The Impact of Research on Low Doses of Ionizing Radiation on Cancer Risks

These few paragraphs are a summary & interpretation of the following 15 page commentary "The Impact of Research on Low Doses of Ionizing Radiation on Cancer Risks"

Research data generated over the past 70 plus years has demonstrated that either high or low doses of radiation delivered at a low dose-rate is less effective at all levels of biological organization in producing biological change than when the same total dose is delivered at a high dose-rate. Dose-rate is an important variable in understanding radiation risk**. Recent research has helped us to understand the mechanisms involved in these differences. It has been determined that when low doses of radiation delivered at a low dose rate, as was the case for the fallout, the radiation activates a unique set of genes which result in biological responses that are protective. This could be thought of as being similar to the fight or flight response. Thus, low doses of radiation activate genes that modify and protect against subsequent radiation insults. An analogy could be an immunization against a disease where the body is primed by a modified disease agent and more capable of dealing with future attacks.**

The responses to low doses are unique and seem to suggest the need for a rather large Dose, dose-rate effectiveness factors DDREF and a non-linear dose-response relationship. At high dose-rates, using the LNT model, the cancer risk is estimated to be 10% per Sv (NRC/NAS 2006). In the low dose range, less than 10 mSv, such a response cannot be detected in humans.

The implications of this research when relating it to radiation dose received via fallout from the Nevada Test Site to the downwind region is that **when low doses delivered at a low dose-rate,** one would not expect any increase in cancer rates because fallout by its very nature is received in a chronic fashion (received over time) versus acutely (all at once). And the published doses to the offsite public fall in the low dose range. An examination of the historical cancer rates published by the Utah Cancer Registry and the National Cancer Institute supports this conclusion. These data are reported elsewhere on this web site.

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The Impact of Research on Low Doses of Ionizing Radiation on Cancer Risks

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Summary:

An important questions remaining in radiation biology is the cancer risk after low dose and dose-rates radiation exposure to low-LET radiation. Using modern biology this manuscript provides a review of data from recent research on dose and dose-rate responses in critical pathways as cells progress from normal to cancer. Dose, dose-rate effectiveness factors (DDREF) can be derived for each key event along the critical pathway. This approach widely used by the EPA to evaluate the risk from chemicals where there is little or no human data available can be applied to radiation risk. Dose and dose-rate response relationships for key events, in the critical pathways, help predict the dependence of these variables on cancer risk. Data demonstrate that either high or low doses of radiation delivered at a low dose-rate is less effective at all levels of biological organization in producing biological change than when the same total dose is delivered at a high dose-rate. Dose-rate is an important variable in understanding radiation risk and support the current ICRP recommendation that a dose-rate effectiveness factor be two or greater.

Introduction:

This manuscript uses modern molecular, cellular and whole animal biology to evaluate the key events and critical pathways to cancer to help understand the effect of low dose and dose-rate radiation exposure on biological responses. This approach has been used by the Environmental Protection Agency (EPA) to estimate cancer risk and set standards for environmental chemicals (Julien et al. 2009). The insult is radiation exposure and the focus is to study the influence of dose and dose-rate in the low dose range. The responses to the key events will be evaluated at multiple levels of biological organization from the molecular to the whole animal. The dose-rate effectiveness factors in key events will be compared to hallmarks of Cancer essential for a normal cell to progress to become cancer. Using key events make it possible to use molecular and cellular data to help define the shape of the dose-response relationships in the dose and dose-rate region where it is very difficult to apply human data.

Results and Discussion:

Hallmarks of Cancer

To set the stage for the impact of molecular, cellular, tissue and animal data on cancer risk and the use of key events and critical pathways to the adverse outcome of cancer it is essential to review the changes needed for the progression of normal cells to cancer. These have been called "The Hallmarks of Cancer" and have been carefully reviewed (Hanahan and Weinberg 2000) and updated to include genomic instability, reprogramming of energy metabolism and evading immune destruction (Hanahan and Weinberg 2011). Information is available on the radiation induced dose and dose-rate response relationships for some of these but little is known about the radiation response of others. Some of the events occur early in the progression to cancer and others are late events. Little information is available on the influence of dose and dose-rate on the later events so they are not discussed in this manuscript.

The key events in the critical pathways to radiation induced cancer occur at all levels of biological organization. In this manuscript we will discuss key events at the molecular level, cell and tissue level and the organ and organism levels.

Key Events Molecular Level

At the molecular level the manuscript first focuses on radiation induced DNA damage and changes in Gene expression in the low dose and dose rate range.

DNA damage, repair and signaling

The first key event and an important hallmark of cancer following exposure to ionizing radiation and the deposition of energy in the cells is the induction of changes in the DNA. This damage is the primary cell and molecular data that support argument for the Linear-No-Threshold hypothesis. The linear dose-response relationship for high dose rate, acute radiation induced DNA damage is well defined and covers a wide range of doses (Asaithamby and Chen 2009, Erixon and Cederval 1995). The use of γH2AX as a marker of DNA damage makes it possible to extend the dose-response relationship to very low doses and dose-rates. This technique has become a useful tool (Rothkamm et al. 2007). At high dose-rates there is a linear dose-response for the induction of DNA alterations. Research has also suggested that repair of DNA damage in the low dose region is limited (Lobrich et al. 2005, Rothkramm and Lobrich 2009). This was postulated to be related to the inability of low doses to induce a sufficient amount of DNA damage to stimulate the induction of DNA repair genes (Rothkamm ea al. 2007). Both of these papers suggested that since the response is linear and there is no DNA repair at low doses the risk will increase linearly with dose. Such observations also have suggested that risk may be larger than predicted by linear extrapolation from high doses. Such data suggest that the dose, dose-rate effectiveness factor (DDREF) should be unity.

Studies on the influence of dose-rate on DNA damage suggest that it has a marked influence on the response. Recent studies demonstrated that when a dose, 400 times higher than natural background, was delivered at a low dose-rate it was not possible to detect DNA damage. DNA damage in these studies included base damage, micronuclei, or p53-inducable gene expression. None of these were increased above the background level when the dose-rate is low. However, when the same dose was delivered at high dose-rates DNA damage was readily measured (Olipitz et al. 2012). A dose-rate effectiveness factor is high but cannot be calculated since at low dose-rate the response was not measurable.

Similar studies on the influence of dose-rate on repair of DNA damage following either high or low dose rate delivered up to high total doses. When the same total doses were delivered at low or high dose-rates there was a marked difference in the frequency of γH2AX, a marker of DNA damage and repair. These observations are shown in Figure 1 where γH2AX foci/cell is plotted against radiation dose delivered at either a high or low dose-rate (Ishizaki et al. 2004). Such data result in a dose-rate effectiveness factor for the induction of γH2AX of about 35. These data suggest that the slope of DNA damage and repair is very dependent on dose-rate with low dose-rate being much less effective in producing DNA damage than high dose-rates.

Figure 1

Recent publications suggest that DNA repair centers, radiation induced foci (RFI) are formed following exposure to ionizing radiation. Research determined that formation of these centers was not linearly related to radiation dose. Following low doses of ionizing radiation (100 mGy) the number of repair centers per unit of dose was about four times higher than observed for high doses (2.0 Gy). From these studies the authors suggested a non-linear dose-response relationship with

repair being more effective after low doses (Neumaier et al. 2012). Such studies suggest that DNA damage does not increase linearly with dose. These studies are in marked contrast with the studies of (Rothkramm and Lobrich 2009) who suggested little or no repair of DNA damage following low dose or dose-rate exposures. Additional studies on the influence of dose-rate on the formation of DNA repair centers are needed. Dose-rate has a marked influence on the induction of repair centers and results in a very high dose-rate effectiveness factor.

Gene expression as a function of dose and dose-rate

Extensive advances in biological and physical sciences over the past 20 years have made it possible to measure radiation induced biological changes in the low dose and dose-rate region which were not possible in the past. These advances are associated with sequencing of the genome and the development and use of gene expression arrays. Using gene expression arrays it is now possible to measure radiation induced changes in gene expression in thousands of genes at the same time. An example of the changes in gene expression in 22,283 genes as a function of radiation dose is shown in Figure 2. It was determined that radiation exposure results in marked changes in gene expression with genes both up and down-regulation at all doses evaluated. The data demonstrated that the genes change expression pattern as a function of radiation dose. Following high dose-rate exposure, the pattern of gene expression changed markedly as a function of total dose. The figure illustrates that at doses below 10 cGy (0.1 Gy) the expression pattern is similar. At higher doses the patterns shift with high doses 200-400 cGy (2-4 Gy) the patterns are similar (Yin et al. 2003). The dose transition point in gene expression as is important as the type of genes, proteins and pathways have been characterized. At doses below 0.1 Gy many "protective" processes seem to be activated (up-regulated (blue)) and the genes down-regulated (red) change as a function of dose (Dauer et al. 2010). Such studies demonstrate that the mechanism of action and response to Key events and critical pathways change as a function of radiation dose.

Figure 2

Studies on gene expression using low dose-rate exposures were also conducted and illustrated that different genes were activated as a function of dose-rate, time after exposure and tissue type (Amundson et al. 2003b). All of these variables become important in understanding the risks associated with low dose-rate exposures. Again many of the genes activated by low dose-rate exposures seem to be involved in normal physiological processes that protect the body from harm. When this information is used to evaluate key events in critical pathways they suggest protective processes are induced by low doses and dose-rates of radiation exposure at the cell and molecular level. Such observations suggest that the DDREF for these low dose-rate exposures cannot be calculated but must be very high. The molecular data evaluating key events suggest that our current use of LNT for evaluating risk in the low dose and dose-rate region are conservative and must include a large DDREF.

Key Events Cellular and Tissue Level

At the cellular and tissue level there are many radiation induced key events on the critical pathway to cancer following low dose and dose-rate exposure. Some of these are mutations, chromosome aberrations, cell killing, cell/cell and cell/matrix communication and cell

transformation. Because of space limitations only chromosome aberrations and cell transformation will be discussed. Dose and dose-rate response data are available for these endpoints.

An endpoint used to measure chromosome damage is the frequency of radiation induced micronuclei. The dose-response relationship for the induction of micronuclei following exposure to high-dose-rates and for a range of different radiation types can be describe by a linear or linear-quadric dose-response functions (Mill et al. 1996). However, when the dose-rate is low micronuclei induced do not follow linear kinetics. In fact, studies *in vitro* demonstrated that following low total dose exposures (0.1 Gy) the frequency of micronuclei/cell was higher than the control values when the dose was delivered as an acute exposure. However, when the same dose was protracted over 48 hours the level of micronuclei observed in the cells was lower than observed in control population of cells (deToledo et al. 2006). Such data suggest that low dose-rates may be protective for the induction of micronuclei. Many other endpoints have been measured at low dose-rate and show similar responses. Because of the difference in the shape of the dose-response relationships for the induction of chromosome aberrations following high (non-linear) and low dose-rates (linear) it is difficult to derive a single value for a dose-rate-effectiveness factor. If the frequency of chromosome aberrations following a dose of one gray is used as a reference there is a range of DDREF from 2-6 (Brooks 1980, Brooks et al. 2009).

Data on micronuclei support the concept that adaptive protection exists for the induction of chromosome aberrations in the low dose and dose-rate region (deToledo et al. 2006; Dauer et al. 2010, Feinendegen et al. 2011). When the cellular or molecular response following the radiation exposure are less than observed in the control cells the data suggest that a protective factor should be calculated (Scott 2004, 2007).

Cell Transformation

A number of different systems were developed to follow the progression of cells from the normal state to a "transformed" state. Cells in culture have acquired many of the hallmarks of cancer and require only a few more changes to become "transformed". With these systems, it was possible to expose the cells to graded acute doses of radiation and carefully measure the frequency of cell transformation. Many studies were conducted measuring cell transformation that demonstrated that low doses of ionizing radiation delivered at a high dose-rate decreased the spontaneous frequency of cell transformation below that observed in control cells receiving no radiation exposure (Azzam et al.1996; Redpath 2007; Mitchell et al. 1997.

It was important to determine the role of dose-rate on the induction of cell transformation. Cell transformation frequency was influenced by dose-rate (Elmore et al.2008). Cells were exposed to multiple dose rates. Exposure to low dose-rate resulted in a decrease in the frequency of cell transformation below the level seen in the controls over a much wider dose range, up to1000 mGy, than was observed for high dose-rate exposures (Redpath 2007). Thus, low dose-rate exposure may have a protective effect over a much broader total dose range than observed for single acute exposure. These dose and dose-rate responses that decrease cell transformation need to be included in key events and critical pathways models and used in cancer risk evaluation.

Key Events Organ and Organism level

Key events from all level of biological organization are integrated into the organs and -organisms to result in the final outcome or critical event of radiation-induced cancer. At the organ and organism level we will review the following key events that can influence the frequency, time of onset and shape of the dose-response relationships for cancer. All of these are important and require careful consideration. Many other hallmarks of cancer are also important but there is little information on the influence of radiation dose or dose-rate so they will not be discussed. The only events reviewed in this manuscript include the new observation of Epigenetic Alterations as well as Cancer in Experimental Animals.

Epigenetic changes mice

Epigenetic changes do not involve changes in DNA sequences or the loss of DNA. Epigenetic changes involve methylation and activation of small RNAs. Epigenetic changes are observed in many types of cancer and may represent a key event in cancer progression (Feinberg 2004). It has been suggested that epigenetic influences during development may play an important role in the development of cancer and other genetic diseases in adults (Dolinoy et al. 2007). Environmental exposures to a number of different insults can change the offspring in a way that suggest that epigenetic mechanisms could play an important role in human health and disease (Dolinoy et al. 2007).

Only a limited amount of research has been conducted on the effect of acute low-dose radiation exposures *in utero* on epigenetic effects. Studies were conducted using the agouti viable yellow (A^w) mouse model exposed to acute exposure of 0.004-0.1 Gy. The radiation was delivered at the time during gestation when chemical treatment induced the highest level of epigenetic damage (Bernal et al. 2013). A brief summary of the data can be seen in Figure 3 where the percent of Avy male offspring with different coat colors are plotted against radiation dose (cGy) delivered *in utero*.

Figure 3

The radiation exposure resulted in hyper-methylation of the DNA and a change in the ratio of the coat color of the pups. Pups with yellow coat have a phenotype that includes being diabetic, obese, and cancer prone while pups that have an agouti-brown coat color are non-diabetic, thin and cancer resistant. This study provides data that demonstrate that low doses of ionizing radiation delivered to embryonic stem cells during early development causes both dose- and sex-dependent epigenetically induced changes at the Avy locus of this mouse. The radiation exposure related to a dose-related increased the frequency of pups with agouti-brown coat color that reached a peak at 0.025 Gy (2.5 rads) then decreased as the dose increased to 0.1 Gy or 10 rads). These mice are not obese and are resistant to diabetes and cancer. Even after the peak value at 0.025 Gy there were still twice as many offspring irradiated with low dose (0.076 Gy) had brown coats than were observed in the control offspring. The epigenetic effects were more pronounced in the male offspring. Low dose radiation exposure in this model mouse system produce an effect that is protective and decreases the risk and frequency of cancer in the offspring (Bernal et al. 2013). The data suggest the possibility of a negative risk term for estimating radiation induced risks from epigenetic effects. There is no current data on the influence of dose-rate on epigenetic changes. Such information is extremely important and suggests an area of additional needed research.

Cancer induction in lungs from Inhaled beta-gamma emitting radionuclides

In the past, limited human data were available on the effects of dose-rate on cancer risk especially following internally deposited radioactive materials. Extensive studies were initiated in the Beagle dog to provide data on the role of dose, dose-distribution and dose-rate in cancer induction. The extensive animal data on the effects of internally deposited radioactive material have been summarized (Stannard 1988). In this manuscript we discuss only the influence of inhaled beta-gamma emitting radionuclides and the role of dose and dose-rate on lung cancer induction.

Research was conducted to study the role of dose distribution, total dose and dose-rate on cancer in the lung induced by inhalation of beta-gamma emitting radionuclide. This research used different radionuclides with a range of effective half-lives in the lung ^{90}Sr (600 days), ^{144}Ce (180 days), ^{91}Y (50 days) or ^{90}Y (2.5 days). They were all put into a fused clay matrix the activity and inhaled as small particles so the activity stayed in the lungs and the lung associated lymph nodes. This resulted in a large lung dose delivered over a range of dose-rates and little dose to the remainder of the body (Brooks et al. 2009).

Figure 4 shows the dose-response relationship for survival and includes the causes of death.

Figure 4

After high dose-rates (1.5-3.0 Gy/day) with a cell cycle in the lung epithelial cells of about 30 days there would be (45-90 Gy/cell cycle), almost all the animals died within about one year after the inhalation from acute radiation induced lung pneumonitus and fibrosis (Brooks et al. 2009). However, when dose-rate was decreased (0.2-1.0 Gy/day or 6.0-30 Gy/cell cycle) many the dogs did not die early from acute lung damage. Almost all the dogs with these high doses and dose-rates developed lung cancer. Similar time patterns of pathology developed following inhalation of each of the radionuclides.

When the dose-rate was lowered to a level where the animals did not develop chronic lung and inflammatory diseases the life-span and lung cancer frequency was not significantly different from the controls. This effect was seen even though the lung dose was as high as 20 Gy. If this dose was delivered as an acute lung exposure all the dogs would quickly die. This illustrates that dose-rate and dose-distribution are both important especially when the total exposure and dose is high. Using the information that 0.1 Gy results in 100 “hits/cell indicates that an acute exposure to 20 Gy would result in 20,000 hits. If the turnover time of cells in the lung epithelium is about 30 days and it takes ^{91} Y 180 days to deliver 90% of the dose (20 Gy), then on the average, each cell would receive an estimated 3,300 “hits/cell/cell cycle”. Figure 5 provides information to demonstrate that these large numbers of hits and hits/cell cycle resulted in no life shortening or increase in lung cancer frequency. Such data illustrate the ability of the lung to repair damage and further supports the presence of a large dose-rate effectiveness factor (Brooks et al. 2009).

Figure 5

There are strong relationships between environmentally induced cellular oxidative stress, chronic inflammation, particle overloading and the induction of cancer. Many inflammatory diseases have been shown to be major risk factors in the production of both esophageal and lung

cancer. Thus, loss of control of the ROS levels in tissues and the induction of chronic inflammation both play an important role during the induction of lung cancer.

Summary

Responses at all level of biological organization are lower following low dose-rate exposure than observed after exposures to high dose-rates. The responses to low doses are unique and seem to suggest the need for a rather large DDREF and a non-linear dose-response relationship. At high dose-rates, using the LNT model, the cancer risk is estimated to be 10% per Sv (NRC/NAS 2006). In the low dose range, less than 10 mSv, such a response cannot be detected in humans. The molecular, cellular and animal data reported here support the current levels of regulation for the control of radiation exposure and suggest that they are adequately protective. The data also indicate that the LNT used in standard setting and to control radiation exposures over estimates the radiation risk for the induction of cancer in the low dose and dose-rate range.

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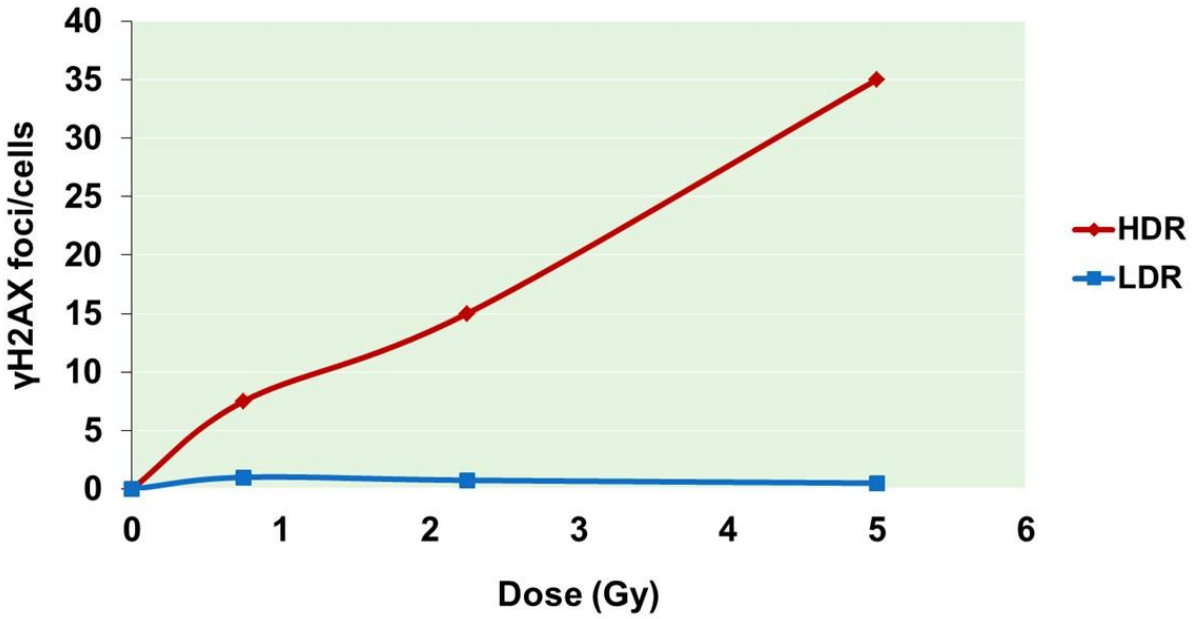
List of Figures

Figure 1.

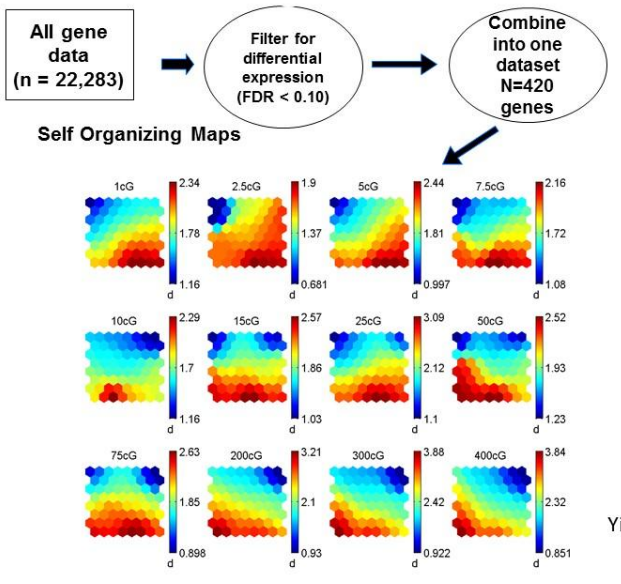
Figure 1 illustrates the influence of dose-rate on the induction of γH2AX induction. High dose-rate results in a linear increase as a function of dose whereas the slope of the dose-response relationship for low dose-rate is much lower, a factor of about 35 times.



Ishizaki et al. 2004

Figure 2

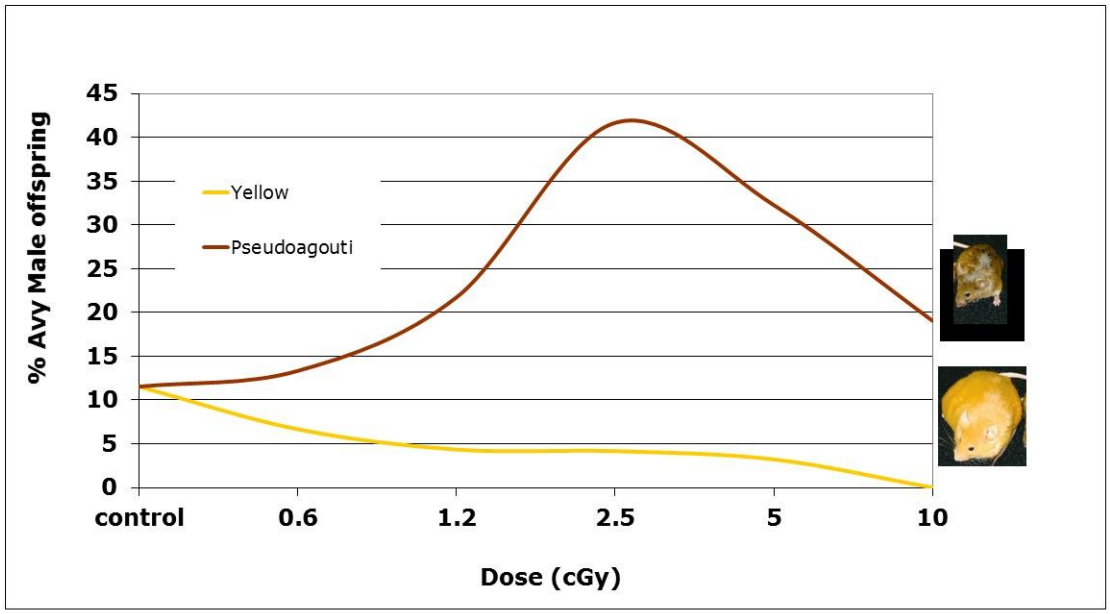
This figure shows that there is a transition in the types of genes that are up and down regulated between 0.1 and 0.2 Gy. Low dose genes seem to be protective against radiation exposure while high dose genes are not.



Yin et. al. 2003

Figure 3

Figure 3 is the epigenetic response of Avy male mice exposed *in utero* to graded low doses of radiation delivered at a high dose-rate. The frequency of "normal" mice increased to a peak value after 2.5 cGy (0.025 Gy) and the frequency of yellow, over-weight, diabetic and cancer prone mice decreased below the level observed in the control population.



Bernell and Jirtle 2011

Figure 4

Figure 4 provides an example of the cause of death as a function of time and total dose to the lung following inhalation of ^{91}Y. At very high dose-rates the animals all died within one year from acute lung disease, as the dose-rate decreased the animals survived longer and many developed lung cancer. As the dose-rate further decreased there was no change in life span or lung cancer frequency.

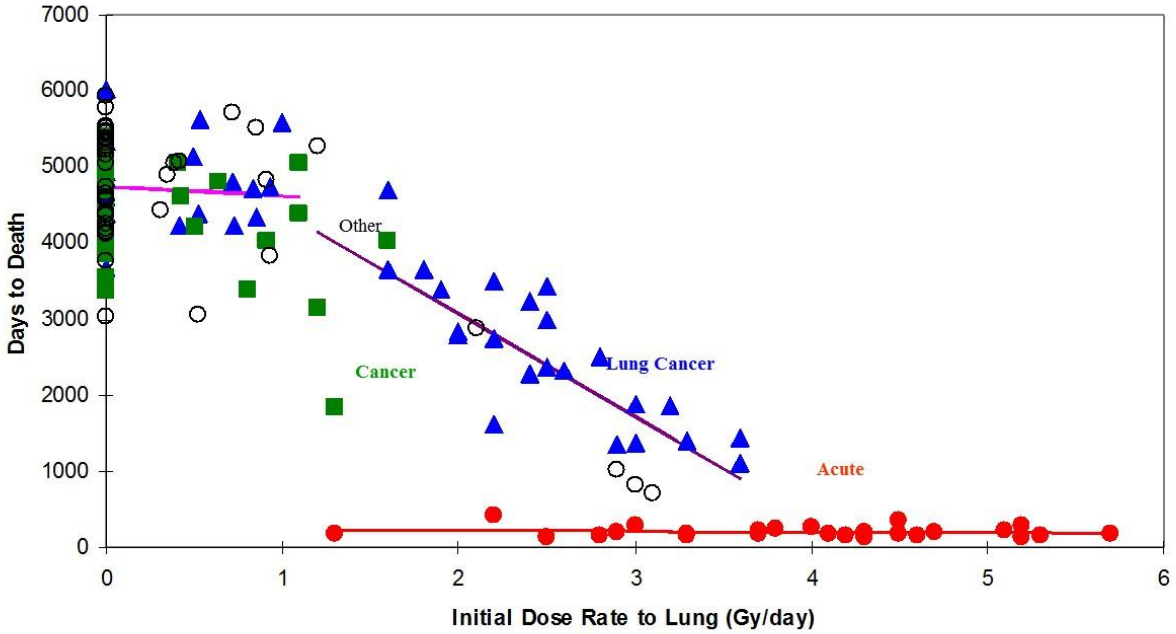
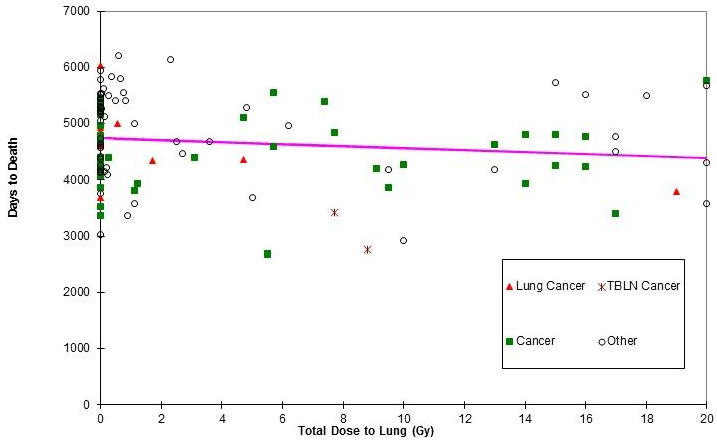


Figure 5

All the dogs in the low LET inhalation studies (Brooks et al. 2009) with total doses to the lungs less than 20 Gy were evaluated for life shortening, total cancer incidence and lung cancer. The figure illustrates that there was no detectable change in lifespan, total cancer frequency or lung cancer. The small animal numbers remains a problem but the data support a marked protective influence of low dose and non-uniform dose-distribution.



	Lung Cancer	Total Cancer
Control	8/54= **15%**	26/54= **48%**
Exposed	4/64= **6%**	29/64= **45%**