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The impact of dose rate on the linear no threshold hypothesis

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ABSTRACT

The goal of this manuscript is to define the role of dose rate and dose protraction on the induction of biological changes at all levels of biological organization. Both total dose and the time frame over which it is delivered are important as the body has great capacity to repair all types of biological damage. The importance of dose rate has been recognized almost from the time that radiation was discovered and has been included in radiation standards as a Dose, Dose Rate, Effectiveness Factor (DDREF) and a Dose Rate Effectiveness Factor (DREF). This manuscript will evaluate the role of dose rate at the molecular, cellular, tissue, experimental animals and humans to demonstrate that dose rate is an important variable in estimating radiation cancer risk and other biological effects. The impact of low-dose rates on the Linear-No-Threshold Hypothesis (LNTH) will be reviewed since if the LNTH is not valid it is not possible to calculate a single value for a DDREF or DREF. Finally, extensive human experience is briefly reviewed to show that the radiation risks are not underestimated and that radiation at environmental levels has limited impact on total human cancer risk.

1. Introduction

Radiation standards are set primarily based on human epidemiology studies with a focus on the A-bomb survivors. These data are evaluated using the Linear-No-Threshold Hypothesis (LNTH) to derive risk factors. This event exposed a large human population to graded radiation doses delivered in a very short time. Serious efforts made it possible to estimate individual doses and to relate the cause of death and the frequency of disease, especially cancer to the dose of that individual. The exposed population was compared to a carefully matched control group not exposed to the bomb. Such exposures as well as studies on radiation therapy patients have been shown to increase cancer frequency [1,2,3,6]. These studies also suggest an increase in several non-cancer endpoints such as cardiovascular disease [4] cataracts [5] and stroke [6,7]. It is important to note that the two populations compared, those exposed to the bomb and those not exposed have very different life experiences. In addition to the radiation from the bomb, the exposed population was exposed to trauma, blast, burns and stress, all of which may contribute to the excess cancer observed. Most of the excess cancers were in the highest dose groups with little significant difference seen in those with lower doses.

To evaluate the scientific validity of the Liner-No-Threshold Hypothesis (LNTH) for radiation risk assessment, it is critical to understand and account for, the substantial influence of both dose and dose rate with respect to potential adverse effects on biological systems. Since the first demonstration of the impact of radiation on biological organisms it was recognized that when the same dose of radiation was delivered over a short period of time it was more effective in producing biological changes than when it was given over a longer time. Consideration of both have been involved in regulation of radiation exposure to protect workers and the public from harm. The use of the LNTH in standard setting has included a Dose-Dose Rate Effectiveness Factor (DDREF) that recognizes the responses to low doses and low-dose rates are less effective in increasing risk than single acute exposures (National Council for Radiation Protection and Measurement [8,9] United Nations Scientific committee on the Effects of Atomic Radiation [10,11] and National Research Council/National Academy of Sciences [12]. The recognition of the influence of dose and dose-rate in the low dose range has resulted in a range of values for the DDREF, for example 1.5 [12], 2.0 for the ICRP 2007, and the French Academy suggested that at low doses and dose rates the DDREF may be very high [13]. Recently the German Commission on Radiological Protection (Strahlenschutzkommission [SSK] suggested that the DDREF be abolished, that is that it be set at 1.0 [129]. If, as suggested by the German group, the DDREF is 1.0, the LNTH is applicable in all situations. In addition, it would be accurate to use collective dose to estimate risk regardless of dose rate and there needs to be no consideration of the role of dose rate on risk. The Health Physics Society strongly opposes this practice and suggests that collective dose should play little role in risk assessment [14]. Using collective dose, it is possible to sum many small doses or doses delivered at a low-dose rate to a large population and derive a large total collective dose. This collective dose combined

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with a risk factor derived from a single acute exposure, has been used to calculate a predicted number of excess cancers from such treatments as CT scans [15].

To better understand risk associated with low-dose rate exposure it is important to define the terms used. The use of DDREF has always been considered necessary for converting cancer risks derived at relatively high and acute doses, primarily from epidemiological studies of the A-bomb survivors [1,2,3,6] to calculate risks in the low dose (< 100 mGy) and dose-rate (< 5 mGy/h) range. However, it has been proposed that it is more appropriate to consider both a low dose effectiveness factor (LDEF) and a dose-rate effectiveness factor (DREF) for risk estimate calculations [16,17].

The LDEF is calculated as the ratio of the slope of the linear extrapolation from a point on the linear quadratic (LQ) curve and the slope of the linear component of this LQ curve. Thus, for acceptance of this approach, it is essential to establish the dose-response relationship for the induction of cancer and show that it fits a LQ function. For leukemia in the A-bomb data this seems to be the case while there are still uncertainties associated with the effects of low doses for solid cancers which have been postulated to be linear [3]. Recent studies suggest that using the shape of the dose response curve to estimate a dose rate effectiveness factor does not fit the data [18]. Comparing slopes of dose-response relationships derived for high and low-dose rate exposures provides more accurate assessment of the DDREF. This has been demonstrated for both human data [18] and for large mouse studies [19]. These studies all demonstrated DDREF values that were greater than 2.0 and suggested the need to reevaluate the current values used for standards. Calculation of a DDREF assumes that the dose-response relationship in the low dose region is linear. If it is not linear then it is not possible to calculate a single value for a DDREF.

The more acceptable way to calculate a DREF is by comparing the ratio of the slope of the dose response for acute doses to that for the same doses delivered at a low-dose rate [16,19,20]. With this approach it is possible to evaluate the influence of high doses delivered at a low-dose rate such as deposition of internally deposited radioactive materials in Beagle dogs [21,22].

The development of modern molecular and cellular biology combined with new technology made it possible to measure biological responses in the low dose region that were not possible in the past. The application of these techniques to low doses and dose-rates by the Department of Energy Low Dose Radiation Research Program (http://lowdose.energy.gov). The program made it possible to measure radiation responses in the low dose and dose-rate region [23]. Similar approaches have been used in the European Union (MELODI, Epirad bio, Store and DoReMi) (http://www.doremi-noe.net) the Japanese research IES (http://www.ies.or.jp/index_e.html) and the Korean Society for Radiation Bioscience (http://www.ksrb.kr/english/into/intor_01.asp). This research demonstrated the need for major paradigm shifts in the field of radiation biology [24].

- Hit theory must be replaced by cell/cell communication and the role of the response of the whole organ not single cells as critical for in cancer induction. Many multiple level biological organization changes are required to induce cancer [25].
- The mutation theory of cancer and the role of mutations in the induction of cancer demonstrate that mutations play a role in cancer induction but alone may not be sufficient to produce this complex disease. The single mutation theory of cancer must be questioned.
- Extensive research demonstrated adaptive protection mechanisms at many levels of biological organization [26]. Marked differences in the cell and molecular responses observed in the low dose and dose-rate region compared to those seen in the high dose region demonstrated that the LNTH cannot be supported by new cell and molecular data [27].

This manuscript is organized to present data at all levels of biological organization. The data at the cell and molecular level are presented first to provide a mechanistic basis for the manuscript. Experimental animal data was required to link the mechanistic data to real cancer data with all defense systems in place. To provide a better basis for the cancer risks in humans experimental dog data is used. Finally, human data where large populations were exposed to low doses are briefly reviewed. This brief explanation helps the reader follow the flow of the manuscript.

Using modern data, the influence of dose-rate has been evaluated at the cell and molecular level on the key events in the critical pathways to the induction of cancer [20]. This approach is similar to how the Environmental Protection Agency (EPA) establishes regulatory limits for many chemicals [28–30]. This research resulted in a DREF of much greater than one demonstrated for many of these important changes in the progression of normal cells to become cancer [20].

Observations on the influence of dose rate in whole animal studies have been published for many years. Without exception the protraction of radiation dose results in less biological change than observed with a single acute exposure, regardless of the endpoint measured [21,22]. The majority of the data show large thresholds below which increased cancer frequency cannot be detected.

This experimental data is supported by low-dose rate exposure to human and taken as a whole supports a DDREF much greater than one and shows that collective dose is not a useful concept.

2. Results

2.1. Molecular, cellular and tissue data

2.1.1. Background information

Radiation standards have, for the most part, been established based on human epidemiology data using the LNTH extrapolation from the high dose data combined with a DDREF factor for the low dose and dose rate exposures. Data from molecular, cellular and tissues have been evaluated but had little impact on standards in the past. As the level of sophistication in these fields has developed the power to measure both adverse and beneficial biological changes in the low dose region has increased. It is now possible to measure the influence of both dose and dose-rate on the critical steps needed to change a normal cell into a cancer. These steps have been summarized, published and updated [25] and called the Hallmarks of Cancer (Fig. 1). These changes are observed in cancer and seem to be essential for the evasion of defenses, progression, development and metastasis in cancer production.

Using these Hallmarks as a guide, studies on the role of dose rate on molecular, cellular and tissue level changes in key events along the critical pathways needed for the development of cancer have been conducted and reviewed [20]. When comparing the responses of these sensitive molecular, cellular and tissue systems following exposure to high and low-dose rates of low linear energy transfer (LET) ionizing radiation three major categories of responses were observed and are discussed in the following sections.

- First, there are many publications where single or small numbers of doses were delivered at either a high or low-dose rate. In these studies, a marked response was observed following high dose rate with little or no response for the same endpoint exposed to the same dose but delivered at a low-dose rate. Since the response to the low-dose rate is zero or not detected it is not possible to directly derive a DREF. However, these studies suggest a very high DREF. To estimate DREF from any study one divides the response to the high dose rate by the response to the low-dose rate, in many of these studies, zero. Dividing any value by zero results in infinity, making it impossible to assign a numerical value.
- Second, studies were conducted where complete dose-response data were available following exposure to high and low-dose rates. For such studies the linear slopes of the dose-response relationships

were compared and the slope of the response following a high dose rate exposure was divided by the slope of the low-dose rate and a positive DREF factor derived. In most cases these studies supported a DREF value much greater than one with some with values as high as 30.

- Finally, there were several studies where the exposure to low dose or dose rate resulted in a decrease in the molecular, cellular or tissue responses below that observed for the controls. For such endpoints a negative or protective DREF value would be derived. This suggests a protective effect for low dose and dose-rate and such data would require the use of negative values in any model to describe risk [31,32].

Much of the early data on the biological responses induced by low doses of radiation were derived from the U.S. Department of Energy Low Dose Research Program and have been summarized in a book [27]. This book and other publications provides insight on the data at the molecular, cellular and tissue level [20,27]. A brief summary of the three types of studies described above is provided in the following sections.

2.2. Molecular and cellular changes

2.2.1. A single dose delivered at a high vs low-dose rate

Single or small numbers of different doses were delivered at a high or low-dose rate and cell and molecular measurements were made to evaluate the influence of dose rate on biological responses. These measurements were made at several different levels of biological organization. For many endpoints it was possible to measure a response following a low dose given at a high dose rate, but no response was detected when the same dose was delivered at a low-dose rate. If there is zero response following exposure to low-dose rates and the biological response following acute exposures is divided by zero or the response following low-dose rate exposure this results in infinity which has little meaning. Perhaps if the doses would have been higher for the chronic exposure a response could have been detected. This was seen for DNA damage where low doses given at a low-dose rate resulted in no detectable response while the same dose delivered as an acute exposure resulted in a readily measurable response [33]. This could be related to the non-linear formation of DNA repair foci where, per unit of dose, there were many more foci after low doses than were observed after higher doses [34]. However, these data are in direct conflict with data which demonstrated that at low doses, the dose required to trigger repair of DNA was not activated and no repair was detected [35,36]. More research is needed to resolve these differences in DNA repair in the low dose and dose-rate region.

Chernobyl created an interesting experimental setting. The dose from the accident in some locations was very high (greater than 1.0 Gy/year) but the dose was delivered at a low-dose rate. Attempts were made to measure mitochondrial DNA damage in bank voles exposed to this radiation environment and none was detected. However, if the same dose was delivered as an acute exposure marked damage was detected [37]. Studies were conducted to detect the induction of micronuclei in the bank voles and the same result found. No response to the low-dose rate exposure with a marked response following high dose rate [131]. Additional studies were conducted with C57B/6 and BALB/c mice to determine if this response was related to the evaluated animal species with the same result [38], which supported the earlier work on micronuclei [39]. These measurements suggested that the dose rate effectiveness factor is very large.

2.2.2. Complete dose response, high and low-dose rate (Response higher than controls)

The second type of studies reviewed [20] had data that had complete dose-response relationships with both high and low dose-rates both of which resulted in an increased level of cell and molecular change above that seen in the controls. For these data sets, it was possible to fit the data and compare the linear slopes of the dose-response relationships to derive a dose rate effectiveness factor (DREF). These data also represent a range of different levels of biological organization. At the DNA damage and repair level the frequency of γH2AX foci was measured as a function of dose rate over a range of doses up to 5.0 Gy. Following both high and low-dose rate exposure there was a linear increase in the frequency of γH2AX foci. When the slopes of the lines were compared it resulted in a very large DREF, about 30.0. Such data makes a strong case that the LNTH is not valid and that collective dose cannot be used when the doses are delivered at different dose rates.

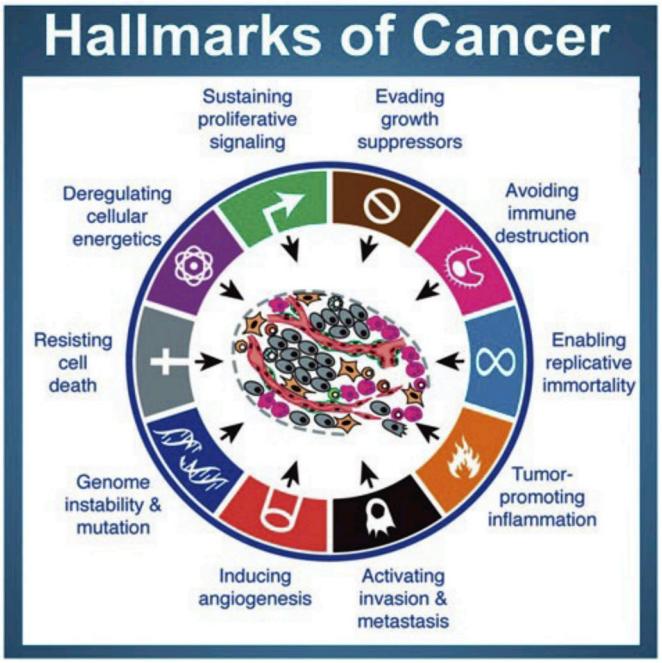

Fig. 1. The Hallmarks of Cancer demonstrates the changes that must take place for a cancer to be expressed. These changes range from the molecular to the whole tissue and illustrate that there are multiple changes needed to result in cancer. Most of these are not related to a simple mutation but involve tissue and whole animal responses [25].

Changes in gene expression and alterations in metabolic pathways have also been evaluated as a function of dose-rate. It was determined that the gene expression changes as a function of dose [40–42] and that the types of genes expressed at high doses are different from those produced following low-dose rates. Many of the genes activated at by low dose and low-dose rate exposures were involved in processes that seem to be protective while many of the genes activated after high doses are responses to damage. It was demonstrated that changes in oxidation/reduction pathways were modified as a function of dose and dose rate [44]. Changes in MnSOD and NF-kB were noted with low doses being suggestive of protective changes and high doses as damaging [45,46]; [123]). Many of these studies were summarized by Ref. [47]. It was also determined that different sets of genes were activated as a function of dose rate, time after exposure, and tissue types and that many of these genes were related to the induction of stress responses [48]. Extensive research has suggested that changes in gene expression can also be used as a biomarker of radiation dose for either high or low-dose rate exposure [49–51]. Many of these studies suggest that the LNTH is not valid with a DREF greater than one but none of them are useful in estimating a value for DREF.

Dose-response relationships have been measured for the induction of chromosome aberrations in the liver of Chinese hamsters after exposure to both acute and protracted whole-body exposure to ^{60}Co or

protracted exposure from internally deposited radioactive materials. Since the dose-response relationship was linear for the protracted exposure and non-linear for the acute exposure it was not possible to derive a single value for a DREF. If the response at a single dose, such as 1.0 Gy was used as the basis for the comparison, values of about 2.0 were derived with the values increasing as dose increased [52]. Similar values (1.8) were derived for chromosome aberrations in human blood lymphocytes given dose rates that varied from 400 to 1.9 rads/hour and comparing the responses again at a total dose of 1.0 Gy [53]. Using advanced chromosome painting techniques, it was possible to derive an alpha coefficient for the induction of chromosome translocations, the aberrations thought to be the most important in the induction of cancer [54]. This linear coefficient makes it possible to compare acute and chronic exposures. Using these advanced chromosome techniques [55] was possible to estimate DREFs which ranged from 2.0 to 3.0 depending on the dose used for the comparison.

Several studies focused on induction of chromosome aberrations in Chinese hamsters which were injected with ^{90}Sr-^{90}Y. In these studies, the aberration frequency increased as a function of dose rate [56,57]. It was postulated that the dose accumulated in each cell cycle was responsible for the damage observed at metaphase in these rapidly dividing cells [20].

Dose-response relationships were observed and measured as a function of both high and low-dose rate and the frequency of micronuclei in lung fibroblasts showed a linear dose-response relationships (Fig. 2). This makes it possible to divide the slopes of the lines and directly derive a DREF. When the acute exposure response was compared to that following a 4 h protraction of the same dose (dose rate 0.96, 1.95 and 2.9 Gy/hr) the DREF was 2.6, this value increased to 6.0 as the exposure time was increased to 67 h and the dose rate decreased (dose rate 0.059, 0.12, and 0.17 Gy/hr) [58]. Such data demonstrate that collective dose cannot be used and that dose rate is very important. These data do not provide scientific support for the LNTH without the use of a DREF.

For cell killing, measured as the ability to form colonies following exposure, the impact of dose rate was very dependent on the genetic background of the cells with a range from 1.0 to 10.0. With the same genetic background, it was determined that the DREF was greater than 10.0 as the dose rate continued to decrease [59]. Thus, cell killing shows a marked dose rate effect with repair in the low dose and dose rate range providing additional data that does not support the use of collective dose or the LNTH.

2.2.3. Complete dose response, high and low-dose rate (Response to low dose lower than controls)

The third type of response found as a function of low dose and dose rate exposures was when the radiation resulted in a decrease in the response below that observed in the controls.

Programmed cell death or apoptosis plays a critical role during fetal development as cells die during differentiation to produce organs. Recently it has been shown that apoptosis is also induced by exposure to ionizing radiation [60]. A critical observation about apoptosis is that it can be induced differentially in transformed cells resulting in a higher frequency of death. This differential cell killing results in a decreased risk following exposure to low doses of radiation with a decrease in the number of transformed cells. In the low dose and dose region of the dose-response relationship the frequency of transformed cells undergoing apoptosis was demonstrated to be higher than normal cells [61,132] . This selective apoptosis of transformed or damaged cells may result in a decrease in cancer risk and can be used to explain why low doses of radiation has been shown in some studies to reduce both cell transformation [62,63] and mutation frequency [64]. Such observations cannot be ignored and provide direct evidence that at low doses and dose rate the risk is either not measurable or may in fact be protective.

Very low doses delivered at a high dose rate have been shown to decrease the frequency of transformed cells to values below that observed in the control cells [62]. When the dose was delivered at a low-dose rate the frequency of transformed cells remained below the level observed in the controls for total doses as high as one Gy [65]. This is illustrated in (Fig. 3). It is important to note that each experiment on cell transformation must be related to its own control value since long term culture also increased the cell transformation frequency.

For transmitted mutations in mice it was determined early in the history of radiation biology that protracted exposures were less effective in producing mutations than single acute exposures to the same dose [66,67] with a DREF of 3.0 suggesting a non-linear dose response. Further research was conducted to determine the type of mutations that were produced by the radiation and it was determined that most of the dose-rate effect was seen for large deletions, such as those mostly produced by ionizing radiation, again with a DREF of about 3.0 [68]. When other types of DNA changes, which resulted in transmitted mutations were evaluated it was determined that the high and low-dose rate resulted in similar frequency of mutations suggesting that the DREF would be 1.0 for mutations that did not include large deletions and gross rearrangements [68].

2.3. Animal studies

2.3.1. Rodents

Moving from the molecular, cellular and tissue levels of biological organization it is critical to evaluate the whole animal responses to low-dose rate radiation exposures. Extensive research has been conducted using animals to demonstrate the influence of dose, dose rate and dose distribution on the induction of cancer. This manuscript starts by discussing rodent studies, which demonstrated that whole-body exposure to low-dose rate was less effective than high-dose rate in producing several different types of cancer [69]. These data, along with other information, were used by BEIR VII to estimate a DDREF of 1.5. There are several problems with rodent studies. First, many rodents die of specific diseases at early times so that the limited lifespan does not provide the needed latent period for the observation of radiation induced cancer. Second, the type of cancer produced by radiation is dependent on the rodent strain. It seems that each type of laboratory rodent produces a unique cancer type following radiation exposure so that they do not have the wide range of different cancers seen in humans. In addition, some rodents are very resistant to radiation while others are more sensitive. For example, rats develop a high frequency of lung cancer when exposed to radon while hamsters do not have a dose related increase in lung cancer. Some strains of mice are very resistant to radiation induced cancer, C57B/6 while other strains BALBc are more sensitive. These differences make extrapolation of cancer risk in rodents across species to humans almost impossible. Rodent studies conducted at the Argonne National Laboratory have been published and after careful reviews [19]. confirmed that the data on radiation induced life shortening could not be fit to a linear quadratic function used to evaluate the influence of dose rate in human studies (BEIR VII). To evaluate the influence of dose rate it is important to compare the slopes of dose-response relationships. The animal data all support the use of either a negative or high DREF suggested that dose rate has a marked impact on cancer frequency. These high values for DREF do not support the LNTH and make the use of a dose rate factor of one suggested (German Commission on radiation Protection 2016) non-supportable by basic science. Thus, there are dose rate effects at every level of biological organization from the molecular to experimental animals.

2.3.2. Dog experiments

Many years of research using the Beagle dog as the experimental animal, have been conducted and published on the health effects of internally deposited radioactive materials. The dog makes a good experimental animal. It has a long-life span and makes studies on latent period useful. The dog develops a spectrum of tumor types that are

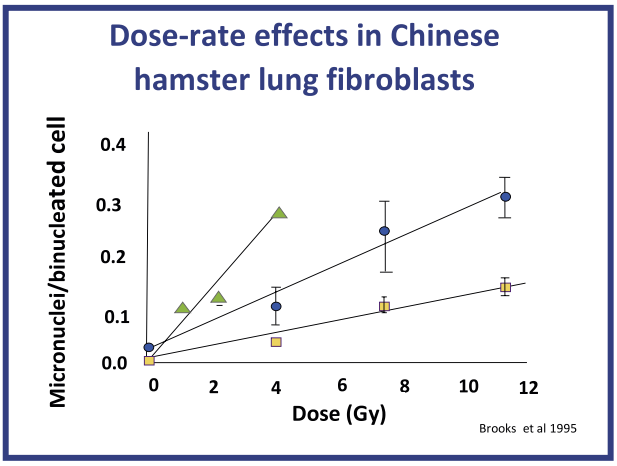

Fig. 2. This figure plots exposure in Gy against the frequency of micronuclei in lung fibroblasts. The figure demonstrates that low-dose rate exposures are less effective in producing chromosome damage than acute exposure [58].

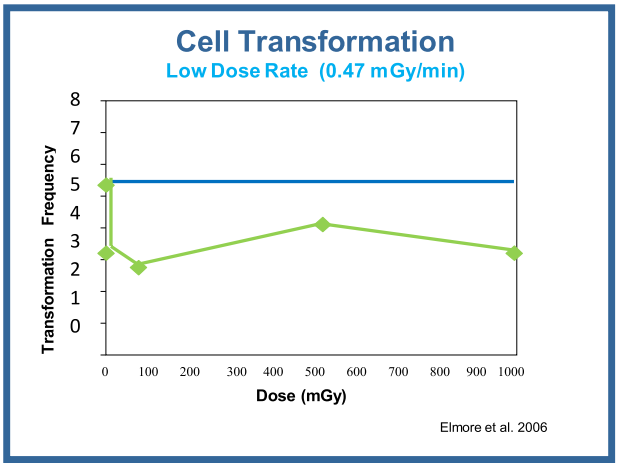

Fig. 3. Cell transformation frequency is plotted as a function of radiation dose. The dose was delivered at a low-dose rate 0.47 mGy/min with doses up to 1000 mGy (1.0 Gy). These low-dose rate exposures resulted in a depression of the cell transformation frequency below that observed in the controls [65].

similar to those seen in humans. Following single acute exposure to radiation the induced cancer frequencies are similar to that observed in humans [70]. The dog is large enough that each animal can be treated as a clinical subject so that important biological changes like pulmonary function [133], blood counts [71], blood chemistry [72] and histopathology and tumor type [73] can be measured as a function of time after the exposure. This animal model makes it possible to carefully define the distribution, dose and changing dose rate for each individual and to relate these dosimetric parameters to the biological changes observed. Extensive summaries of the experimental designs and results of the dog studies were published in two books [21,22]. Lifetime dog studies conducted at several different laboratories, were carefully integrated and monitored and were designed to determine the dose and dose-rate effects of radiation. Of special note is that the dog was used to study the impact of internally deposited radioactive materials (both high and low-LET) on cancer frequency and distribution. It was possible to relate the dose distribution with the cancer distribution so that it was possible to determine if the cancers were induced in the organs where the nuclide was concentrated. The studies demonstrated that the organ with the highest concentration and the highest dose was the organ at highest risk. With this non-uniform dose distribution very high doses could be delivered to these organs and the animals followed over their life time. After very high radiation doses were delivered at a low-dose rate, a very high (almost 100%) of the dogs developed cancer [74]. Many of the high-dose dogs had tumors in the tissue that received the highest doses, in these tissues cellular disorganization and chronic inflammatory disease were both observed. Both play a major role in the production of cancer [75]. It was possible to fit a linear dose response to each of the tissues and risk coefficients. The major problem associated with the analysis of this data was that for many organs the dose rate provided a better relationship between exposure and cancer frequency than total dose [76]. These data suggest that the use of the LNTH is not valid for these studies.

2.4. Whole body exposures

Early in the dog research projects there was a lack of careful evaluation of the influence of low doses delivered at either a high or low-dose rate. The first question addressed was what is the influence of dose rate following whole body exposures? Uniform dose distribution was achieved by exposure of dogs in a confined space to the gamma rays from an external ^{60} Co source. The details of this protocol have been published. Briefly, the dogs were exposed to whole body for 20 h per day for different time periods. Some of them were exposed for most of their lives to graded-dose rates. This made it possible to define the role of dose and dose rate on radiation induced disease. The results of these studies have been carefully summarized. Dogs were exposed to a range of well-defined dose rates and the biological changes determined [77–80]. Because of the short latent period, the primary cancer type and biological change observed in these animals was related to blood diseases. As the dose rate decreased to below about 5 rads/day (50 mGy/day) there was little change in life span. The incidence of leukemia and other blood related diseases increased at high-dose rates but was not increased when the dose rate was below this 5 rads/day (50 mGy/day) where there was no cancer frequency change. Although the sample size is small, the high dose and dose rates used suggest a threshold dose and dose rate below which no adverse biological effect can be detected in this experimental model.

2.5. Internally deposited radioactive material in dogs

2.5.1. Bone

Deposition of radioactive material in the body results in a chronic low-dose rate radiation exposure to the target organ associated with the radionuclide. Deposition of radioactive material in the bone has long been known to cause bone cancer. This was first seen in the radium dial painters who ingested large amounts of radium when they dipped their brushes in radium paint and tipped them with their mouth. The details of these studies have been carefully reviewed [81] and it was demonstrated that only dial painters with large doses to the bone had an increase in bone cancer [127]. There was an apparent threshold dose of almost 1000 rads (10 Gy) to the bone below which no cancers were observed. These studies demonstrated that the bone is a very radiation resistant organ, resulted in an appropriate tissue weighting factor for bone, and suggested a threshold in the dose-response relationship which does not support the LNTH.

Studies were initiated to determine if similar dose-response relationships would be observed following deposition of low LET beta-gamma emitting radionuclides. To study the impact of low LET radiation on bone cancer, animals were fed ^{90}Sr from before birth throughout their lives and the frequency of bone cancer determined. This radionuclide concentrates in bone and follows the same metabolic pathway as Calcium so the dose distribution in the bone was fairly uniform. These studies demonstrated that cancers were produced primarily in the bone, the site of the major dose [82]. It was determined that the frequency of bone cancers changed as a function of dose-rate, not total dose and the radiation related disease described by a simple model dependent on two variables for both high and low LET radiation [83]. Three dimensional plots of the data demonstrated that following

low-dose rate exposure that the dose-rate response was very non-linear [84]. Data analysis indicated that there was no increase in bone cancer over a very large range of radiation doses 2000 rads (20 Gy) and for induced leukemia and other soft tissue carcinomas about 1000 rads (10 Gy) [76]. For this organ there was a threshold dose and dose rate below which no differences could be detected between the controls and the exposed animals. In fact, the frequency of bone cancer was higher in the controlled animals than observed in the low dose and dose-rate groups. The author suggested that at these low-dose rates the lifespan is the limiting factor, as the dose accumulated over the lifespan of the animals is not adequate to induced cancer or life shortening. This paper provides a useful review of the results of the studies. The analysis was expanded to include animals that inhaled radioactive materials and had doses to the lung. Again the response changed as a function of dose rate not total dose [85]. Such studies demonstrate that very large total doses and dose rates are required to increase cancer frequency in the bone. Such data have been important in setting tissue weighting factors with bone being very radiation resistant [86,87]. The use of tissue weighting factors could be considered as a recognition of the thresholds demonstrated in the bone following exposure to both high and low LET delivered over a long period of time.

2.5.2. Lung

Inhaled radioactive materials concentrate in the lung and associated lymph nodes and provide the primary target for the radiation dose. For example, it was determined that when beta-gamma emitting radionuclides (^{90}Y, ^{91}Y, ^{144}Ce and ^{90}Sr) were locked into fused clay particles, the material was concentrated and retained for long periods of time in the lung and associated lymph nodes with almost no dose to the remainder of the body. These radionuclides have a wide range of physical half-lives so they deliver their dose with a changing dose-rate over a wide range of different times. Table 1 below shows the physical half-life, the effective half-life and the time required to deliver 90 percent of the total dose for each of the radionuclides [74].

The dose, dose rate, time of death, and the onset and type of cancers induced following these exposures has been previously reported [16]. When the dose and dose rates were very high the dogs died from lung disease, radiation induced pneumonitis and fibrosis in less than two years. The higher the initial dose rate from ^{90}Y, where 90 percent of the dose was delivered in eight days resulted in the earliest deaths. As the dose rate decreased the very high doses still resulted in early deaths. The evaluated lung data fits to the same functions as used in the bone and suggested that these data could also be described with similar simple functions). The dose rate to the lungs of these dogs was calculated using two different methods. First, the total dose to the lungs was divided by the time of death and used as a measure of dose rate [85]. This provided a method to convert all the data to “dose rate” and to fit all the data to very simple functions. This technique seemed to be useful in risk assessment and showed that dose rate was the important parameter for estimating cancer risk from internally deposited radioactive material. However, because of the very different effective half-lives shown above this metric does not represent the way that the energy was delivered or the biology of the response from these very different dose patterns, with ^{90}Y depositing half of its energy in 2.5 days and ^{90}Sr exposing and depositing energy for 600 days. This method of calculating dose rate is the total dose divided by the latent period of the cancer which is longer when the dose rate is delivered at a lower rate. Using this metric of dose rate ^{90}Sr was the least effective of the radionuclides and ^{90}Y the most effective per unit of dose rate.

Additional studies were conducted to determine a better metric for measuring dose rate for internally deposited radioactive material since the dose rate can change rapidly as a function of time depending on the radionuclide under study. It seemed appropriate to use the dose rate delivered at the time of the effective half-life. At this time half the dose would be delivered at a higher dose rate and half at a lower dose rate [88]. Thus, the dose rate was calculated at the point where 50 percent of the cumulative dose had been delivered (DR_{50}). Using this metric, which reflects the effective half-life of the radionuclide, it was shown that the order of effectiveness for the induction of lung cancer for the radionuclides studies was opposite than derived by Ref. [85]. That is per unit dose rate ^{90} Sr was the most effective and ^{90} Y the least. This seems to match the biology of the dose delivered per cell cycle or the damage that could be essential in the production of lung cancer.

Table 1
The physical and effective half-lives and the length of time required for deposition of 90% of the total dose for radionuclide infused aluminosilicate particles. This table is designed to illustrate the different exposure patterns following inhalation of beta gamma emitting radionuclides with a range (^{90}Sr 29 years and ^{90}Y 2.6 days) of different physical half-lives. This exposure results in a wide range of dose rate patterns that must be defined with useful metrics.

Radio nuclide	Physical half-life	Effective half-life in lung (d)	Time to deliver 90% of total dose
^{90}Sr	29 y	600	5.5 y
^{144}Ce	285 d	175	1.6 y
^{91}Y	59 d	50	0.5 y
^{90}Y	2.6 d	2.5	8.0 d

This metric provided a basis to determine what the biological impact of the dose rate would be in terms of how much dose was delivered for each cell turnover in the lung [75].) With this analysis it was possible to show that the tissue response and the induction of chronic inflammatory disease in the lung is an important biological change required for the induction of lung cancer. At very high doses per cell turnover cell killing was so extensive that the dogs died of acute lung disease. The stronger dogs that received high-dose exposure per cell turnover but survived the acute radiation syndrome of lung disease, developed a very high frequency of lung cancer regardless of the radionuclide inhaled. As the dose per cell turnover decreased to a level where these chronic inflammatory and fibrotic responses were not initiated. The lung cancer frequency drops to a level that was no higher than that observed in the control animals and the life span was not significantly reduced. When either total dose or dose per cell cycle was used as the matrix of exposure there was no increase in lung cancer frequency or life span in dogs that had a total dose of less than 2500 rads (25 Gy) to the lungs [16] or a dose per cell cycle of equal to or less than 250 rads/cell turnover (2.5 Gy/cell turnover) for ^{90}Sr, 1000 rads/cell tuirnover (10 Gy/cell turnover) for ^{144}Ce, 1100 rads/cell turnover (11 Gy/cell turnover) for ^{91}Y and 6000 rads/cell turnover (60 Gy/cell turnover) for ^{90}Y. These very high doses which did not increase cancer frequency or shorten life span make a very strong argument for a threshold below which little damage can be detected. If this high dose were to be delivered as a single whole-body acute exposure it would result in early lethality of 100 percent of the dogs. Thus, even protracting the dose over a few days and having a non-uniform distribution of the dose in the body allows for recovery that is significant in extending the life span and decreasing the cancer frequency and must be considered in modeling risk. Thus, there is a huge influence of dose rate and dose distribution on both cancer incidence and survival with a suggestion that in many cases negative terms are needed in risk evaluation [89]. Such an observation suggests different mechanism of radiation induced cancer from internally deposited radioactive material where the organ response is critical. For internally deposited radioactive materials the dose rate is low and the distribution of dose is non-uniform. This non-uniform dose distribution leaves many protective systems intact which are impacted by acute whole-body radiation exposure. For example, much of the immune system and the bone marrow is not modified by deposition of radionuclides in the lung. It seems that cancer is more of a complex tissue response and is not dependent on a single mutation or change in a single cell to modify all the key events in the critical pathways to cancer. As has been stated in the past “it takes a tissue to make a tumor (Bracellow-Hoff 2001)” and the whole tissue

and animal responses are the critical target for cancer. . It is important to be able to relate the induction of cancer in the lung to radiation induced tissue disruption, fibrosis and the induction of an inflammatory response. Without these tissue changes it seems that there is little risk for radiation induced lung cancer. Such studies point to the complex nature of cancer and suggest that all systems of the body are involved in both the induction and the protection against the production of cancer [26]. For low-dose rate exposure scenarios; tissue and whole-body responses seem to play a major role in the risk for cancer [26,90,91]. For many of these responses there are thresholds with total doses, dose per cell turnover and dose rates below which no change in risk can be observed. These thresholds demonstrate that the LNTH is not an accurate scientific evaluation of risk in the low dose region.

2.5.3. Liver

Some radionuclides concentrate in the liver, are retained for long periods of time and result in high doses to this organ. For example, ^{144}Ce- ^{144} Pr a beta gamma emitter, and several alpha emitters, ^{239} Pu, ^{241}Am, ^{252} Cf concentrate in human liver [86,87] as well as in dogs (Stannard 1987; NCRP 135), Primates [92], Grasshopper mouse [130] and the Chinese hamster [93]. Most laboratory rats and mice clear many of these radionuclides rapidly from the liver making them of little use in study of liver cancer from internally deposited radionuclides [93]. In addition, colloidal materials such as Thorotrast used for imaging, concentrated in the liver. Thorotrast is an alpha emitter and was injected into people as a contrast medium to evaluate wounds. This resulted in large alpha doses to the liver and increased human cancer incidence in the liver (NCRP 135). This material provides a good reference for the animal studies on the induction of liver cancer and derivation of risk coefficients for liver cancer (NCRP 135). Risk coefficients were derived for the liver using the LNTH model and are reported in (NCRP 135; [94,95]. From this report values of 15–40 liver cancers 10^{-4} Gy $^{-1}$ for beta-gamma emitting radionuclides and 560 10^{-4} Gy $^{-1}$ liver cancers for alpha emitters were estimated. Thus, alpha particles are about ten times as effective as beta-gamma exposures in producing cancer in the liver. The major problem and area of future research is the shape of the dose-response relationship in the low-dose region. Because of the long latent period for the induction of liver cancer (20–30 years in the low-dose groups) and the limited numbers of humans in these low-dose groups it was not possible to determine the shape of the dose-response relationship. There was a suggestion that the risk was lower in the low-dose groups suggesting non-linear dose-response relationships (ICRP 135). The role that liver injury plays in the induction of cancer in the liver is important. These very large doses produced by Thorotrast produce extensive chromosome damage and cell killing [96]. The interaction between liver damage from alcohol consumption and radiation exposure to ^{241}Am causes a marked increase in liver cancer in dogs [130]. Stimulation of cell proliferation following injection with ^{144}Ce-^{144}Pr also increases the frequency of liver cancer [97]. All these effects suggest that injury, cell proliferation, tissue disorganization and inflammatory disease have marked influence on cancer induced by low-dose rate radiation exposure. At doses below the levels required to produce these tissue effects there seems to be a threshold which provides data to suggest that the LNTH model does not apply to internally deposited radioactive material and large threshold values must be considered.

2.6. Human experience

2.6.1. High background areas

When one thinks about exposure to low-dose rate over a long time period the first thing that comes to mind is the wide range of doses from natural background. These doses vary over a wide range with some areas having background doses a couple of orders of magnitude higher than that seen in the rest of the world [98]. This range of high natural radiation areas (HNRA) are related to elevation and changes in content of natural radioactive materials in the earth like uranium and radon. A useful chart has been prepared by Dr. Noelle Metting from the DOE Low Dose Radiation Research Program (http://wwwlowdose.energy.gov and illustrates the range of natural background levels. In the U. S. 2–4 mGy/year covers the range of background dose without including medical exposures. Around the world there are areas with normal high background radiation driven by elevation and the presence of naturally occurring radionuclides. The Kerala Coast of India has a range from 8 to 20 mSv/year, Guarapari Brazil 30–40 mSv/year, and Ramsar, Iran 150–400 mSv/year.

Several epidemiological studies in the high background areas have failed to show a significant increase in cancer frequency in these areas. These studies have been reviewed and there seems to be major problems in the dosimetry associated with the studies and further research is required [99]. The fact that the dose cannot be related to the individual with the disease limits the power of the studies. However, the lack of a detectable response to these increased levels of low-dose rate exposure over a life time suggest that such low doses have minimal impact on cancer risk.

2.6.2. Added radiation dose from nuclear weapons testing

The second area of concern is addition of radiation exposure to the population above the normal existing natural background and the potential impact of these added doses which may correlate to an increase in cancer frequency. During the development of the Atomic weapons there have been huge populations, almost all the world, exposed to added low doses of radiation by fallout from nuclear tests. More than one hundred nuclear weapons were tested above ground at the Nevada test site with many more tested around the world. The total number of nuclear tests, the megatonnage yield and the country testing the weapons is shown in Table 2. The table shows that the U. S. tested the most nuclear weapons 1032 and the Soviet Union had the highest megatonnage yield 247. Thus, there was a total of 2029 weapons tested above ground with a total yield of 428 megatons. The megatonnage yield is directly related to the amount of radiation produced by each weapon. However, other variables are important in evaluating the dose, such as the location of the test relative to human populations, the elevation where the test was detonated (high elevation shots do not produce the same level of radioactive fallout as ground shots) and the composition of the weapon. Since the weapons were tested in both the northern and southern hemisphere the nuclear weapons tests resulted in an increase in background radiation dose to most of the population in the world. Areas close to the test sites received much higher doses than world-wide averages. With this increased radiation exposure from nuclear weapons tests it was postulated that there may be a detectable increase in cancer frequency. To test this hypothesis, the frequency of childhood leukemia, the cancer which is the most sensitive to radiation induced increase, was followed as a function of time in ten areas around the world. The results of these studies are shown in Fig. 4 [100].

The frequency of childhood leukemia is plotted as a function of time. The time shown on the figure was before 1950 and includes the time when testing above ground ended 1963 and followed through until 1990. Since childhood leukemia has a short latent period this time

Table 2
Nuclear tests around the world 1945–1996.

Country Testing	Number of Tests	Megatonnage Atmosphere
USA	1032	141
Soviet Union	715	247
UK	45	8
France	210	10
China	22	22
Pakistan	2	Not available
India	3	Not available
Total	2029	428

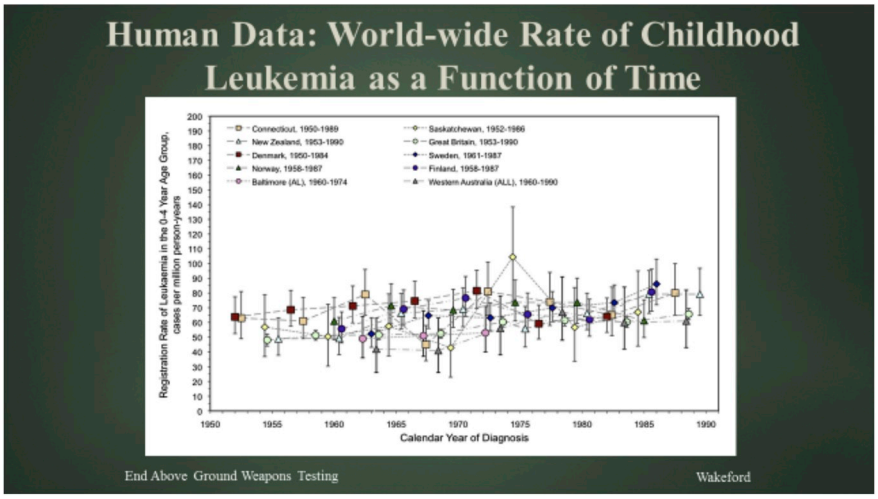

Fig. 4. The world-wide rate of childhood leukemia as a function of time. The figure illustrates that even though childhood leukemia is thought to be a cancer type that is the most sensitive to increased induction by radiation that there has been no significant change in the frequency as a function of the atomic bomb testing [100].

would be adequate to show any radiation induced increase in the disease. The figure demonstrates that there is no detectable increase in childhood leukemia as the result of nuclear weapons tests. Thus, using the most sensitive biomarker of radiation induced cancer, it was not possible to demonstrate a change in cancer as the result of world-wide fallout.

Some localized areas, like Utah, Arizona and Nevada, had population exposures from fallout that resulted in higher doses (40–60 mGy, 4.0–6.0 rad total dose) in the range of the current annual doses used to regulate nuclear exposures to workers in the nuclear industry (5 rem/year 50 mSv/year). This dose was two to three times as high as the 20 mGy/year dose used to determine that it was safe to return to the homes in Fukushima.

The distribution of radiation doses across the U. S. is shown as gamma ray exposure at 1 m above ground (Fig. 5). This figure does not take into account the total dose from beta and alpha particle exposures associated with the fallout so it may underestimate the total dose to these populations. However, these populations received their dose over a long period of time delivered at a low-dose rate.

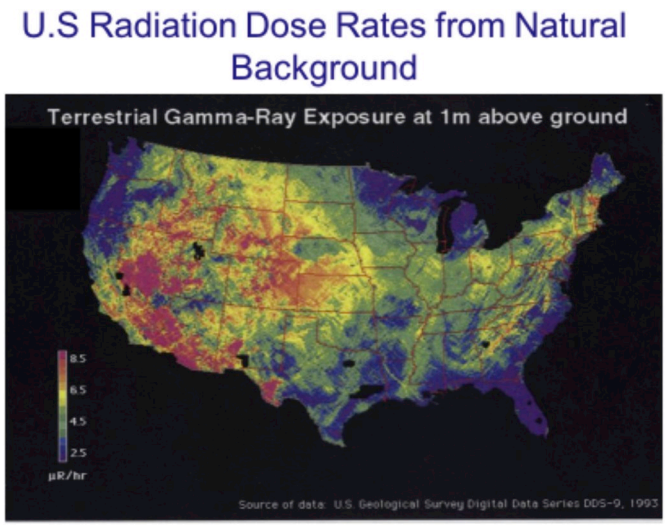

Fig. 5. This map of the U. S. shows the background dose rates for radiation measured 1 m above ground. The dose rates are shown to be influenced by both nuclear weapons testing in Nevada and elevation. This does not include exposures from internally deposited radioactive materials or beta particles.

The question then becomes, with these added low-dose rate and doses from the fallout was there an increase in cancer frequency? Data on cancer incidence in the U. S. (Fig. 6) shows that Utah has the lowest cancer frequency in the U. S. Additional data on cancer by county demonstrated that Washington County, the county with the highest fallout levels and where the highest doses occurred, have the second lowest cancer frequency in the state. To evaluate the impact of these doses on total cancer frequency in the U. S. it is of interest to compare the radiation exposures from fallout and background radiation exposures (Fig. 5) to the background cancer frequency (Fig. 6).

These figures demonstrate that the states with the highest background, the high mountain states and areas exposed to fallout from nuclear weapons testing have the lowest cancer incidence. Such data suggest that low doses of radiation delivered at a low-dose rate do not increase cancer incidence to a detectable level and that extrapolation of and predicting increased cancer risk into the low dose and dose-rate region is not supported. Thus, the LNTH is not applicable to these situations. Since these low doses are not postulated to cause a large increase in cancer any effect from the radiation could be masked by many other confounding factors such as life style and smoking. These factors have been shown to have a marked influence on the cancer incidence. Fig. 7 shows the current thinking on the environmental factors that may impact cancer frequency. What causes cancer?

Since a large fraction of the population in Utah and Idaho are members of the Church of Jesus Christ of Latter Day Saints (Mormons) and do not smoke or use alcohol, both of which are major environmental factors in the production of cancer, this life style may be the primary cause for the low-cancer frequency in these states. The urban versus rural differences and other healthier life styles may also play a role in the differences. The take home message from this discussion is that the added radiation dose from fallout delivered at a low dose did not result influence cancer frequency and is not a measurable cause of cancer. The low frequency of radiation induced cancer predicted in the low dose and dose-rate region by all the national and international committees of 5 percent/Sv or 0.005 percent/mSv is supported by these data. With a high and variable background rate of cancer about 40 percent which is dependent on sex, genetic background and life style and a high frequency of deaths produced by cancer 20 + percent it is not possible to detect any potential increase from doses in the mSv range. Radiation is not a big hitter in the production of cancer in the low-dose region. Thus, using the LNTH to predict excess cancer from fallout or natural background radiation is not supported by these documented data.

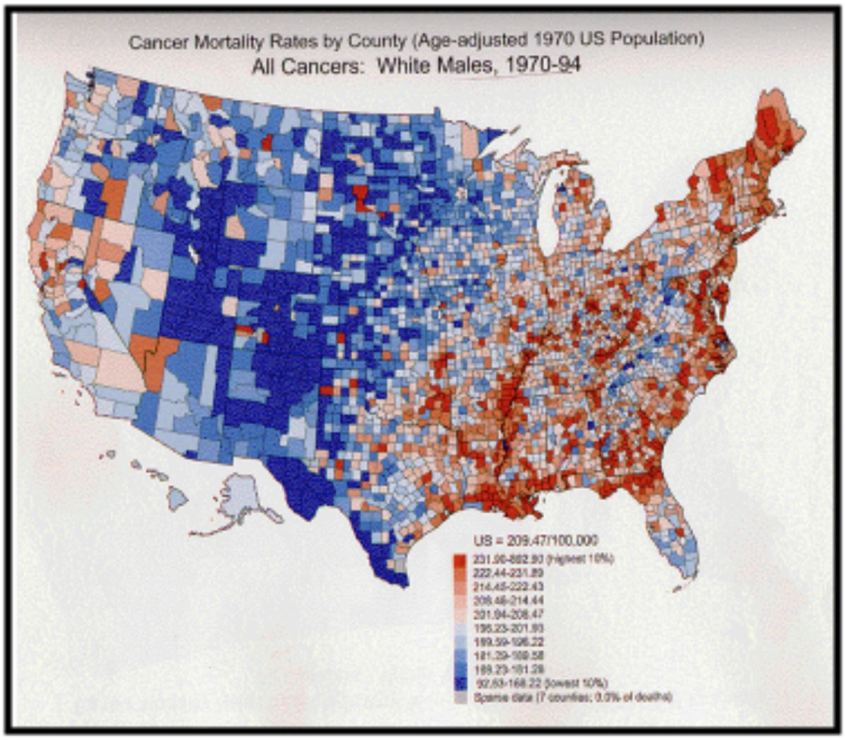

Fig. 6. This is the same map of the U. S. that illustrates the Cancer Mortality rate for white males 1970–1994. Red are high areas of cancer and blue are low. The areas with the high radiation dose rates have the lowest cancer mortality rates. A high cancer mortality rate is shown to follow the Mississippi river.

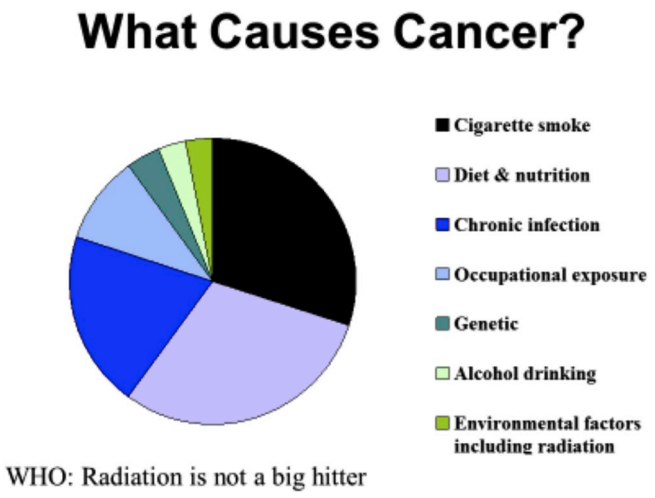

Fig. 7. This figure is taken from the World Health Organization and provides the background information needed to determine the major causes of cancer. Cigarette smoking and diet are two of the major causes of cancer. Environmental factors including radiation are one of the smaller causes of cancer. This figure illustrates how hard it is to determine the induced cancer following low dose and dose-rate radiation exposures.

3. Discussion

3.1. Paradigm shifts

With the sequencing of the genome, the development of gene expression arrays and many other technological advances in molecular biology research progressed rapidly into measuring more refined molecular and cellular endpoints. The newer data made it evident that many of the long-standing paradigm in radiation biology needed to be reconsidered [24,27]. The required paradigm shifts have forced the field of radiation biology to take a new look at many well accepted concepts in the field. For example, the hit theory for describing radiation biology needs to be replaced by a wider view of radiation biology. Since the discovery of radiation induced bystander effects, cell/cell and cell/tissue communication, result in a much larger target than a single cell for the interaction of radiation with biological systems. The single hit on a DNA molecular may produce a mutation in a single cell as an explanation for radiation induced cancer. This is not the whole story, there is a need to expand the concept to include more of a systems biology approach. DNA hits by radiation trigger many biological processes including radiation induced changes in gene and protein expression as well as post radiation modification of proteins. Research also demonstrated that radiation can induce many epigenetic changes which must be considered in risk evaluations [101]. These changes were further supported by unpredicted changes in physiology and critical pathways to cancer. It became obvious that the changes induced at the molecular level by single acute exposure to high doses were very different than those induced by low doses of radiation.

The observation of adaptive protection following low doses brought into question the long standing LNTH theory of radiation induced damage. Many molecular and cellular endpoints showed a decrease in biological response below that seen in the controls following low doses or low-dose rate radiation exposure. Each of these important paradigm shifts must be reviewed, discussed and the potential impact on radiation rules and standards evaluated.

3.2. Hit theory

The interaction of radiation with matter is described as individual energetic events interacting with single cells. These events have enough energy to cause ionizations and produce changes in important molecules. This was called the “hit theory” and many biological changes were directly related to the number of hits, the time between hits and the type of hits or energy deposition events. This provided the framework for the development of the LNTH since single hits produced important single changes in critical molecules and it was postulated that

every ionization resulted in damage and increased risk. This concept was used for most of the past research in the field of radiation biology. It was not until the development of microbeams and the ability to hit a known cell and follow its response as well as the response of neighboring cells that the hit theory was called into question. It was observed that when a cell is hit, it communicates with the neighboring cells and the total biological response is dependent not only on the cells hit but also on the response of the organ or tissue. This made the target for radiation interaction much larger than the individual cell and suggested that, much like chemicals that produce similar changes, radiation response is not a single cell event [90]. It was determined the cell/cell communication or bystander effects occurred both *in vitro* and in animal models [102,103] and *in vivo* [104].

3.3. Mutation theory

The genetic or mutation theory of cancer suggested that a single cell receives a single hit, produces a change in DNA and this would result in a radiation induced mutation. Such an altered cell could have a proliferative advantage which would, following cell proliferation, expand the mutated cell population. Further changes would result in loss of control of cell division, metaphasis and cancer. This theory was critical in the development of the LNTH for the description of risk from radiation. Recent research suggested that radiation induced cancer may also work though a wide variety of different mechanism and physiological pathways some of which may be triggered by radiation induced mutations in individual cells.

3.4. Genomic instability

The induction of genomic instability was observed in recent research resulting in the loss of genetic control and the observation of multiple genetic alterations in cell population. This condition was induced by high acute exposure to radiation. Genomic instability has been defined as a late occurring radiation induced change where the target for its induction is much larger than a gene and the cells lose genetic control. Following radiation exposure no changes are observed for several cell divisions. After multiple cell divisions the cells lose genetic control and many types of biological changes are observed, for example chromosome aberrations, polyploidy, apoptosis, and formation of clones with defined chromosome damage and multiple mutations. Genomic instability is often observed during the early stages of cancer development for many types of cancer. Genomic instability has been demonstrated both *in vitro* [105] and in animal models [106]. In all these studies the genetic background of the cells or animals played an important role in the induction of genomic instability. Multiple studies have attempted to demonstrate the induction of genomic instability in normal human cells [107] or human populations [108] and have not been able to demonstrate it. Research on radiation induced genomic instability has been reviewed [109]. Because of the lack of low dose and low-dose rate data it is not possible to estimate the impact of dose-rate on the induction of genomic instability and its potential impact on the LNTH. There have been few studies on the induction of genomic instability in the low dose and dose-rate region. Thus, there remains a controversy on the role of low dose radiation induced genomic instability and cancer induction [110]. This is an area that requires additional research. The data to date have not demonstrated genomic instability in induced by low dose or dose rate and suggest that it may not impact in these regions of the dose-response relationship.

3.5. Adaptive protection

Adaptive responses were first observed and reviewed by Wolff [111]. In their studies where cells were exposed to a small “tickle dose”, followed by a larger “challenge dose”. With this protocol it was observed that the pre-exposure to the small dose made the cells radiation resistant to the induction of chromosome aberrations. The small dose activated protective mechanisms that reduced the frequency of the aberrations below the level predicted by the sum of the two doses. This was only observed if the two doses were separated in time by a few hours. Thus, the potential impact of this adaptive response on cancer risk and radiation standards was thought to be minimal.

As research progressed it was demonstrated that a new type of adaptive response was observed. That is when a small dose of radiation was delivered at either a high or low-dose rate it produced a decrease in many key events in the critical pathways to cancer induction below the level observed in the controls [20]. This adaptive response was reviewed and defined by Feinendegen [26] as adaptive protection. This observation was first related to the induction of cell transformation, a critical step as the cells progress from normal to acquiring the characteristics needed to develop cancer. Many studies were conducted to measure radiation induced cell transformation and demonstrated that low doses of ionizing radiation delivered at either a high [112]; [62]) or low-dose rate [65] decreased the spontaneous frequency of cell transformation below that observed in control cells receiving no radiation exposure. If cell transformation *in vitro* represents a key event in the pathway as cells progress toward radiation induced cancer, then such cellular studies suggest that a negative or protective value may be required in risk models [89,113] which would directly attack the LNTH model. Other endpoints such as the induction of mutations [64,114] also demonstrated a decrease in the frequency of mutations by small doses of radiation.

3.6. Selective apoptosis

The induction of selective apoptosis, programmed cell death, was demonstrated [61]. In these studies, small doses of radiation resulted in selective killing of transformed cells which would result in a decrease in potential cancer cells below the level without the radiation exposure. This observation would provide a mechanism for the observed decrease in cell transformation and mutations described above.

3.7. Whole animal and tissue responses

3.7.1. Reactive oxygen status and inflammatory disease

The induction of chronic inflammatory disease in any tissue can result in an increase in the risk for cancer in that tissue or organ. Tissue damage was evaluated in chemical studies and it was determined that high dose chemical carcinogens which produced extensive tissue damage in the target organs were for the most part, not responsible for the induction of cancers [115]. As the mechanisms of carcinogenesis have been further studied it has become evident that radiation induced increases in levels of reactive oxygen species (ROS) in the tissues and chronic inflammatory disease play an important role in cancer induction. This has been demonstrated for a number of different tissues, bone, lung and liver discussed above [75,76,85,116]. The induction of anti-oxidant, anti-inflammatory cytokines down-regulate these reactive species and restore homeostasis (Schaue et al., 2012). Many molecular and cellular responses have been measured as a function of dose and dose-rate. Changes in gene expression with the up-regulation of genes involved in anti-inflammatory disease have been demonstrated [45,48,117]. These changes seem to be related to changes in mitochondria [118] and the ROS status of the cells [119]: [120]. Low doses of radiation decrease the levels of reactive oxygen species in the tissue which suggest protection against cancer. Other studies have demonstrated that radio-protective chemicals can have a similar impact on the ROS status of the tissues [121]. Low dose and dose-rate radiation can also induce modification of genes can alter ROS status by changing SH-containing chemicals by alteration of MnSOD and SOD-2 [46,122]. These changes have also been postulated to decrease cancer risk. Low

doses can also modify metabolic pathways that may influence the induction of cancer [123]. The data suggests that the mechanisms of action for low doses and high doses of radiation are different and that low doses may result in a decrease in cancer risk. These data help demonstrate that the mechanisms of action are different at high and low doses and do not support the LNTH.

4. Conclusions

By reviewing the literature at all levels of biological organization from the molecular to humans several important points are noted.

- At the cell and molecular level it is obvious that the responses to low doses and dose rates are very different from those following acute high doses. This suggests different mechanisms of action and different metabolic pathways are activated by high and low doses of radiation. Such data provides a strong basis for needed paradigm shifts in radiation biology. These paradigm shifts do not support the scientific basis for the LNTH.
- At the animal level, there are large data bases that demonstrate marked thresholds in the dose-response relationship for cancer induction. This is especially true for non-uniformly distributed internally deposited radioactive materials that can deliver very high doses at low-dose rates. These thresholds have been demonstrated in bone, liver and lung and does not support the LNTH.
- Human data on doses and dose rates, near or a few orders of magnitude above natural background, show no measurable change in cancer frequency. Such data demonstrates that the cancer risk values currently used are conservative and do not underestimate risk. Because of the low incidence of radiation induced cancer per mSv or mGy exposure in humans study populations have to be very large to detect changes predicted by the LNTH. Currently in the range of natural background radiation doses and dose-rates changes in cancer frequency have not been detected.

The LNTH has been useful in setting regulations and has been useful in worker protection in the past. However, extensive past and present research has demonstrated that LNTH is not a good scientific representation of the responses to radiation in the low dose and dose-rate region and should not be used in combination with collective dose to predict cancer frequency. The over-estimate of cancer risk using the LNTH has resulted in extremely high costs with no medical benefit. In addition, the suggestion that every ionization increases risk has contributed to many practices and rules that result in huge expenses and public fear [124]. This excessive fear has caused harm in the past. For example, in Japan during the Fukushima event, the measured doses were not projected to increase cancer frequency, fear and policy resulted in evacuation which resulted in the death of many people. Fear has driven public perception in many areas and made it difficult to use radiation in many areas (medicine, agriculture and power) where it has great benefit. The present manuscript provides an overview of the science associated with radiation at all levels of biological organization from the molecular to humans and demonstrates the need for serious paradigm shifts in the field of radiation biology and suggests the need to reconsider the use of the LNTH in rule making and regulations.

Declarations of interest

ALB was partially funded for this research by Bruce Power. He does not view this as a conflict of interest since they had no input into the production of this manuscript. ALB worked for twenty years at the Lovelace ITRI but was not directly involved in conducting the dog studies. He reviewed and provided early data input.

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Transparency document

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