not a decrease in cancer risk, there is also no observed increase in cancer risk, so the animal data still points to a threshold response over LNT. Finally, concerning the human data, the radon-exposure studies by Cohen have been criticized for his methodology of surveying, while the Taipei apartment residents and remaining studies are said to have too few subjects - generally less than 10,000 - to be conclusive. As before, the epidemiological studies presented here are compatible with a hormesis response, but contain too many uncertainties and confounding factors to *prove* hormesis. However, these epidemiological studies are useful as strong collaborative evidence for the adaptive responses observed *in vitro* and *in vivo*.

5. The Case for Linear No-Threshold

The LNT hypothesis for radiation dose-response is widely accepted and used in risk estimates today because it makes intuitive sense: each radiation track causes a certain amount of damage to

the cell. Each iota of damage then has a certain probability of developing into a malignancy, so increasing or decreasing the radiation dose simply changes the probability of developing a malignancy by a similar proportion. Despite the recent observations of non-linear effects such as adaptive and bystander responses, as long as "the rate limiting radiation damage step is a single cell process," the overall response will still be linear [17]. Cell studies have shown that acute and fractionated exposures of the same dose produce the same damage [Upton 1987, 14 p. 74] and that the frequency of chromosome translocations increase with increasing radiation dose starting as low as 20 mSv [14, p. 57].

LNT responses have also been observed in innumerable mice studies, specifically when looking at myelogenous lymphomas, pituitary tumors, Harderian gland tumors, lung tumors, and mammary gland tumors [Ullrich and Storer 1979]. In all these situations, as well as in the extensive LSS studies of solid tumor incidence compared to dose, a linear response is clearly observed with no evidence for a threshold. In fact, when the LSS data was tested for a threshold, "significant excess risk" was found in the range of 0-10 mSv and no threshold above 0 mSv could be detected [20, 30-31]. When combined with the increased risks found for childhood thyroid cancer after Chernobyl, for leukemia and other cancers in residents near the Mayak plutonium facility, for breast cancer in female fluoroscopy patients in Massachusetts, for breast cancer in scoliosis patients exposed to multiple diagnostic X-rays, for childhood cancer in British children exposed to prenatal X-rays, and other epidemiological studies, the support for LNT is non-trivial.

6. The Threshold Hypothesis

The hypothesis which competes most directly with LNT is the threshold hypothesis, which suggests that below a certain threshold dose, radiation imparts no observable harm on an organism. The threshold hypothesis is difficult to prove because it depends on negative evidence - if no increase in tumors are observed at a certain dose, then perhaps a threshold exists there. However, the human body is not defenseless against DNA damage. There are mechanisms at work within each cell to detect mistakes and other mechanisms to repair those mistakes. Even without radiation exposure, the cells work every day to repair the damage caused by UV light and other carcinogens, which is about 1 mutation per day. Since a radiation dose of 100 mSv is estimated to cause only 0.004 long-term mutations in a cell [28], this slight increase in mutations barely makes a difference compared to what human cells are already equipped to handle.

As cell studies become more sophisticated, evidence for a threshold type response has increased. Discoveries of the adaptive response, bystander response, HRS/IRR, and dose-rate/inverse dose-rate effects also imply that cellular repair of radiation damage is not constant at every dose. The adaptive response, in particular, shows that cells can achieve almost complete repair at low doses. Even if the adaptive effect does not result in significant hormesis, it can at least negate the effects of radiation, resulting in a threshold response. The HRS response, which occurs at doses below 200 mGy, also eliminates damaged cells - if mutated cells are completely eliminated, then there is no risk of cancer arising from those mutations. The effects of bystander and inverse dose-

rate effects are less positive, but as long as the compensatory repair from the adaptive and HRS responses outweigh the damage from these phenomena, as some studies suggest, then the overall, long-term effect will be no damage.

Epidemiology and animal studies which support the threshold response include: people exposed to atomic bomb testing; residents near the Hanford plutonium processing site; adults after the Chernobyl accident; fluoroscopy-treated tuberculosis patients in Canada and Massachusetts who were at risk for lung cancer; residents of naturally high background radiation areas in China, Iran, India, and Brazil; occupational nuclear industry workers; and a large proportion of animal studies. Radiation-induced sarcoma in human connective tissue is known to follow a threshold response because the cells are normally non-cycling and need to be stimulated into cycling to develop cancer [17]. The non-tumor-inducing doses, which have been calculated by Tanooka for many animal studies and even for leukemia in the LSS, present another line of argument for threshold. Even the BEIR report, which is a strong champion of LNT theory, admits that skin cancer, bone cancer, and thymic leukemia in mice all exhibit clearly threshold responses.

7. Threshold or No Threshold?

The evidence for LNT and threshold responses should be critiqued together, because pretty much any criticism of a no-threshold theory implies that a threshold exists, and vice versa. Proponents of the LNT argue that every track of ionizing radiation that traverses a cell causes a measurable amount of DNA damage, while proponents of a threshold retort that at some dose the incurred damage becomes so small or the cell repair is so thorough that the harm becomes negligible. On another level, supporters of LNT claim that every dose of radiation is associated with a measurable increase in a population's cancer risk, while supporters of a threshold claim that the increased risk at some dose becomes so low that it is not worth worrying about. As shown previously, support exists for both theories, and the LSS, many of the studies are equally compatible with both theories - it all depends on how the data are tested.

In some ways, no matter what the science ultimately says, the threshold theory is true. At some low dose, the damage done by ionizing radiation will become so small as to be virtually undetectable. In truth, the question is not whether or not a threshold exists, but *where* the threshold exists. Whether or not there is damage accruing in a single cell, at some point the probability of getting radiogenic cancer becomes so much smaller than the likelihood of getting cancer from any other source that it is simply not worth the resources needed to remove that risk. At an average background dose of 2.5 mSv/year, most people on earth have been exposed to 100 mSv of background radiation by the time they are 40 years old, yet very little is done about this background radiation. Why is this the case? Because somewhere in the analysis - whether consciously or unconsciously - people decided that the vast resources and inconvenience it would take to eliminate background radiation from our houses, air, ground, and food was simply not worth the potential benefits.

Even in the LSS, the source of most risk estimates in use today, there is implicit assumption of a threshold: the control group consists of survivors who were exposed to less than 5 mSv of acute radiation (in addition to background dose). Whether this 5 Sv is a threshold by scientific fact or merely human convenience, we treat it like a threshold. Similarly, the controls for U.S. A-bomb test workers had doses of less than 2.5 mSv, while some controls in the Chernobyl study had doses of 40-100 mSv! Meanwhile, other studies of lung radon exposure in homes, cancer fluoroscopy-treated tuberculosis patients, or HBNR area residents involved doses that are barely above 5 mSv themselves. These inconsistencies in defining controls vs. exposed populations further make risks difficult to calculate.

8. Risk Estimates and Why It Matters

Nevertheless, since the results of current risk estimates are the basis for all government-imposed limits, it is worth examining what these numbers mean. Radiation risk estimates use LNT models that vary by age at exposure, attained age, and sex, and also include a dose and dose rate effectiveness factor (DDREF) of 1.5 to partially account for the reduced risk at low doses. The BEIR VII [14] and UNSCEAR 2008 [16] reports both provide cancer risk estimates in terms of elevated relative risk per Sievert (ERR/Sv) and lifetime attributable risk (LAR). Some values for ERR, which is defined as the rate in exposed population divided by the rate in the unexposed population minus one, are listed in Table 14. The other measured of increased risk is LAR, which is defined as the estimated lifetime risk of cancer incidence or mortality, and some representative values are shown in Tables 15-16. The estimates for both ERR and LAR vary widely depending on sex, age at exposure, and organ at risk, so only a selected number of examples using solid cancer incidence are listed in the interest of space. Many more extensive tables for both incidence and mortality of solid cancers and leukemia are available in chapter 12 of the BEIR report.

It is unclear how to relate ERR and LAR estimates, since the ERR numbers seem to indicate much higher risks than the LAR. For instance, the higher LAR for solid cancer incidence in 30 year old females exposed to 100 mGy (100 mSv at low LET) is 1,065 cases out of 100,000 exposed people, or 10,650 cases / 100,000 exposures at 1 Sv. By definition, the ERR should then be (10,650+36,900)/100,000 / 36,900/100,000 - 1, which gives 0.289. However, the ERR listed by BEIR for a 30 year old female exposed at age 30 is somewhere between 0.42-0.63, depending on which reference is chosen. Most of the ERRs are similarly higher than their related LARs.

Table 14. ERR/Sv for incidence of all solid cancers

ERR	Description	Source
0.63	both sexes, without modifying factors for age at exposure or attained age	BEIR VII [14] p. 149, from Thomson 1994 [93]
0.48	both sexes, exposure at age 30 and attained age 70	BEIR p. 147, UNSCEAR 2006 [94]
0.33	males, exposure at age 30 and attained age 60, excluding thyroid and nonmelanoma skin cancers	BEIR p. 271

Table 14. ERR/Sv for incidence of all solid cancers

ERR	Description	Source
0.57	females, exposure at age 30 and attained age 60, excluding thyroid and nonmelanoma skin cancers	BEIR p. 271
0.78	both sexes, age at exposure <15 years	BEIR p. 301
0.63	both sexes, age at exposure 15-30 years	BEIR p. 301
0.42	both sexes, age at exposure 30-45 years	BEIR p. 301
0.43	both sexes, age at exposure 45-60 years	BEIR p. 301
1.7	both sexes, age at exposure 60+ years	BEIR p. 301

Table 15. LAR per 100,000 people for incidence of all solid cancers

LAR/baseline males	LAR/baseline females	Description	Source
800/45,500	1,300/36,900	excess cases from exposure to 100 mGy	BEIR VII p. 281, 291
970/45,500	1,410/36,900	excess cases from exposure to 100 mGy excluding thyroid and nonmelanoma skin cancer	BEIR VII p. 279
2,326/45,500	4,592/36,900	excess cases from exposure to 100 mGy at 0 years old	BEIR p. 311
602/45,500	1,002/36,900	excess cases from exposure to 100 mGy at 30 years old	BEIR p. 311
407/45,500	529/36,900	excess cases from exposure to 100 mGy at 60 years old	BEIR p. 311
554/45,500	968/36,900	excess cases from exposure to 1 mGy per year	BEIR p. 312
2,699/45,500	4,025/36,900	excess cases from exposure to 10 mGy per year from ages 18-64	BEIR p. 312

BEIR VII provides examples in Appendix 12D of how to apply LARs, assuming that risks scales linearly. Of course, some cancers have a greater mortality rate than others, and LAR alone cannot say whether the cancer will develop one year or forty years after exposure, but it gives a rough estimate of the risks predicted by LNT. If a 30 year old male living in the U.S. received a 10 mSv whole body dose of radiation, for instance, his excess risk of developing any solid cancer in his lifetime would be (10/100)*602 divided by 100,000 equals 0.000602, to use the higher LAR in Table 16. This is a risk of about 1 in 1,661.

Using the BEIR LNT numbers, the risks for all solid cancers are also greater than the risks for any cancer in any one organ, which might result from a localized accidental exposure or medical procedure. However, the baseline risk of solid tumor incidence in U.S. males is 45,500 cases per

100,000 people, or a 1 in 2.2 chance of developing (not necessarily dying from) cancer. If the additional risk of 10 mSv can be added to make 46,100 cases per 100,000 people, the new risk of solid tumor incidence is only 2.17 - a large risk, but not much larger than the baseline. Similarly, exposure to 10 mSv a year from ages 18-65 makes the risk for males 1 in 2.07 and for females 1 in 2.44 (compared to a baseline of 1 in 2.7). If solid cancer mortality is calculated instead of incidence, the baseline rates for males and females, respectively, are 1 in 4.5 and 1 in 5.7. These are higher than the likelihood of dying by cancer, which is 1 in 7 according to the National Safety Council fact sheet in 2008.

Table 16. LAR per 100,000 people for mortality of all solid cancers

LAR/baseline males	LAR/baseline females	Description	Source
410/22,100	610/17,500	excess deaths from exposure to 100 mGy, all ages	BEIR VII p. 281, 291
480/22,100	740/17,500	excess deaths from exposure to 100 mGy excluding thyroid and nonmelanoma skin cancer	BEIR VII p. 280
1,028/22,100	1,717/17,500	excess deaths from exposure to 100 mGy at 0 years old	BEIR p. 311
317/22,100	491/17,500	excess deaths from exposure to 100 mGy at 30 years old	BEIR p. 311
246/22,100	354/17,500	excess deaths from exposure to 100 mGy at 60 years old	BEIR p. 311
285/22,100	459/17,500	excess deaths from exposure to 1 mGy per year	BEIR p. 312
1,410/22,100	2,169/17,500	excess deaths from exposure to 10 mGy per year from ages 18-64	BEIR p. 312

All these risk estimates are based on an LNT analysis of the LSS. However, while a LNT model may assume that risk increases with every year, a threshold model would say that the human body is able to completely repair the damage from 100 mSv/year (0.0114 mSv/hr), or that the adaptive response makes the body resistant to any further damage at 100 mSv/year. According to the threshold theory, 10 mGy of exposure a year would be very different from 10 mGy of acute dose. If the body is able to repair cell damage from year to year, then the health effects of exposure to 10 mSv/year should be no different from the effects of exposure to 10 mSv ever. In such a case, even if the same LARs from the LSS are used, the increase risk would be at most 102.8 excess cases/100,000 newborn males or 1,717 excess cases/100,000 newborn females, resulting in total odds of 1 in 4.5 and 1 in 5.66, respectively - practically no different from the baseline risks! Thus, if a threshold existed at 100 mSv, the radiation risk estimates and safety regulations would need to be adjusted, and perhaps the resources that would be required to reduce annual radiation levels from 100 mSv to 1 mSv could be better used elsewhere.

9. Concluding Thoughts

A final thought on low-dose radiation involves the idea of consistency. Whether the LNT or threshold theory is true, or even supralinearity or hormesis, humans are often inconsistent in our treatment of perceived risks. Even though two situations may have similar risks, people will find one situation permissible and another unjustifiably dangerous. For radiation risks, doses to the public must be kept under 1 mSv/year, even though people living in Denver, CO are exposed to 1.7 mSv of cosmic radiation every year with no apparent health effects. Airline pilots and attendants are regularly exposed to at least 1-2 mSv of cosmic radiation a year, but they are not closely monitored for radiation dose. Additionally, no warnings are issued against taking a trip to HNBR regions of Brazil or India, even though the background doses there are 8-20 mSv above the background level of the U.S. and thus many times higher than the NRC regulations. Or consider a chest CT scan, which delivers 6.9 mSv per scan. If 6.9 mSv of acute radiation dose is permissible for someone at least once a year, why not 6.9 mSv of elevated background dose spread out throughout an entire year?

In April 2012, a year after the Fukushima accident, cleanup efforts are supposed to be happening wherever the radiation dose exceeds government regulations. Entire towns are still off limits because the annual dose from the ground is projected to be greater than 50 mSv[] or even 20 mSv [], leaving many people in the area homeless and jobless. But what if the threshold theory is true, and doses of up to 100 mSv/yr actually result in no detectable health risks? This would mean that people are being unnecessarily kept away and prevented from working on their farms for negligible health effects. Recall that the annual dose in some parts of Araxa, Brazil is higher than 20 mSv while the average dose examined in the three-country nuclear worker studies was 30-40 mSv/yr, and that these studies found no significant increase in solid cancers or leukemias from those doses. Animal and cell studies occasionally use doses as low as 100 mSv, but very few have looked for cell responses at dose rates as low as the 0.0057 mSv/hr that leads to 100 mSv/yr. The threshold theory, if true, would allow the current radiation risk estimates and thus regulations to relax substantially. Even if the LNT-based LARs are kept, as long as there is some amount of cellular repair throughout the year, then current radiation requirements are unnecessarily and perhaps wastefully stringent. Although the evidence does not "conclusively" prove that a threshold exists, existing studies also are not conclusive about a threshold *not* existing, and governments assume a LNT model instead of a threshold not because it is the more scientifically convincing, but because it is the more conservative estimate, so that they will not be blamed in case excess cancers are found.

The available data for low-dose radiation risks, though, is not definitive enough to cause a change in radiation regulations. Epidemiological studies are the most popularly cited support for any viewpoint, but low-dose radiation risks are almost impossible to detect at any significant level using population studies, and even if risks are detected, strictly speaking they can only show correlation between radiation dose and cancer, not causation. Since each of the four low-dose hypotheses are supported by at least a few papers with large sample sizes and that control confounding factors, epidemiology alone does not seem able to offer convincing evidence for

one low dose response above all the others. Epidemiological studies at low dose-rates also need huge populations over long periods of time in order to be statistically significant, and they have to control for confounding factors such as smoking, chemical carcinogens, and genetic trends. Since these studies are expensive, time-consuming, labor consuming, and yet associated with high uncertainties, perhaps they are not the most productive way to conduct further research on doses of less than 100 mSv.

Instead, studies looking at tumor incidence in animal models or at DNA damage and repair *in vitro* after low doses of irradiation may give a better idea of the true processes and effects of radiation. Animal studies so far suggest a threshold dose for cancer incidence and other health effects in mice, while cellular studies vary from bystander and genetic instability effects that support supra-linearity to adaptive responses that support hormesis. Altogether, recent studies present many challenged to the LNT model. The balance between these observed effects and the mechanisms by which they occur still need to be further clarified both *in vitro* and *in vivo*, and it seems that only research in this direction, rather than in large-scale epidemiological studies, will provide more clarity and insight into the health effects of low doses of radiation. The question of these effects is not merely academic, either. The residents of six Japanese prefectures have been evacuated from their homes and may have to stay away for the next decade because of annual doses of 20-50 mSv, which is equivalent to less than 0.006 mSv/hr. For their sakes, as well as for the sake of future populations who may be exposed to such accidents, the truth about low-dose radiation health effects still needs to be found.

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