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The Linear Non-Threshold Hypothesis-A Failed Concept

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Abstract

The linear non-threshold (LNT) hypothesis is based on the premise that the smallest amount of ionizing radiation produces a biological detriment. It implies that exposure to low-dose radiation be minimized. The LNT approach causes fear and anxiety regarding the beneficial use of radiation and radioactive materials. Contrary to its intended goal of protecting workers and the public, the LNT premise causes physical and economic harm by encouraging radiophobia.

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1. Introduction

The basis for radiation protection recommendations and limits assumes the validity of the linear-non-threshold hypothesis. Although there is considerable research that contradicts the LNT hypothesis, this model remains the basis for radiation protection regulations and assessments of radiation induced detriment [1][2][3][4].

The current radiation safety basis derived from the LNT hypothesis was introduced following the assertion of the linear dose dependence of leukemia in atomic bomb survivors and in mutations in drosophila. Both of these observations occurred at high doses, and these studies are not applicable to low-dose radiation. Linking the two high-dose radiation data sets and extrapolating linearly to low-doses is an assumption that merits challenge. Subsequent discussion will examine the LNT issue in more detail.

A corollary to the LNT hypothesis is the introduction of the collective-dose assumption. Collective dose is the sum of individual doses in an exposed group, and is a method for quantifying detriment in a population group. This assumption

presumes that small doses to large populations can be summed to predict a set of calculated health effects that are representative of the population risk.

Collective dose overstates the presumed risk and equivalent collective doses do not imply equivalent risk. For example, a large dose to members of a small group is not equivalent to a small dose to members of a large group, even if the collective doses are the same. For groups in which individual lifetime doses are less than 100 mSv above background, collective dose is a speculative and uncertain measure of risk [5]. It should not be used for estimating the health risks or radiation induced detriment to an exposed population. Unfortunately, this occurs routinely and adds to the public's radiophobia regarding the use of radiation and radioactive materials [6][7][8].

The previous discussion has provided an overview of the foundations for radiation protection regulations [9][10][11][12][13] and their LNT foundation. Subsequent commentary reviews the data refuting the LNT hypothesis. A review of this data is necessary because the subject is complex and often focuses on limited aspects of the LNT hypothesis. As will be noted in subsequent discussion, LNT supporters have not addressed this topic in a comprehensive manner that includes a range of radiobiological effects, human immune system response to low-dose ionizing radiation, hormesis, and threshold effects.

2. LNT vs. Reality

The LNT hypothesis only considers the detrimental effects of radiation. As the radiation exposure increases, the associated damage cumulates. There are no damage thresholds, and any exposure results in harm. The duration of the exposure does not matter. A given total dose delivered over a day, week, or year results in the same harm. These assumptions are significant flaws in the LNT approach. In particular, radiation induced biological detriment is time dependent, and repairs typically occur within a 24 hour period [14][15].

Well known repair mechanism and mitigation processes are mostly ignored within the scope of the LNT hypothesis. These include, but are not limited to the human immune system and its associated innate and adaptive components, apoptosis, biological repair mechanisms, DNA repair mechanisms, and adaptive response.

2.1. Overview of Cell Damage

Ionizing radiation affects the cell via both direct and indirect mechanisms[2][3][16][17]. These mechanisms produce toxic species by producing free radicals, chemical agents and ionic species that disrupt cellular processes and structures, damage and alter DNA, and impact cellular chemical processes. These effects are highly dependent on the delivered dose and dose rate of the ionizing radiation. The repair mechanisms are extremely effective at low doses, and the cell recovers within about 24 hours after the radiation exposure. It is only at high doses and dose rates that radiation damage is not fully repaired.

The reactive species (e.g., H_2O_2, reactive oxygen and reactive nitrogen species, and ions including Fe^{++}, Fe^{+++}, O^-,

and OH^-) are mitigated by a variety of cellular processes utilizing chemical agents that counter their effects [18]. These chemical species including superoxide dismutase (SOD) are very effective at low doses in eliminating the detrimental effects. Natural cellular defense mechanisms also combat additional radiation induced effects including lipid peroxidation, protein oxidation, oxidative alterations to mtDNA and nDNA, and inactivation of enzymes.

Refs. 19 and 20 provides a more quantitative description to the aforementioned cellular repair mechanisms. The human body has on average 10^{14} cells. Each of these cells undergoes ~10^9 events/day caused by normal oxidative processes that create free radicals including reactive oxygen species (ROS) that generate secondary reaction products. These species damage cellular structures including DNA. Total DNA alterations are reduced to about 10^6 through the action of antioxidants including glutathione (GSH), SOD, catalase, and peroxidase. As a comparison, the ratio of metabolic to environmental doses of about 1 mSv/y is ~$2x10^8$.

Repair mechanisms including enzymes and cell cycle control reduce the metabolic defects to about 10^2 effects/cell. These defects include persistent DNA alterations. As a comparison, the ratio of these persistent DNA alterations to environmental doses of about 1 mSv/y is ~10^7.

Additional mechanisms including apoptosis, necrosis, differentiation, and immune response further reduce the number of mutations to about 1. The ratio of oxidative to environmental dose damage is about 10^7.

Ref. 19 clearly illustrates the effectiveness of cellular and collective body repair mechanisms that operate at low doses. Natural oxidative damage significantly overwhelms radiation damage. This is consistent with the doubling dose estimated to be about 1 Sv noted in BEIR VII [19].

2.2. DNA Damage and Repair Basics

The LNT hypothesis assumes detrimental effects arise at the cellular level and are related to the associated radiation damage to DNA. However, the LNT hypothesis does not specifically address subsequent DNA repair mechanisms. In view of this situation, a brief review of DNA damage and basic repair mechanisms are provided.

Each cell in the human body suffers multiple DNA breaks per day[20]. Given this level of damage, repair mechanisms are required to preserve the body and maintain its various functions. These mechanisms are crucial to understanding the validity of the LNT hypothesis.

At a fundamental level, DNA consists of nucleotides with the bases adenine (A), guanine (G), cytosine (C), and thymine (T) [21]. Within the DNA double helix, A in one strand is always paired with T in the other, and C is always paired with G. These pairings are vulnerable to damage. For example, the C-G pairing can be disrupted such that cytosine loses an amino group. When this occurs, the damaged segments tend to pair with adenine which can produce a mutation if the defect is not properly repaired. This change can alter the genetic information encoded within the original macromolecular structure and could theoretically lead to a biological detriment.

Fortunately, there are robust mechanisms for repairing DNA. Cells contain several DNA repair systems that correct

alterations. These repair mechanisms fall into two general categories which include the repair of damaged bases and incorrectly paired bases during replication. In most cases, DNA repair is a multi-step process that includes detection of an abnormality in the DNA structure, removal of the flawed DNA, and synthesizing normal DNA.

Genetic information is stored in the DNA helix and repair facilitating enzymes monitor the strands and replace damaged nucleotides. Most DNA repair mechanisms utilize the duplicate genetic information in each of the two DNA strands. Damage on one strand is repaired by an enzyme and a corrected section is produced using the duplicate coding in the undamaged strand. In a sense, the DNA strand is a computer program having multiple redundant paths with the capability to repair damaged sections of the code.

There are three fundamental mechanisms associated with DNA repair[21]. These are base excision repair (BER), nucleotide excision repair (NER), and mismatch repair. BER corrects a variety of defects that affect the bases A, C, G, and T without causing structural damage to the DNA strand. In base excision repair, the damaged base is removed, and this action is followed by excision of the resulting sugar phosphate.

NER fixes various abnormalities that either interfere with the normal base pairings or distort the helical DNA structure. In nucleotide excision repair, the damaged portion of the DNA strand is removed from the double helix. In both cases, the gap left in the strand is filled by sequential action, and the undamaged DNA strand is utilized as the repair template. This is an example of the inherent redundancy associated with the DNA structure and its associated repair mechanisms.

Mismatch repair corrects defects when DNA is replicated, recombined, and mismatched. This repair method is strand-specific. During DNA synthesis, the new strand will include errors. The mismatch repair mechanism distinguishes the new strand from the original template, and corrections are made to ensure the new strand matches the original segment.

DNA damage induced by ionizing radiation is significantly less severe than the spontaneous damage that occurs from other causes. Most spontaneous changes in DNA are temporary and are immediately corrected by the collection of DNA repair mechanisms. Heat, metabolic transients, various sources of natural ionizing and nonionizing radiation, and exposure to chemicals in the environment create thousands of DNA random changes per day in a human cell. However, only a few survive as mutations in the DNA sequence. For example, less than one in 1000 base changes in DNA creates a permanent mutation [22]. Most are efficiently eliminated by the DNA repair mechanisms.

The number of natural mutations is significantly larger than those created by low-dose ionizing radiation. If low-dose radiation is a hazard, one would expect that the natural mutations would propagate cancer at a rate larger than observed. Since this does not occur, the DNA repair mechanisms and human immune system must function efficiently to remove both naturally occurring abnormalities and those caused by low-doses of ionizing radiation. Although this is a very qualitative argument, the rate of natural mutations suggests the repair mechanisms should mitigate the detrimental effects of low-dose ionizing radiation. The LNT approach does not incorporate the complete response of the human body to mitigate the effects of low doses of ionizing radiation.

DNA repair and other natural body processes, including the human immune system, provide a robust means to protect the body from a range of agents. These processes are also expected to facilitate the repair of damage caused by low-

dose ionizing radiation. This subject is addressed in subsequent discussion.

2.3. Immune System Response

The immune system consists of two basic components (i.e., the innate and adaptive Systems)[23]. Innate immunity provides immediate protection against microbial invasion. It is always present in healthy individuals and facilitates the blockage of microbe/harmful agent entry into the body. The innate system rapidly eliminates microbes/harmful agents that do succeed in entering the body.

Immunity is the body's first line of defense. Macroscopically, it includes physical (e.g., skin, hair, and mucous) and chemical (e.g., sweat, tears, saliva, stomach acid and urine) barriers. If foreign agents breach these barriers and enter the tissues or circulation, several other components of the innate immune system defend against them. These include basophils, dendritic cells, eosinophils, macrophages (primarily white blood cells), natural killer cells, natural killer T cells, neutrophils, and T cells. In addition to providing early defense against foreign agents including radiation damage induced defects, free radicals, and chemical species, the innate immune response is a prerequisite to triggering the adaptive component of the immune response system.

Adaptive immunity develops more slowly and provides specialized defense against foreign agents. The adaptive component includes the growth and differentiation of lymphocytes in response to foreign agents. It subsequently adapts to the presence of these agents. Specific components of the adaptive immune system include antibodies, B cells, CD4+T cells, CD8+T cells, and T cells.

Adaptive immune responses are an important defense mechanism against foreign agents including microbes that are capable of causing disease, and may have evolved to resist the response of the innate immune system. These foreign agents include radiation induced structures and associated chemical agents.

Given the 24 hour repair time for radiation damage, the innate immune system provides the dominant response to repair radiation induced damage. When combined with the other repair mechanisms, the human body exhibits an effective response to mitigate the effects of low doses of ionizing radiation.

2.4. Temporal Considerations

The time period for recovery from cellular damage is about 24 hours[14][15][24][25]. The LNT hypothesis essentially ignores the repair time, inherent repair mechanisms, and collective body response to mitigate the radiation damage.

According to the LNT hypothesis, only the total delivered dose matters. For example, US Regulations summarized in 10CFR20 [9] and 10CFR835 [10] establish an annual dose limit for the whole body and associated organs. In view of the 24 hour repair period and the viability of repair mechanisms at low doses, the annual dose limits are not consistent with the basic radiobiology principles. Damage repair depends on the dose delivered in a 24 hour period. These considerations invalidate both the annual dose limit concept as well as the LNT hypothesis upon which it is based.

3. The Atomic Bomb Survivor Data

Before discussing specific data that negates the LNT hypothesis, the BEIR VII[19] contention regarding atomic bomb survivor data is addressed. According to BEIR VII, one of the most important data sets for determining health effects of low-dose radiation are the atomic bomb survivor statistics. Atomic bomb survivor data summarized in the RERF Reports are frequently quoted to validate the LNT hypothesis, and to establish the extrapolated low-dose detriment.

RERF Report 14 by Ozasa et al.[26] updated the RERF Report 13[27] results. RERF 13 noted that formal dose-threshold analysis indicated no threshold; i.e., zero dose was the best estimate of the threshold. However, Ozasa et al. observe that: "*Although the linear model provided the best fit in the full dose range, statistically significant upward curvature was observed when the dose range was limited to 0–2 Gy (θ = 0.81, P = 0.02) (Tables 6 and 7). The curvature over the 0– 2-Gy range has become stronger over time, going from θ = 0.20 for the period 1950–1985 to 0.81 for 1950–2003, and has become significant with longer observation (Table 7)".* In the preceding quote θ is the curvature of the fit and P is the statistical significance (likelihood test). The reader should recall that RERF Report 13 [27] was a significant basis for establishing the credibility of the LNT hypothesis in the BEIR reports as well as a portion of the basis for US radiation protection regulations (e.g., 10CFR20 and 10CFR835).

Ozasa et al.[26] conclude that a linear non-threshold model fits the excess relative risk curve for solid cancers as a function of weighted colon dose for the full dose range. However, the authors suggest that a linear-quadratic (LQ) model provides the best if the data is restricted to a dose of 2 Gy.

A cursory examination of the published data in the 0 – 2 Gy range shows a definite depression in the curve that is an obvious deviation from linearity. This depression occurs at about 400 mGy [28]. In addition, the excess relative risk (ERR) is negative at low-dose values that suggests the need to correct the data for the bias in the baseline cancer rate. Doss [29] suggests this correction is 20% and reformulates the ERR[30].

Following Doss[30], the calculated ERR values can be corrected for such a bias using the following equation

$$ERR' = \frac{(1 + ERR)(100 + \delta)}{100} - 1 \quad (1)$$

where is the value of ERR corrected for the bias, and δ is the percentage bias in the baseline cancer mortality rate. Doss [30] uses a –20% bias which is based on the observed reduction in low-dose radiation cohorts in some population studies.

The correction as applied by Doss[30] shifts the ERRs to lower values resulting in negative ERR values for all the doses below about 600 mGy. Although there are fluctuations in the corrected ERR values for doses below about 300 mGy, the overall topology of negative ERR values for doses below about 600 mGy is suggestive of a hormetic or cancer preventive effect of low-dose radiation that has been previously observed in animal and human studies [12][29][30][31][32][33][34][35][36][37].

Given this analysis, Doss[30] suggests that the qualitative shape of the dose response curve of the atomic bomb survivor data has a plausible explanation using a radiation hormesis model. This explanation results when the ERR data is corrected for the likely bias in the baseline cancer rate. However, there is no explanation for the observed reduction in ERR values in the 300 – 700 mGy dose range within the context of the LNT model.

As a further evaluation of the Ozasa et al. results[26], the ERR solid cancer data was fit to the power series:

$$ERR = \sum_{i=0}^{N} a_i d^i \quad (2)$$

where N+1 is the number of terms in the expansion, $\mathbf{a_i}$ are coefficients determined from a fit to the RERF 14 solid cancer data below 2 Gy, and d is the weighted colon dose. The fit was limited to N ≤ 8, but considers functional forms typically used to evaluate radiological data.

The functional form of Eq. 2 is not intended to be a rigorous mathematical exercise because the error bars on the data were not included. The intent of the fit is to only evaluate the functional form and to investigate the optimum mathematical relationship to the data. Although this is a somewhat simplistic presentation, it does assess the departure of the data from the assumed functional form required by the LNT hypothesis.

The restriction to utilizing linear and linear quadratic mathematical functions has been the usual standard for radiological data analysis. However, this paper generalizes that approach to consider other polynomial forms. In particular, the existence of a threshold and minima in the data below 2 Gy as suggested by Doss [28][29][30] are investigated in a more general manner. The results of the numerical analysis are summarized in subsequent discussion.

Although there are numerous approaches to compare data sets, this paper uses the PSI-Plot™ computational package and its associated analysis features [38]. In comparing data sets, the fit parameter (Ψ) is used:

$$\Psi = \sum_{i=1}^{m} (O_i - C_i)^2 \quad (3)$$

where m is the number of elements in the data set, O_i is the RERF 14 solid cancer ERR value[26], and C_i are the corresponding polynomial fit values from Eq. 2. The area under the polynomial fit curves is also presented in Table 1. The area is calculated over the range of Ozasa et al. data below 2 Gy [26].

The simple-minded analysis summarized in Table 1 is not intended to be definitive, and its only purpose is to determine if the basic LNT requirements including no thresholds and deviations from a linear fit are appropriate. The analysis includes the linear (N = 1), linear quadratic (N = 2), and higher order polynomial fits (N = 3 – 8). The fit parameter provides an indication of how well the various N values reproduce the data. The N = 1 and N = 2 cases are typically used in health physics applications. However, higher order polynomial fits have typically been excluded from previous analyses.

Table 1. Polynomial Fits to the Excess Relative Risk for Solid Cancers as a Function of Weighted Colon Dose Data Below 2 Gy[a]

Polynomial Order (i in Eq. 3)	Minimum in Polynomial (mGy)			Threshold (mGy)	Ψ (Eq. 2)	Area under polynomial fit (ERR-Gy)
	First	Second	Third			
1	---	---	---	12	0.646	0.979
2	---	---	---	-26	0.640	0.961
3	187	---	---	---	0.558	0.975
4	553	---	---	30	0.367	0.981
5	49	718	---	---	0.288	1.02
6	352	1016	---	29	0.155	1.05
7	41	531	1290	---	0.0574	1.11
8	45	530	1282	---	0.0572	1.11

[a]Osaza et al. [26].

The results of Table 1 offer the possibility of a threshold in the 10 – 30 mGy range for N = 1, 4, and 6. However, a threshold is not observed in all data fits. In fact, the N = 2 fit has a negative threshold (-26 mGy).

Minima are also predicted by the N = 3 – 8 data evaluations. The minima vary with the polynomial order used in the analysis, but are suggested by the data. The first minimum lies in the 40 – 550 mSv range for N = 3 – 8. As expected the fit improves as more parameters are included. This is illustrated by the decreasing value of the fit parameter in Table 1.

The author does not attempt to draw specific conclusions regarding the magnitude of the threshold or position of the minima. However, the polynomial fits do suggest the non-linearity in the data. These calculations are also supportive of the nonlinearity contentions provided by Doss [28][29][30] and acknowledged by Ozasa et al.[26].

The area under the curve is a nontraditional approach for judging the goodness of the fit. However, as noted in Fig. 1, the N = 1 (linear) and N = 2 (linear-quadratic) fits clearly do not fit the data (without consideration of error bars) as well as the N > 2 curves. This issue is exaggerated because the data error bars were not included in the simple-minded analysis.

4. Biological Evidence against the LNT Hypothesis

DNA damage occurs within the body through a variety of mechanisms even in the absence of low-dose radiation. As noted in Section 2.0, the body has natural defense mechanisms to repair this damage and minimize its propagation. These mechanisms operate deterministically and below a dose threshold there is likely no propagation of DNA damage or biological detriment. This threshold suggests an inherent weakness in the LNT hypothesis. Above this threshold, the effects of ionizing radiation overwhelms the DNA repair processes and produces a net biological detriment, and this damage can be propagated beyond DNA to higher levels structures including cells, tissues, organs, and whole body [31][32][33][34][35][36][37][38][39].

As noted in Section 2.0, there are three repair mechanisms that inhibit damage propagation. These mechanisms can be recast in more qualitative terms as physical or metabolic processes that incorporate the innate and adaptive immune systems. Physical defenses precede metabolic defenses. The physical defense mechanisms act immediately to scavenge toxic chemical species and free radicals produced by ionizing radiation interactions with tissue. Physical mechanisms also include molecular repair of cellular structures including DNA; removal of damaged cells by apoptosis, necrosis, and phagocytosis; cell differentiation and senescence; and response of the immune system to facilitate removal of damaged cells. Within the context of this paper, the immune system includes all body defense mechanisms. These mechanisms combat biological and other agents that damage cells or inhibit cellular repair processes, and other processes that return the body to its normal state when under attack by various agents.

Following these actions, base excision repair, nucleotide excision repair, and mismatch repair replace lost DNA elements. In addition, metabolic defense mechanisms arise from normal cellular processes that produce chemical agents that facilitate repair. Some of these repair mechanisms are effective for more than a year and all create temporary protection against radioactive and toxic materials. Following Feinendegen et al. [35] adaptive protections reach a maximum after single tissue absorbed doses in the range of 100–200 mSv, but are ineffective at higher doses. Low-dose rates initiate maximum protection if delivered repetitively at certain time intervals. Adaptive protection preventing about 2–3 % of lifetime cancer risk would fully balance a calculated, induced cancer risk at about 100 mSv which is in agreement with epidemiological data and consistent with an hormetic effect. To date, radiation protection regulations and low-dose risk assessments do not recognize hormesis and the positive aspects of low-dose radiation. A summary of the limitations of the LNT hypothesis associated with radiation protection regulations was provided by Doss [28].

5. General Arguments against the LNT Hypothesis

Support for the LNT hypothesis is not universal and numerous organizations including the American Nuclear Society [40], French Academy of Sciences [41], French National Academy of Medicine [41], and Health Physics Society [42][43] have expressed various degrees of opposition to the LNT approach. In addition to the arguments of these organizations, the LNT hypothesis can be reviewed in terms of its inherent assumptions from a physiological, cancer risk, dose threshold, radiation carcinogenesis, radiation biology, background radiation, and dose modeling perspectives.

This section provides an overview of the relevant data in terms of general data categories. References are provided as warranted, but the specific details [44][45][46][47][48][49][50][51][52][53][54][55][56][57][58][59][60][61][62][63][64][65][66][67][68][69][70][71][72][73][74][75][76][77][78][79][80][81][82][83][84][85][86][87][88][89][90][91][92][93][94][95][96][97][98][99][100][101][102][103][104][105][106][107][108][109][110][111][112][113][114][115][116][117][118][119][120][121][122][123][124][125][126][127][128] are provided in subsequent discussion.

5.1. Physiological Considerations

There are shortcomings in the LNT hypothesis that have not been fully evaluated. The LNT hypothesis does not

incorporate a number of processes that are present in cellular repair and damage mitigation. For example, biological mechanisms involved in cellular repair are time and dose rate dependent. These mechanisms are not incorporated in the LNT approach since the hypothetical model does not consider the temporal dynamics of a DNA break or the various biological repair mechanisms.

The LNT hypothesis also does not include the evolutional development of a species and its adaptation to the natural radiation environment. An evolving species would minimize the low-dose radiation influence as a risk factor in its survival by developing an immune and repair system that was compatible with the natural background radiation environment.

In a similar manner, the LNT hypothesis does not account for DNA repair and its varied and effective mechanisms at low-doses. Ionizing radiation damage to DNA can include a double strand break that severs the double helix. These breaks are repaired or reconnected by the aggregation of cellular proteins. At low-doses, these cellular repair mechanisms are efficient. However, at high-doses, the more extensive DNA damage tends to form clusters. These damage clusters facilitate improper repairs that can lead to a biological detriment. Specific detriments include mutations (chromosome rearrangements) or cancer (malfunctioning cells). Since DNA repair is less effective at high-doses, it is problematic to extrapolate the high-dose results to low-doses when DNA repair effectiveness varies as a function of dose. This simple description provides an explanation of the increased risk of cancer at high-doses, but it does not validate the LNT hypothesis. The LNT hypothesis focuses on detriment and fails to consider the wealth of repair mechanisms that function effectively at low doses.

Other mechanisms, including adaptive response, suggest that a biological insult (e.g., radiation exposure) enhances the body's ability to address further insults by activating its defense and repair mechanisms. Adaptive response proposes that a low-dose of radiation preconditions the body to withstand additional radiation exposure. This occurs because the initial exposure activates the collection of biological repair mechanisms (e.g., B and T cell response systems).

There is also evidence to suggest that low-doses of ionizing radiation stimulate cellular defense mechanisms that protect the individual against disease. In addition, low-dose radiation can have a positive biological impact. This process is known as hormesis and has been observed experimentally in lower life forms. Hormesis and adaptive response present additional challenges to the LNT hypothesis.

A future system of radiation dose limits cannot ignore the specific differences in biological repair effectiveness at low- and high-doses. In addition, hormesis and adaptive response must be evaluated without regard to the historical LNT bias. The use of dose and dose rate effectiveness factors [53] acknowledges the inherent difference between high- and low-dose exposures. However, a complete set of factors must be considered in establishing a valid model for radiation detriment.

For example, Doss[28] notes that autopsy studies have shown that the presence of cancer cells is not a decisive factor in the physical manifestation of clinical cancer. However, immune system suppression in organ transplant patients more than doubles the cancer risk. This supports an important immune system role in limiting occult cancers. Doss further notes that low-dose radiation elevates immune response, and so it may reduce rather than increase the risk of cancer [28]. The

beneficial effects of low-dose radiation have been noted in numerous publications. However, the most recent BEIR VII report [19] reviewed, but did not accept the role of hormesis and its challenge to the LNT hypothesis.

The LNT hypothesis focuses attention on DNA damage leading to further health detriments including cancer and hereditary effects. DNA damage is only one factor in assessing detriment, and medical researchers suggest that it is not a decisive factor. By focusing on DNA damage, the LNT hypothesis mostly ignores the response of the immune system, which is an important factor in determining the physical detriment. In addition, adaptive response appears to be a valid effect that stimulates the immune system and permits it to function at an optimum level to counter the ionizing radiation detriment.

From a physiological perspective there are three fundamental issues in the current radiation safety basis established using the LNT hypothesis. First, the LNT hypothesis focuses its attention on DNA damage and mutations which are not the only factors affecting the onset and propagation of cancer. Second, the LNT approach essentially ignores the effect of the immune system response which is an important factor modulating the occurrence of cancer. The effect of radiation on immune system response is not linear, since low-dose radiation stimulates the immune system, and high-dose radiation suppresses it. Third, the LNT model ignores the large variability in cancer rates by specifying no threshold. Lifetime cancer risks are likely to have large errors arising from the variability in confounding factors. Moreover, cancer rates also vary from year to year and location.

These issues suggest a thorough review of the LNT radiation safety basis is warranted. Although it is the basis for current radiation protection regulations, there are numerous publications that suggest there is no justification for continuing the use of the current LNT radiation safety paradigm. The LNT hypothesis has contributed to an unjustified fear of low-dose radiation, and has inhibited the application of beneficial applications of low-dose radiation.

5.2. Cancer-Risk Arguments

Raabe [44] presents cancer-risk arguments against the LNT hypothesis. He notes that the development of a radiation-induced malignant tumor is not the result of a single random interaction of the ionizing radiation with an isolated cell. Raabe offers the following arguments against the LNT hypothesis and suggests that major revisions of methodology and standards are needed:

1. The cancer risk associated with ionizing radiation exposure is a non-linear function of the lifetime average dose rate to the affected tissues;
2. Cancer risk exhibits a virtual threshold at low lifetime average dose rates;
3. Cumulative radiation dose is not an accurate or appropriate measure of cancer risk, but it is useful for describing the virtual threshold for various exposures.
4. High-dose rate atomic bomb survivor data from Hiroshima and Nagasaki cannot be used to estimate cancer risk from ionizing radiation exposures over long times and at low-dose rates.

Based on these considerations, currently accepted ionizing radiation detriment models should be reevaluated to

assess the validity of LNT estimates of ionizing radiation cancer risk. Other arguments offered by the Health Physics Society [42][43] suggest that the LNT hypothesis is an oversimplification. The LNT approach can be rejected for specific cancer types (e.g., bone cancer and chronic lymphocytic leukemia). In addition, significant heritable genetic damage has not been observed in human studies. The effects of various biological mechanisms (e.g., DNA repair and adaptive response) on the induction of cancers and genetic mutations as a function of dose and dose rate have not been thoroughly investigated. These mechanisms do not appear to be credibly modeled by a linear-non-threshold model.

5.3. Threshold Dose limits

The credibility of the LNT hypothesis is further challenged by the observation that radiogenic health effects have not been consistently demonstrated below 100 mSv [42][43]. Primary cancers have been observed in humans only at doses exceeding about 100 mSv delivered at high-dose rates. Below this threshold, estimates of radiation detriment are speculative. As noted previously, risk estimates in exposed populations are based on epidemiological studies of well-defined groups (e.g., the Japanese atomic bomb survivors and medical therapy patients) exposed to relatively high-doses delivered at high-dose rates. Adverse health effects have not been observed in individuals exposed to chronic doses less than 100 mSv.

In its Radiation Risk in Perspective Position Statement, the Health Physics Society (HPS) concluded that risk estimates should be limited to individuals receiving a dose of 50 mSv in one year or a lifetime dose of 100 mSv [42][43]. This dose is in addition to natural background. Below these doses, risk estimates should not be performed. In addition, the HPS recommends that expressions of risk should only be qualitative and presented as a range of values based on uncertainties. This range of uncertainty values should include the inability to detect any increased health detriment, which acknowledges that zero health effects are a credible outcome.

5.4. Radiation Carcinogenesis

Raabe [44][45][46][47] notes that ionizing radiation carcinogenesis is not a linear function of cumulated dose. Moreover, it is not a stochastic single cell phenomenon. Carcinogenesis is a whole organ process that is dependent on a variety of factors including the lifetime average dose to the sensitive organ cells. As a collective process, the arguments of Doss [28] suggest a whole body response including the importance of the human immune system. The elimination of a single cell effect and influence of collective body defense mechanisms suggest the LNT response model is an oversimplification of the onset and development of carcinogenesis.

5.5. Radiation Biology Considerations

Ionizing radiation can damage DNA through direct molecular events (e.g., ionization and excitation) or through indirect mechanisms including chemical reactions caused by reactive oxygen species produced by radiation induced reactions. Tubiana et al. [48] observe that these species are also an abundant consequence of natural oxygen metabolic processes. Animal life would be unsustainable without natural defenses against reactive oxygen species. Accordingly, the human

body has adapted to the effects of both direct and indirect radiation effects through prolonged exposure to natural background radiation and normal biological functions required for growth and sustaining life.

Natural defense mechanisms occur throughout the cell life cycle and accommodate DNA repair and apoptosis. These actions decrease the probability of chromosome aberrations and genomic instability in a manner that is most effective at low-doses [33][49]. Tubiana et al. [48] note that the mutagenic effect per unit dose varies with dose rate and reaches a minimum in the range of 1–10 mGy/min [35][41]. This dose rate effect is approximately equal to the rate of reactive species inducing DNA damage during oxidative stress [50]. In humans, chromosome aberrations are not produced by doses less than 100 mSv or at low-dose rates [43][44][55]. Large studies have not revealed an increased incidence of chromosomal aberrations at doses below 20 mSv [34].

If the LNT hypothesis is correct, damaged cells are created and their numbers increase with increasing dose. At low-doses, the human cellular response does not follow this assumed production sequence, and eliminates damaged or malfunctioning cells through death or terminates their proliferation. The elimination of cells with damaged DNA can occur through apoptosis (controlled death) shortly following irradiation in the range of a few mSv to about 200 mSv [15][32][48]. These mechanisms are less effective at higher doses.

5.6. High Background Radiation

The population living in Kerala, India experiences background radiation levels up to 70 mSv a year[48]. This radiation level is much higher than other locations in India, but no increased cancer risk has been observed. In Yangjiang, China and the surrounding area, the population is exposed to two levels of annual background radiation (i.e., 6.4 and 2.4 mSv). In spite of this significant difference in annual dose, there was no increase in cancer incidence or mortality. The higher level of background radiation was confirmed by an increased incidence of chromosomal aberration, but no excess in cancer incidence was observed [48].

The observation of an increase in chromosome aberrations without a proportional increase in the incidence of cancer appears to negate the LNT contention regarding the causal relationship between a chromosomal aberration and cancers at low-doses. This observation contradicts the LNT hypothesis and is another example of its failure to properly consider established data. It is worth noting that proponents of the LNT hypothesis, as embodied by the BEIR Reports, do not utilize data from these high background areas to assess the validity of its assumed linear approach.

5.7. Use of Modifying Factors

Modifying factors were introduced in ICRP 26[52] to relate the effective dose equivalent to the absorbed dose. The dose and dose rate effectiveness factor (DDREF) [53] follows in the spirit of a modifying factor to account for a biological effect or modification of that effect. In particular, the DDREF attempts to overcome discrepancies between epidemiological data and LNT predictions. As such, the use of modifying factors illustrates an inherent weakness in the LNT hypothesis. If the LNT approach were absolutely valid, no modifications would be required and high-dose and dose

rate data could be extrapolated linearly to zero dose. Clearly, the pure LNT hypothesis is invalid, but modifying factors have been used to justify an amended approach. However, the literature does not make this distinction, and continues to refer to the LNT hypothesis without qualification.

The use of a DDREF implies that for low-doses and/or dose rates, the probability for DNA damage to be carcinogenic is reduced by the DDREF value. In the Case of BEIR VII, a DDREF value of 1.5 is judged to be appropriate for low LET radiation for effective doses below 1 Sv [53]. However, the LNT proponents suggest the DDREF leaves unchanged the concept that even the smallest dose can induce cancer.

The high-dose data is extrapolated to zero dose, but the slope of the line below 1 Sv is reduced by the DDREF and subsequently extrapolated to zero dose. This approach leads to a discontinuity at 1 Sv which is clearly nonlinear.

The DDREF is composed of two component factors that are conceptually distinct from a biological perspective. These factors are dose effectiveness factor (DEF) that applies to low acute doses, and the dose rate effectiveness factor (DREF) that is affected by low protracted doses where long-term kinetics of target/stem cells in tissue may modify the dose response [53].

These factors attempt to assign an*ad hoc* parameter to explain an inherent weakness in the LNT hypothesis. The DEF, DREF, and DDREF appear to be an attempt to salvage a flawed concept. From the author's perspective, thresholds, hormesis, adaptive response, and immune system function are more credible concepts to explain the biological effects of low level radiation exposure than the aforementioned effectiveness factors.

6. Data Negating the LNT Hypothesis

This section summarizes specific data that contradicts the LNT hypothesis. The documentation provides direct as well as supporting data that suggests the LNT hypothesis is flawed and in need of significant revision. For each data reference, separate sections provide its impact on the LNT hypothesis as well as the primary conclusions derived from the work. The summarized research not only supports the need for a revision of the LNT hypothesis, but also suggests that thresholds, hormesis, the immune system, and adaptive response are important considerations in determining the appropriate dose response relationship. In addition, the dose response characteristics of low-dose radiation are significantly different than in the high-dose region, and the LNT hypothesis extrapolations from the high-dose region are not justified.

6.1. Relevant Data

The studies summarized in Section 6 vary in size and scope. Some studies are limited to a particular age group or population having specific characteristics. The reader is referred to the specific study for details regarding its purpose and scope. The content of Section 6 is significant in that there are numerous studies challenging the LNT hypothesis directly or specific aspects underlying its basic assumptions.

Much of the data summarized in Section 6 has been available to the BEIR and ICRP committees, but have not been incorporated into their reports. Although it is understandable that there are differences in technical perspective in some studies, numerous research efforts provide strong evidence for LNT weaknesses. In particular, revisions to data incorporated into Cardis et al. [54] and RERF Report 14 [26] have not been incorporated into BEIR and ICRP Reports (e.g., initial BEIR VIII [55] discussions and ICRP 131 [53]). These omissions are significant because data issues clearly challenge the LNT hypothesis.

6.1.1. Frigerio et al. [56]

Frigerio et al. [56] observe a trend of lower US cancer mortality rates associated with higher background radiation levels. This evidence supports a trend of reduced cancers with increasing background radiation dose which is in conflict with the LNT hypothesis.

6.1.2. Evans [57] and Rowland [58]

Evans [57] and Rowland [58] note a threshold dose of ~10 Gy for induction of bone sarcomas in radium dial painters. There is no observed increase in cancers below this threshold. This threshold was affirmed by Rowland. The LNT hypothesis is negated because the dose response curve exhibits a well defined threshold.

6.1.3. Chaffey et al. [59]

Chaffey et al. [59] investigated the survival of lymphosarcoma patients treated with whole body irradiation and chemotherapy. Low-dose radiation (150 mGy) applied 10 times during 5 weeks (Total dose of 1.5 Gy) had a therapeutic effect in treating the cancers. Low-dose radiation has a positive biological impact (i.e., hormesis) in contrast with the predicted detriment resulting from the LNT hypothesis.

6.1.4. Alemayehu and Cochran [60], and Siegel et al. [61][62]

Alemayehu and Cochran [60] are a recent example of authors that support the LNT hypothesis. Ref. 62 is utilized by national and international organizations as support for LNT model. Siegel et al. [61][62] note the arguments of Alemayehu and Cochran do not justify the extrapolation from very high to zero dose. In general, international and national authoritative bodies have not incorporated the extensive data that suggest the LNT proponents have failed to adequately evaluate studies supporting hormesis, thresholds, and nonlinear trends in the relevant data. The LNT hypothesis must be validated by data. Invoking an approach as a valid model, because national and international organizations support its use, is not a sound scientific justification, and propagates the flawed LNT hypothesis.

6.1.5. Bursch et al. [63] and Chandra et al. [64]

At low-doses, Bursch et al. [63] and Chandra et al. [64] observe that the human cellular response does not follow the LNT hypothesis. The human body eliminates damaged cells through death (e.g., apoptosis) or terminates their

proliferation. The elimination of cells with damaged DNA can occur through apoptosis shortly following irradiation in the range of a few mSv to about 200 mSv. These mechanisms are less effective at higher doses. Following the LNT hypothesis, damaged cells are created and their numbers increase with increasing dose without mitigation or removal. This contention is in conflict with observations. Cellular mechanisms effectively eliminate damaged cells at low-doses.

6.1.6. Kostyuchenko and Krestinina [65]

Kostyuchenko and Krestinina [65] investigated the long-term irradiation effects in the population evacuated from contaminated areas in the East-Urals. Significantly reduced cancer mortality rates relative to the control group were observed in the 120 mGy and 500 mGy cohorts from evacuated villages near the Mayak Chemical Combine (Chelyabinsk-65). Mayak was a Soviet nuclear waste reprocessing and production facility similar to the Hanford Site in the US. The dose response curve exhibits a U-shaped minimum that occurs near 120 mSv. This minimum is in conflict with the LNT hypothesis.

6.1.7. Cohen [66]

Cohen [66] observed reduced lung cancer mortality rates with increased residential radon levels in US counties. This study finds that with or without corrections for variations in smoking prevalence, there is a strong tendency for lung cancer rates to decrease with increasing radon exposure which is in sharp contrast to the increase expected from the linear non-threshold theory. Reduced lung cancer mortality rates with increased residential radon levels are in conflict with the LNT prediction that detrimental effects should increase with dose.

6.1.8. Imaida et al. [67] and Greaves [68]

Imaida et al.[67] note that the cancer mortality rate increases drastically with age, but the percentage of patients with cancerous mutations is unchanged. Graves [68] observes that almost all individuals have cancerous mutations, but everyone does not develop cancer. Failure to link increasing mutations with cancer risk suggests the LNT hypothesis is flawed with respect to its inherent cancer induction assumption. The LNT hypothesis presumes that increased mutations mean increased cancers, but mutations do not imply cancer. These results are in sharp contrast to the LNT assertions.

6.1.9. Dikomey and Brammer [69] and Shrivastav et al. [49]

Natural defense mechanisms occur throughout the cell life cycle and accommodate DNA repair or apoptosis. Dikomey and Brammer [69] and Shrivastav et al. [49] observe that these actions decrease the probability of chromosome aberrations and genomic instability in a manner that is most effective at low-doses. The dose dependence of DNA repair mechanisms is inconsistent with the LNT hypothesis. Although the LNT makes no allowance for the various repair approaches, these repair mechanisms are most effective at low-doses. This dose dependence in inconsistent with the LNT hypothesis.

6.1.10. Vilenchik and Knudson [71][72]

Vilenchik and Knudson [71][72] observe that the mutations per unit dose vary with dose rate and reach a minimum in the

range of 1–10 mGy/min. The dose dependence of mutations is inconsistent with the LNT hypothesis.

6.1.11. UNSCEAR 2000 [128], Hooker et al. [73], Loucas et al. [74], and Zeng et al. [51]

Studies including those of Hooker et al.[73], Loucas et al. [44], and Zeng et al.[51] observe that human chromosome aberrations are not produced by doses less than 100 mSv or at low-dose rates. Large studies including UNSCEAR 2000 [128] have not revealed an increased incidence of chromosomal aberrations at doses below 20 mSv. Radiation induced detriment as a function of dose is inconsistent with the LNT hypothesis.

6.1.12. Cuttler and Pollycove [75]

Cuttler and Pollycove [75] note a reduction of breast cancer mortality in tuberculosis patients. The dose response curve for breast cancer deaths as a function of breast dose has a minimum at about 150 mGy. Cuttler and Pollycove observe that patients, receiving a total dose in the range from 50 to 300 mGy, had a breast cancer incidence up to one-third less than the background incidence. These authors also note that a hormetic model provides a better fit to the data than the LNT hypothesis. The shape of the dose response curve for breast cancer deaths as a function of breast dose is non-linear and exhibits a distinct minimum. These data are in direct conflict with the LNT hypothesis.

6.1.13. Preston et al. [27], Ozasa et al. [26], and Doss [29]

RERF 13 has been superseded by RERF 14 and this report no longer definitively supports the LNT hypothesis. Doss [29] observes that the shape of the dose-response curve, with correction for bias in the baseline cancer rate, is consistent with the concept of radiation hormesis. The 2003 data set of RERF 13 [27] has been superceded by the 2012 data of RERF 14 [26]. This revision yields a nonlinear dose response curve that is not consistent with the LNT hypothesis.

6.1.14. Wakeford and Little [76], Brent [77], and Doss and Little [78]

In a point-counterpoint paper by Doss and Little[78], Doss provides a rebuttal to the arguments of Wakefield and Little [76]. The occurrence of leukemia was observed only following high-dose radiation. The associated risk coefficients were based on an LNT model that created the impression of increased risk at low-doses. However, the LNT based effect has not been observed. Again, the LNT model fails to properly represent the observed data.

As noted by Brent[77], cohort studies, that are generally a better approach than case controlled studies, yield no increased leukemia risk. Assuming the applicability of the LNT model creates a bias that overestimates the observed leukemia risk.

6.1.15. Sakamoto [79]

Sakamoto [79] observed improved survival of non- Hodgkin's Lymphoma patients when subjected to 100 - 150 mGy total-body irradiations combined with radiation treatments directly to the tumor site using a total dose of 1.5 Gy. Suppression of distant metastasis of tumor cells was also observed by Sakamoto following low-doses of total-body

irradiation. Low-dose radiation has a hormetic effect that is in conflict with the predictions of the LNT hypothesis.

6.1.16. Cardis et al. [54] and Canadian Nuclear Safety Commission (2011) [80]

Cardis et al.[54] was quoted by the BEIR VII[19] Report. Initial BEIR VIII efforts[55] utilized this data to infer an increased cancer risk from low-dose radiation and to validate the LNT based radiation cancer risk. The combined data from 15 countries show a statistically significant increase in cancers in radiation workers which led the authors to conclude that low-dose radiation increases the cancer risk. This result was driven by the Canadian data that suggested a much higher risk than data from other countries. However, problems were identified in the Canadian data by the Canadian Nuclear Safety Commission [80]. Subsequently, the CNSC withdrew the Canadian data from use. Removing this data from the 15 country study invalidates the low-dose radiation cancer risk conclusion of Cardis et al. The revised Canadian data no longer supports the LNT hypothesis. However, these and similar data continue to be utilized to justify the LNT approach.

6.1.17. Sponsler and Cameron [81]

Sponsler and Cameron[81] published a summary of their nuclear shipyard worker study (1980–1988) that involved a large cohort exposed to low-dose rate gamma radiation. The median cumulative dose for the main cohort of shipyard workers was 35.8 mGy (2.8 mGy x 12.8 years).

The authors observed significantly reduced cancer mortality in the workers subjected to median cumulative radiation doses of 35.8 mGy in comparison to non-radiation workers. These higher-dose workers demonstrated significantly lower circulatory, respiratory, and all-cause mortality than did unexposed workers. Mortality from all cancers was also lower in the exposed cohort. The LNT hypothesis, which predicts increasing detriment at higher doses, is in conflict with the observed results.

6.1.18. Hwang et al. [82] and Doss [29]

Hwang et al.[82] assessed the cancer risks in a Taiwanese population that received prolonged low-dose rate γ-irradiation for about 10 years as a result of occupying buildings containing ^{60}Co-contaminated steel. As reported by Doss [29], a statistically significant reduction was observed for all cancers in the apartment residents receiving an average dose of about 50 mSv. This reduction continued in the 2008 follow-up report as described by Doss [29].

The Taiwan data[82], having an average dose of 50 mSv in a cohort of about 8,000, provide statistically meaningful results that is inconsistent with the LNT hypothesis. LNT sample size arguments suggest that low- dose research is extremely difficult for typical occupational doses. This contention is negated by more careful analyses [29][82].

The Taiwan data strongly suggest that low-doses have a hormetic effect which is inconsistent with the LNT hypothesis. Smaller sample sizes than predicted by the LNT hypothesis lead to meaningful results for low-dose radiation.

6.1.19. Tubiana and Aurengo [41]

The French Academies of Science and Medicine reviewed the validity of the LNT dose response relationship. Tubiana and Aurengo conclude that the LNT hypothesis overestimates the radiological risk. In addition, use of the LNT hypothesis may discourage physicians and patients from utilizing radiological examinations because the risk is assumed to be large.

The arguments of Tubiana and Aurengo[41] against the validity of LNT hypothesis are based on various data including the following: (1) there is no epidemiological evidence for cancer excess in humans for doses below 100 mSv, (2) there is no experimental animal data for carcinogenic effects for doses below 100 mSv, (3) practical thresholds or hormetic effects have been observed in a large number of experimental studies, and (4) DNA repair and elimination by the death of cells with DNA damage varies with dose and dose rate. A review of human and environmental data does not support the LNT hypothesis that increasing dose leads to an increased radiological detriment.

6.1.20. Pollycove [83]

The human immune system is a key factor in cancer development, but it is essentially ignored by the LNT hypothesis. As described by Polycove [83], DNA alterations from background radiation produce about one additional mutation per 10 million cells/d. These values apply to a young adult, living in a low LET background of 1 mSv/y. As ageing progresses, mutations accumulate and gradually degrade the antimutagenic system, and mortality increases correspondingly. Cancer increases at about the fourth power of age.

Pollycove notes that genomic, cellular, animal and human data have shown that low-dose ionizing radiation, including acute doses up to 300 mGy, stimulates the immune system. However, high-dose ionizing radiation suppresses the immune system. Studies of cancer in animals and clinical trials of patients with cancer also show, with high statistical confidence, the beneficial effects of low-dose radiation.

The LNT hypothesis mostly ignores the human immune system that is an important factor in establishing the dose response function. Low-doses of radiation have a positive benefit in contrast to the LNT hypothesis.

6.1.21. Orsini et al. [84], Woods et al. [85] and Fogarty et al. [86]

Fogarty et al.[86] observe that high-intensity exercise produces free radicals that causes increased DNA damage. Woods et al. [85] determine that cardiovascular exercise training results in improved antibody responses to influenza vaccination by boosting the immune system response. Orsini et al. [84] suggest that higher levels of physical activity and an active lifestyle are associated with reduced cancer incidence and mortality and increased cancer survival.

These studies are consistent with an immune suppression model associated with cancer development. An enhanced immune system response reduces the risk of cancers. The LNT hypothesis fails to consider the impact of the immune system. By ignoring one of many biological repair and mitigation mechanisms, the LNT is biased toward detriment, and fails to consider natural mechanisms to negate the negative effects of low-dose and dose rate ionizing radiation.

6.1.22. Rithidech and Scott [32]

Rithidech and Scott[32] demonstrate gamma ray hormesis during low-dose neutron irradiation. The gamma rays are derived from (n, γ) neutron capture reactions in tissue. This protective effect may be responsible for the neutron RBE energy dependence when the total radiation dose is ≤100 mGy. The authors suggest that the hormetic effect is based on the gamma-ray activation of high-fidelity DNA repair and stimulation of apoptosis in aberrant cells. Therefore, the RBE for neutron induced stochastic radiobiological effects may depend on physical (e.g., LET and lineal energy spectra) as well as biological (DNA repair and apoptosis) effects. Stimulation of the immune system by low-doses of gamma rays could also impact the low-dose neutron RBE for *in vivo* radiobiological effects such as cancer. The observed hormetic effect is inconsistent with the LNT hypothesis and its inherent focus on detrimental effects..

6.1.23. Yablokov et al. [87], Levinger [88], and Siegel et al.[61][62]

Siegel et al. note that the data of Yablokov et al.[87], as interpreted by Levinger[88], do not indicate a linear response. When properly interpreted, the data suggest the existence of a threshold. Siegel et al. [61][62] observe that the data of Yablokov et al. support a threshold when properly evaluated. The existence of a threshold is inconsistent with the LNT hypothesis.

6.1.24. Shimizu et al. [89], Levinger [88], and Siegel et al.[61][62]

Siegel et al.[61][62] note that Figures 1 and 2 of Shimizu et al.[89] do not indicate linear responses down to 0.1 Gy or 0.05 Gy as asserted by Levinger [88]. However, if properly interpreted, these data suggest thresholds. Shimizu et al. admit that the existence of risk below 0.5 Gy is “unclear.” Levinger asserts without evidence that the LNT hypothesis is probably true. Siegel et al. observe that the data support a threshold when properly evaluated. The existence of a threshold is inconsistent with the LNT hypothesis.

6.1.25. Koana and Tsujimura [90]

Koana and Tsujimura [90] determined a U-shaped dose-response relationship for mutation frequency in Drosophila as a function of absorbed dose. These data suggest that DNA repair was responsible for the U-shaped dose-response relationship in Drosophila. The dose response curve is not linear as proposed by the LNT hypothesis.

6.1.26. American Association of Physicists in Medicine Position Statement PP 25-A[91]

The American Association of Physicists in Medicine (AAPM) Position Statement PP 25-A

> *“acknowledges that medical imaging procedures should be appropriate and conducted at the lowest radiation dose consistent with acquisition of the desired information. Discussion of risks related to radiation dose from medical imaging procedures should be accompanied by acknowledgement of the benefits of the procedures. Risks of medical imaging at effective doses below 50 mSv for single procedures or 100 mSv for multiple procedures over*

> *short time periods are too low to be detectable and may be nonexistent. Predictions of hypothetical cancer incidence and deaths in patient populations exposed to such low-doses are highly speculative and should be discouraged. These predictions are harmful because they lead to sensationalistic articles in the public media that cause some patients and parents to refuse medical imaging procedures, placing them at substantial risk by not receiving the clinical benefits of the prescribed procedures."*

This AAPM declaration directly contradicts the LNT hypothesis. Patient radiophobia of low doses of ionizing radiation are an unfortunate consequence of the LNT hypothesis and associated ALARA concept. The predictions of the LNT hypothesis are inappropriate for decisions involving the use of low-dose medical imaging. Risks for effective doses below 50 mSv for single procedures or 100 mSv for multiple procedures over short time periods are too low to be detectable and may be nonexistent. By discouraging the use of useful diagnostic techniques, the LNT hypothesis does inherent harm to the patient and limits assessments by the physician.

6.1.27. Tubiana et al. [92]

Tubiana et al.[92] investigate a new method of assessing the dose-carcinogenic effect relationship in radiotherapy patients exposed to ionizing radiation. A reduction of second cancers per kg of tissue was noted in regions of the body receiving an absorbed dose of about 200 mGy when compared to regions not subjected to any radiation dose. Second cancers decreased with increasing absorbed dose up to about 200 mGy which is in conflict with the LNT hypothesis. The LNT hypothesis predicts increasing detriment with increasing dose.

6.1.28. Beyea [93] and Siegel et al.[61][62]

Siegel et al.[61][62] note that the data analysis of Beyea[93] is flawed and promulgates an illegitimate statistical approach. A more rigorous analysis does not support the LNT hypothesis. Siegel et al. suggest that the Soviet Techna River data analysis is flawed, and a valid assessment methodology does not support the LNT hypothesis.

6.1.29. Ozasa et al. [26]

The latest update (RERF Report 14)[26] of the Japanese atomic bomb survivor data no longer supports the LNT model. The dose-response data are not linear and have noticeable curvature. Bomb survivor data is the gold-standard for the presumed basis for the LNT hypothesis. Observation of curvature in the dose response data, undermines the LNT approach to radiation protection and the associated radiological risk. A basic tenant of the LNT hypothesis is invalidated by the most recent Japanese atomic bomb survivor data evaluation.

6.1.30. Levin [94], Oliveira- Cobucci et al.[95], and Yang et al.[96]

Oliveira-Cobucci et al.[94] note that suppression of the immune system increases the cancer risk in transplant and HIV patients by a factor of about three. These data demonstrate the importance of the immune system for minimizing cancer progression.

In investigating T-cell-mediated immunity, Levin[94] observes that the immune system response declines rapidly with age. These data qualitatively explain the age-related increase in cancers. Yang et al. [96] report that low-doses of ionizing radiation induce a direct expansion and activation of the defense system, which provides a potential mechanism for stimulation to enhance adaptive cellular immunity. These data suggest that low-dose radiation boosts the immune system.

The LNT hypothesis fails to consider the immune system which is an important consideration in determining cancer risk. Stimulating the immune system mitigates cancer progression, but this important effect is not included in the LNT cancer assertions.

6.1.31. Pearce et al. [97], UNSCEAR 2013 [98], Boice [99], Journy et al. [100], and Leuraud et al. [101]

Pearce et al.[97] observed an increased incidence of cancers following childhood CT brain scans, and is routinely quoted as evidence for an enhanced cancer risk from low-dose radiation (e.g., Leuraud et al. [101]). The authors suggest that the brain cancer risk increases with radiation dose. Boyce [99] noted the Pearce et al. study must be interpreted with caution.

The reasons for performing the CT exams were not known, and the dosimetric approaches did not include individual dose reconstructions or account for the possibility for missed examinations. UNSCEAR 2013 [98] concluded that the associations may have resulted from confounding factors, and not radiation exposure. The reported cancer associations may have been related to the patients' underlying health conditions that prompted the examinations.

The study design contains weaknesses that cast doubt on its conclusions. Other studies considered the reason for performing CT scans and noted no increase in cancer risk with CT radiation dose, (e.g., (Journy et al. [100]). Journy et al. suggest that the indication for examinations, whether suspected cancer or cancer-predisposing factors, should be considered to avoid overestimation of the cancer risks associated with CT scans. The study used to justify the LNT hypothesis has been challenged for containing significant flaws in its design. As noted in previous discussion, statistically invalid and poor study designs have been used to justify the LNT approach. More rigorous analyses and properly designed research projects fail to support the LNT hypothesis and its underlying assumptions.

6.1.32. Levin [94] and DeGregori [102]

In a study of young animals, DeGregori[102] observed that cells dividing at the highest rates are most susceptible to mutations which is the expected result. In addition, the accumulation of mutations also occurs at the highest division rates.

However, Levin [94] notes that the immune system response is at its highest level when an organism is at a young age. Levin’s work suggests that cancer rates would be at the lowest levels at young age which is supported by the immune suppression model of cancer. The low cancer rates observed in the young is consistent with the immune suppression model of cancer, but is in conflict with the mutation model.

Although mutations are necessary for causing cancers, they are not the only cause. Suppression of the immune

system is a key factor that causes cancers and this consideration is not included within the scope of the LNT hypothesis.

In addition there is not a one-to-one correspondence between a mutation and cancer. The previously mentioned suppression mechanisms either repair, mitigate, or eliminate mutations, but these factors are not included in the LNT hypothesis.

6.1.33. Little et al. [103], Little [104], Akiba [105], and Doss [78]

Little and coworkers[103] suggest an excess radiation risk at dose levels below 500 mSv, and also argue that there is accumulating evidence from the Japanese atomic bomb survivors and various other moderate and low-dose exposed groups of an excess risk of cataracts. However, Akiba [105] performed an extensive review of the contentions of Little et al. and Little [104]. A variety of radiation and associated detriment information are evaluated by Akiba including data from the Mayak Production Association workers, Electricite de France workers, Chernobyl emergency workers, and Japanese atomic bomb survivors. Akiba notes that the heart disease meta-analysis combined low-dose rate and high-dose rate data. This combination transferred the high-dose radiation risk to the low-dose region. Doss [78] notes that the Chernobyl and atomic bomb survivor data do show a threshold dose for cataracts requiring surgery. The arguments of Akiba and Doss negate the contentions of Little and coworkers. The existence of a threshold negates the LNT hypothesis.

6.1.34. Feinendegen et al. [35]

Feinendegen et al.[35] note that low-dose radiation activates defense mechanisms. This adaptive response results in protective measures. The protective features include, but are not limited to, antioxidants, DNA repair enzymes, and apoptosis. These mechanisms reduce the damage that would have occurred in the absence of the low-dose radiation. Low-doses have a hormetic effect which is inconsistent with the LNT hypothesis.

6.1.35. Ferlay et al. [106] and World Nuclear Association [107]

The data of Ferlay et al.[106] and the World Nuclear Association [107] support reduced cancer rates in European countries with the highest background radiation levels. Evidence supports a trend of reduced cancers with increasing background radiation dose which is in conflict with the LNT hypothesis. The LNT model suggests the opposite effect.

6.1.36. Osipov et al. [108]

The data of Osipov et al.[108] indirectly indicate that low level ionizing radiation *in vivo* may trigger repair of DNA double strand breaks. There is a dose threshold for this defense mechanism. These molecular level *in vivo* data suggest that the dose-response for DNA double strand breaks at very low-doses and dose rates is not linear. A nonlinear dose response curve is in conflict with the basis assertions of the LNT hypothesis.

6.1.37. BEIR VIII Planning Meeting [55]

At a 2014 BEIR VIII Planning Meeting[55], the committee continued to rely on data supporting the LNT hypothesis, and

ignored non supportive data. The initial BEIR VIII effort did not recognize the major change in the nature of Atomic Bomb Survivor data (Ozasa et al. [26], Doss [109], and Cuttler [110]). BEIR VIII planning quoted the 15-country study of radiation workers as evidence for low-dose radiation cancer risk (Cardis et al. [54]), in spite of withdrawal of the Canadian data [80]. The initial planning meeting discussions also ignores data illustrating a cancer reduction from low-dose radiation including the Nuclear Shipyard Worker Study (Sponsler and Cameron [81]) and the study of second malignant neoplasms in radiation therapy patients (Tubiana et al. [92]). Initial selection of relevant data for BEIR VIII continues to ignore significant data refuting the LNT hypothesis.

6.1.38. Cuttler [110]

Cuttler [110] notes that the leukemia incidence and associated dose response curve for 96,000 Hiroshima atomic bomb survivors is inconsistent with the LNT model. The dose response curve exhibits a leukemia threshold of about 500 mGy for Hiroshima atomic bomb survivors. The dose response curve exhibits a threshold which is in conflict with the LNT hypothesis.

6.1.39. Allison [111]

Allison [111] observes that the initial effect of physical exercise and low-dose radiation on cells includes chemical action that increases the production of reactive oxidant species. These two stimuli elicit the same protective and adaptive responses. Moreover, a history of exercise and low-dose radiation exposure are both effective at stimulating adaptation. Doses of ionizing radiation at low rates suppress cancer incidence just as exercise does. Low-dose radiation stimulates the immune system and suppresses cancer incidence. This effect is not incorporated in the LNT hypothesis that focuses upon the detrimental effects of radiation exposure.

6.1.40. Cuttler and Welsh [112]

Cuttler and Welsh [112] describe an error in the analysis of leukemia incidence among the 195,000 Japanese atomic bomb survivors. Based on this work, the threshold acute dose for radiation-induced leukemia is about 500 mSv. These authors note that it is reasonable to expect that the thresholds for other cancer types are higher than this level. An error in atomic bomb survivor analysis of leukemia data invalidates an essential date set utilized in formulating the LNT model. Thresholds noted by Cuttler and Welsh are inconsistent with the LNT hypothesis. Cuttler and Welsh provide additional evidence for issues with the LNT hypothesis and its supporting data.

6.1.41. ICRP 131 [53]

ICRP 131 [53] notes that the LNT model is generally consistent with human epidemiological data of cancer induction in human populations exposed to ionizing radiation. The atomic bomb survivor data is judged by ICRP 131 to be the gold standard of human data supporting the LNT hypothesis. This statement fails to consider that the latest update of the atomic bomb survivor data of Ozasa et al. [26] that no longer supports the LNT model. The dose-response data are not linear and have a significant curvature. ICRP 131 also notes that “there are a few clear tissue-specific exceptions to the

general rule and that other models can be equally applied in some cases". As noted in ICRP 131, the general rule is the use of the LNT hypothesis.

In ICRP 131, support for the LNT hypothesis is less assertive than noted in previous ICRP publications. The report also notes that other models can be applied to the data. Key references supporting the LNT basis for ICRP 131 (e.g., RERF 13 [27] atomic bomb survivor data and Cardis et al.[54]) have been shown to be invalid.

6.1.42. Oakley [36]

Oakley [36] reports that low-dose total-body irradiation (TBI) therapy offers an additional radiation treatment for cancer patients. TBI is based upon the concept of radiation hormesis and provides very good success rates. The TBI treatment modality has been reported as an abscopal effect where the localized treatment of a tumor causes not only a shrinking of the treated tumor, but also a shrinking of tumors outside the targeted treatment volume. Compared to the contemporary treatments, such as immunotherapy drugs and localized high-dose radiation, Oakley notes that low-dose radiation stimulates the immune system, and may prove to be superior to other treatment approaches. Hormesis and immune system stimulation provide a cancer therapy approach that is inconsistent with the inherent detriment only effect assumption utilized in the LNT hypothesis.

6.1.43. Pateras et al. [113]

Pateras et al.[113] provide evidence that the DNA damage response and repair (DDR/R) and immune response (ImmR) work together to enhance the function of cellular organisms. For example, DNA and RNA viruses directly and indirectly activate the DDR/R mechanisms in host cells. The DDR/R activation favors the immunogenicity of the incipient cell. Pateras et al. suggest stimulation of DDR/R by cellular insults, including ionizing radiation, triggers innate and adaptive ImmR. Ionizing radiation is a DDR/R inducing agent and is an example of how DDR/R stimulation induces host immunity. The emerging DDR/R–ImmR concept opens up a new avenue of therapeutic options including ionizing radiation to stimulate the immune system response. Ionizing radiation triggers an immune system response that is not considered as an integral aspect of the LNT hypothesis.

6.1.44. Rudant et al. [114]

Rudant et al.[114] study the effects of boosting the human immune system, and its impact on the incidence of childhood leukemia. The immune system in children is enhanced with an increased rate of breastfeeding and earlier childcare attendance in daycare which subjects children to increased rate of infections. Both of these conditions stimulate the immune system and reduce the risk of childhood leukemia. The LNT hypothesis does not consider the effects of the human immune system, and is inherently biased towards the detrimental effects of ionizing radiation.

6.1.45. Tang and Loke [37]

Tang and Loke review the molecular mechanisms of low-dose ionizing radiation (LDIR)-induced hormesis, adaptive

responses, radioresistance, bystander effects, and genomic instability. LDIR has been reported to induce hormesis, adaptive response, radioresistance, bystander effect and genomic instability in living cells, tissues, organs, and the whole body. These radiation-induced responses are affected by an individual's genetic composition as well as other effects including the general health of the individual. The adaptive response may be considered as a special hormetic response or a manifestation of radioresistance. It may protect against bystander damage, but the bystander effect may induce genomic instability.

The interrelationship among different responses suggests that they may have shared signal transduction pathways. Since many different signal transduction pathways are involved in LDIR-induced responses, the same pathways may be shared by different responses. Activation of some of these pathways may induce defensive or beneficial responses such as immunity, detoxification of reactive oxygen species, repair of DNA damage, and stem cell proliferation. However, activation of the same signal transduction pathways may also induce harmful effects such as genomic instability. Tang and Loke suggest that further studies are needed to determine the particular signal transduction pathways that can produce positive effects while preventing LDIR negative effects

The LNT hypothesis does not consider a variety of positive molecular mechanisms and effects attributed to low-dose ionizing radiation. LNT focuses on detriment, and ignores the numerous repair and mitigation mechanisms inherent in humans.

6.1.46. Cohen [115]

Cohen [115] observes that there is no definitive scientific proof that low-doses of radiation from computed tomography (CT) imaging increase cancer risk. From a physician's perspective, Cohen notes that the ALARA and Image Gently Philosophy have caused harm to the profession of radiology and to patients. Accordingly, ALARA and Image Gently as they now exist should be terminated. Patient cancer risk from CT is likely nonexistent or at worst minimal. The risk is equivalent to the normal hazards of daily living. The LNT hypothesis is based on flawed and incomplete assumptions. LNT implementation in using low-dose CT procedures has a negative impact on radiologists and associated patient diagnosis and care.

6.1.47. Cuttler et al. [116]

In a case report, Cuttler et al.[116] describe the improvement in a patient with advanced Alzheimer disease. The individual received 5 computed tomography brain scans of about 40 mGy each over a period of 3 months. Patient improvement appears to be radiation-induced stimulation of the adaptive protection systems. The treatment appears to have partially restored cognition, memory, speech, movement, and appetite. Although a single study, the case study is another example of the positive effects of low-dose radiation in treating disease. Low level radiation exposure appears to trigger adaptive response mechanisms to improve the condition of a patient with Alzheimer disease.

Although Cutler describes an individual case report, the results are consistent with the aforementioned studies that demonstrate the beneficial effects of low level ionizing radiation. These results provide numerous examples of the flaws

inherent in the LNT model.

6.1.48. Grass et al. [117]

Therapeutic effects of radiation therapy apart from those observed at the treatment target (i.e., abscopal effect) have been observed for several decades. However, the underlying mechanisms regulating this phenomenon have not been clearly defined [37]. Grass et al. [117] observe that the immune system is a major consideration in regulating the abscopal effect, and that radiation therapy may enhance immunologic responses to tumors. Harnessing the immune system to target tumors in conjunction with radiation therapy is an emerging field with much promise. To optimize this approach, the host immune system, immunotherapy, and radiation therapy should be evaluated in a comprehensive manner. The LNT hypothesis does not consider the immune system and other mitigative response mechanisms that are important considerations in cancer progression.

6.1.49. Sacks et al. [118]

Sacks et al.[118] note that epidemiological studies that claim to confirm the LNT hypothesis either neglect experimental and/or observational discoveries at the cellular, tissue, and organismal levels, or mention them only to distort or dismiss them. Studies that claim to validate the LNT hypothesis rely on circular reasoning, biased data selection, faulty experimental design, and misleading inferences from weak statistical evidence. Sacks et al. further observe that studies confirming hormesis are firmly based on biological discoveries. In particular, these biological studies demonstrate the validity of hormesis, and confirm the stimulation of biological responses that defend the organism against damage from environmental agents.

Failure of the LNT hypothesis is also suggested from understanding of normal metabolic processes that are far more damaging than all but the most extreme exposures to radiation. However, Sacks et al. note that evolution has provided plants and animals with defense mechanisms that repair such damage or remove the damaged cells. These repair mechanisms confer on the organism even greater ability to defend against subsequent damage.

Sacks et al. summarize the extent of damage caused by the LNT hypothesis in the practice of radiology, radiation regulatory policies, and the popular media culture. The result is mass radiophobia and harmful outcomes, including forced relocations of populations near nuclear power plant accidents (e.g., the 2011 Fukushima Daiichi accident in Japan), reluctance to avail oneself of needed medical imaging studies, and aversion to nuclear energy. All of these LNT driven actions are unwarranted and harmful to humanity.

LNT epidemiological studies are often based on weak or misleading data analysis. The LNT hypothesis fails to consider biological repair mechanisms and the validity of hormesis.

6.2. Summary of Data Negating the LNT Hypothesis

A number of conclusions are suggested by the data summarized in the previous section. These conclusions include

the: (1) importance of the immune system in the suppression of cancers, (2) immune system enhancement following low-dose radiation, (3) positive effects attributed to hormesis in populations exposed to low levels of ionizing radiation, (4) updated atomic bomb survivor data no longer support the LNT hypothesis, (5) key LNT references (e.g., Cardis et al. [54]) being invalidated by updated data, (6) existence of thresholds, (7) use of modifying data (e.g., DEF, DREF, and DDREF)) to support inconsistencies between data and LNT predictions, (8) curative effects of low-dose radiation, (9) importance of DNA and natural repair mechanisms, (10) importance of signal transduction pathways, and (11) inconsistency between the LNT hypothesis risk estimates and actual observations noted in variations in background radiation levels. Any of these conclusions raise questions regarding the validity of the LNT hypothesis. Moreover, the reference data, noted in previous discussion, suggest that the LNT hypothesis is unsustainable and an inappropriate basis for existing radiation protection regulations.

It is generally accepted that a primary reason for cancer is the transformation of a normal cell into a cancer cell through mutations. These mutations occur following DNA damage that causes the cell to malfunction. Greaves [119][120] notes that cancer cells exist in most human bodies, but everyone does not develop cancer. Imaida et al. [67] performed an autopsy study and reviewed the existence of cancer cells as a function of age. Although the percentage of patients with cancer cells was relatively unchanged from ages 50 to 80, the cancer mortality rate increased by more than an order of magnitude between these ages [121]. This increase with a constant concentration of cancer cells indicates there is another cause for the incidence of the aforementioned cancers. In fact, the primary cause of these cancers is the degradation of the immune system as the body ages [93]. As noted previously, the immune system is not incorporated into the LNT hypothesis. Omitting an obvious and important aspect of cancer suppression is a major failing of the LNT hypothesis.

The naturally occurring mutations that exist in most bodies are influenced by ionizing radiation. Feinendegen et al. [35] notes that low level radiation exposure stimulates the immune system, and these increased defenses reduce the number of mutations that would have occurred naturally. This results in fewer mutations overall, and this effect has been observed in animal studies [108].

The effects expected from hormesis are observed in populations exposed to low levels of ionizing radiation. Studies of Frigerio et al. [56] observed a trend of lower US cancer mortality rates associated with higher background radiation levels. Cohen [66] noted a strong tendency for lung cancer rates to decrease with increasing radon exposure, in sharp contrast to the increase expected from the linear non-threshold theory. Ferlay et al. [106], utilizing background radiation estimates from World Nuclear Association [107], published data supporting reduced cancer rates in European countries with the highest background radiation levels

Ozasa et al.[26], Cuttler [110], and Cuttler and Welsh [112] observe that the dose-response data for the Japanese atomic bomb survivors is not linear and has a significant curvature. Doss [29] note the data appears to have a distinct dip at about 500 mSv and this feature was also noted by Cuttler [110] and Cuttler and Welsh [112].

6.3. Fundamental Conflicts

The reports summarized in previous sections were available to the ICRP, NCRP, BEIR, DOE, NRC, and other advisory

and regulatory organizations. However, these organizations do not share the author's conclusions which are an important consideration for the reader. These data illustrate the fundamental issues associated with the LNT hypothesis. These issues involve various interpretations of data and the complete lack of consensus among knowledgeable professionals. However, is this consensus a result of scientific data or a vested interest in the status quo and its associated financial benefits?

A comparison of these data reveals an interesting comparison. The LNT proponents and organizations base their arguments only on presumed damage, and neglect data regarding the biological response of human repair mechanisms and the immune system. The Section 6 reports also provide evidence for hormesis and disease treatment potential as a byproduct of low-dose radiation exposure. These positive benefits are rejected by LNT proponents in spite of growing evidence for their existence in a variety of studies.

There is a growing tide of evidence that is in conflict with the LNT hypothesis. This accumulating research clearly illustrates the inherent weakness of the LNT approach.

6.4. LNT Resolutions

Although the collection of results summarized previously offer evidence that favors rejection of the LNT hypothesis, its proponents ultimately resort to one final argument when presented with the quality and abundance of data summarized in Section 6. This argument relies on the observation that no epidemiological study, with an appropriate unirradiated control group, has definitely demonstrated either the detrimental or beneficial effects of ionizing radiation doses less than 100 mSv in humans. As noted previously, this argument is incorrect and a number of studies demonstrate a beneficial effect. The LNT approach suggests that assessing the risks of low-doses of ionizing radiation would require large scale epidemiological studies with long-term follow-up activities to accurately assess the associated detriment or benefit of the exposure. The previous discussion demonstrates that these conclusions are an artifact of the LNT hypothesis and are also incorrect. Since credible results can be obtained with much smaller sample sizes than suggested by the LNT hypothesis, research that further demonstrates the positive benefit of low-dose radiation should be actively supported. These studies would provide additional data to supplement the research noted in Section 6.

Issues associated with sample size are not new and have been discussed in a number of reports including BEIR III [122], V [123], and VII [124]. Table 2 further supports the discussion in Section 3.2 and illustrates the cohort sizes required for statistically meaningful results [125]. As noted in Table 2, the LNT based sample sizes are clearly challenging as the doses of interest decrease in magnitude.

The sample size arguments summarized in Table 2 are based on LNT model estimates. Previous discussions demonstrate that credible results are obtained with significantly smaller sample sizes than required by the LNT hypothesis. Therefore, sample size arguments utilized by LNT hypothesis proponents do not have merit and are not justified by data.

Table 2. Required Epidemiological Sample Size for Various Doses of Low LET Radiation[a]

Effective dose (mSv)	Required Number of Individuals in the Exposed Group
100	$5x10^4$
10	$5x10^6$
1	$5x10^8$
0.1	$5x10^{10}$
0.01	$5x10^{12}$

[a] *Based on Ref. 127 that used the LNT hypothesis.*

LNT supporters suggest the only regulatory option is to accept the assumed detriment proposed by their flawed hypothesis. This argument is logically inconsistent. Since the LNT hypothesis excludes thresholds, hormesis, impact of the human immune system, and any nonlinear effect, validation of any of these items voids this approach. The wealth of reference data summarized in Section 6 provides ample evidence for nonlinear effects, hormesis, immune system impact, and the existence of thresholds. Therefore, reasonable arguments support the abandonment of the LNT hypothesis and its replacement. If replaced, what is the appropriate model that will serve as the successor to the LNT hypothesis? Potential alternatives to the LNT philosophy are addressed in Section 8.

6.5. New Physical Interpretations Related to Absorbed Dose and DNA Damage

The radiation dose delivered to tissue is typically characterized by the energy absorbed per unit mass or absorbed dose. Absorbed dose is evaluated over a specified volume that is typically characterized by a length scale much larger than a few nm. However, the physical interpretation of the energy deposition mechanism can also be evaluated at the nm scale.

Ostrikov et al.[126] observe that distinct physical phenomena (e.g., plasma production) arise following the localization of energy densities at the microscale and nanoscale realm. These effects can be achieved following the concentration of radiation into small volumes that lead to extreme energy densities. For example, depositing 1 MeV ($1.6x10^{-13}$ J) into a volume of 1000 nm^3 during 100 fs could lead to a power density of 10^{24} W/m^3. The physical effects of DNA damage at these densities have not been rigorously investigated and may provide additional insight into the failure of the LNT hypothesis.

A very preliminary review of these high localized densities suggests that DNA damage would be limited to the immediate reaction volume [126]. It is likely that the redundant, undamaged DNA would facilitate repair of the damaged volume. The inherent redundancy is a key aspect of DNA repair even at these extreme power densities. This localized damage is readily managed by the repair mechanisms summarized in Section 5 which would support the contentions of the Section 6 references.

These high power densities would also minimize the probability of damaged replication because all matter in the volume of these extreme power densities would be obliterated. This approach to radiation damage has yet to be rigorously investigated and at this stage of development remain speculative.

6.6. Medical perspective

From a medical perspective, the LNT theory of radiation carcinogenesis is based on four assumptions[127]. As noted by Marcus [127], each of which is incorrect and rely on illogical and circular reasoning.

The first assumption ignores the repair of radiation damage. More than 150 genes are involved in gene repair. The 2015 Nobel Prize in Chemistry was awarded for determining the mechanisms of DNA repair.

The second assumption is that LNT ignores the delivery time of the radiation dose. A given total dose of radiation delivered slowly is much less damaging than the same quantity delivered instantaneously. Radiation oncology patients routinely receive high doses administered over a time interval (e.g., often over a 6-week period). If the total dose were delivered instantaneously, biological repair mechanisms would be overwhelmed and the damage to normal tissue would be much greater.

The third assumption is that a single radiation interaction that induces one DNA mutation can cause a fatal cancer. However, stem cells that give rise to cancer contain thousands of mutations. As noted by Marcus [127] an individual mutation is not sufficient to cause cancer. In a lifetime, every gene undergoes a mutation on about 10^{10} separate occasions. If the LNT hypothesis were correct, cancer would occur more frequently than observed.

The fourth assumption is that repair mechanisms function in a similar manner at both high and low doses. However, at high doses repair mechanisms (e.g., enzymes) that exist at low doses are often inhibited from being synthesized.

7. Consequences of the LNT Hypothesis

Inappropriate application of the LNT hypothesis has a negative impact on many aspects of our lives. These impacts include aspects of medical imaging, medical research, utilization of radiation and radioactive materials, expansion of nuclear power production, negative impacts of regulation, inappropriate allocation of industrial safety resources, and the inappropriate relocation of the Japanese population following the Fukushima Daiichi accident.

The linear non threshold hypothesis and its illegitimate ALARA (as low as reasonably achievable) progeny have been inappropriately applied to medical imaging [6][7][8]. Credible evidence of imaging-related carcinogenic risk at low absorbed dose (<100 mGy) is nonexistent [61]. Any perceived risk is a hypothetical consequence of the presumed validity of the scientifically unjustified LNT hypothesis. In reality, low-dose radiation does not cause, but more likely helps prevent, cancer. Siegel et al. [61] observe that the LNT hypothesis and associated ALARA concepts are fatally flawed and focus only on molecular damage while ignoring protective, organismal biologic responses. Siegel et al. clearly illustrates the societal harm caused by the LNT hypothesis and ALARA.

The LNT hypothesis also affects acceptance of the use of radiation and radioactive materials, and causes the ALARA concept to create harm rather than the presumed benefit. These concepts create a world in which ALARA becomes “A Law Against Radiation Applications.”

The negative societal impact of the LNT hypothesis and ALARA concept is significant. Negative ramifications include a limitation of research using radiation and radioactive materials, adverse impact on medical diagnoses, limitation of nuclear energy expansion in the United States and Europe, deterrence of the achievement of lower costs for radiation-related services, slowed recovery from the Fukushima Daiichi accident, unnecessary evacuation following the Fukushima Daiichi accident, and contribution to the unwarranted public fear of radiation and radioactive materials.

Radiophobia has inhibited research using low-dose radiation in the detection, prevention, and treatment of cancer and other diseases. Unwarranted fears caused by belief in the LNT hypothesis have also effectively inhibited research involving unique applications of radiation and radioactive materials. These applications include the use of low-dose radiation as a treatment protocol. Patients have refused to undergo CT scans, and physicians are not prescribing these procedures because the LNT hypothesis has created concern about the subsequent radiation detriment. This fear could result in missed diagnoses because imaging doses are too low to produce adequate tissue resolution.

The expansion of nuclear energy in the United States and Europe has been limited because the radioactive releases resulting from Three Mile Island, Chernobyl, and Fukushima Daiichi reinforced unjustified fears regarding the effects of radiation. These effects include incorrect assumptions regarding the connection between cancer and hereditary effects and low doses of ionizing radiation. The associated radiophobia promotes the use of higher-cost and polluting energy-generating sources that negatively affect economic growth and public health.

Increased regulation of radiation and radioactive materials and the associated costs to implement compliance further dampen the expansion and use of radiation and radioactive materials. Regulations affect consumer, medical, industrial, health care, and research applications and result in significantly increased costs with limited benefit.

These concerns are illustrated by a simple example of resource allocation. Nuclear facilities (e.g., power reactors and fuel cycle facilities) devote significantly more personnel and attention to radiation safety driven by the LNT hypothesis and ALARA than to industrial safety. The imagined benefit of saving 0.01 mSv (1 mrem) leads to a larger resource allocation for radiation safety. Commonplace signs and slogans promoting the fact that “Every Millirem Counts” further reinforce ALARA and its misguided basis. The resources devoted to saving trivial doses come at the expense of worker health and safety and prioritize radiation safety based on the ALARA myth over industrial safety. These issues go beyond trip-and-fall hazards. The imagined radiation risk is deemed to be more important than actual risks. For example, steam and chemical burns and heavy load drops are real events that have occurred and caused serious injuries. These are real issues rather than the imagined benefits derived from LNT/ALARA.

8. Conclusions and Recommendations

The reports and associated data, summarized in Section 6, present credible information to challenge the LNT hypothesis. These data strongly favor rejection of the LNT hypothesis. Moreover, the observed positive benefits of low-dose radiation provide a strong basis for elimination of the LNT hypothesis and its associated ALARA principle.

Based on the aforementioned results and the references cited in this paper, the following conclusions and recommendations are offered:

1. High-dose radiation is useful and has a positive effect in treating cancer. The use of radiopharmaceuticals and external beams have a proven record in treating cancer.

2. The biological responses to low-dose and high-dose radiation are fundamentally different. One of the key differences is activation of the human immune system following low-dose radiation exposure.

3. The biological response to ionizing radiation is an important consideration in mitigating the detriment induced by low-dose radiation. As a matter of design, the human immune system is activated by low-dose radiation to counter biological detriments produced by the ionizing radiation. Moreover, a growing body of research supports a net positive benefit from low-dose radiation.

4. Low-dose radiation has been shown in numerous cases to have a positive effect that lowers the risk of cancer and alleviates other medical conditions.

5. Low-dose radiation exposure does not imply risk. In fact, the low-dose radiation has a positive or hormetic effect.

6. Although research involving the effects of low-dose radiation should be encouraged, it should be focused on improving the early medical approaches for utilizing this tool to treat illness, lower cancer risk, and improve longevity. Investigation of signal pathways [37] will be an important consideration in optimizing low-dose treatment approaches.

This research will justify replacing the flawed ALARA concept with the radiation induced disease eradication and suppression (RIDES) approach. The RIDES approach will permit low-dose ionizing radiation to become a powerful medical treatment protocol.

7. Physicians should be free to select treatment methods without being influenced by concerns for the radiation dose delivered to a patient. The physician should act in the best interest of a patient and not be influenced by reports that has been used to encourage minimal dose delivery for imaging procedures. Medical personnel should be free of such influences, and take measures deemed to be in the best interest of patients. The RIDES approach should be implemented when appropriate and replace the ALARA philosophy.

8. *De minimis* dose (DMD) levels should be established below which personnel do not require radiation monitoring or control. Establishing a DMD has several options.

The DMD could be based on the annual background dose (e.g., 3 mSv in the US). Given the variability of background levels throughout the world and the lack of increased cancer incidence at locations of higher dose levels, this approach is

justified and could be set at a higher value. For medical exposures, physicians should have maximum flexibility to treat their patients to ensure their health and well being.

9. Radiation protection regulations based on the DMD and RIDES approaches could be further strengthened by research that investigates variations in genetic susceptibility in radiation workers. Workers found to have a genetic composition that increases the risk of radiological work should be monitored to ensure a positive quality of life.

These considerations are not unique and can be improved by other authors challenging this work, further expanding its content, and offering additional alternatives. There is no magic solution to changing radiation protection regulations from the traditional LNT and ALARA paradigms to a credible science-based approach.. However, there are significant benefits to this approach. These efforts will foster a better allocation of resources, promote worker and patient health and safety, and expand the beneficial uses of radiation and radioactive materials.

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