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Antone L Brooks
Washington State University Tri-Cities, Richland, WA

Edmond Hui
Washington State University Tri-Cities, Richland, WA

Lezlie A Couch
Washington State University Tri-Cities, Richland, WA

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VERY LARGE AMOUNTS OF RADIATION ARE REQUIRED TO PRODUCE CANCER

Antone L. Brooks, T. Edmond Hui, and Lezlie A. Couch □ Washington State University Tri-Cities, Richland, WA

□ The public fear of radiation is in part driven by the Linear No Threshold Hypothesis (LNTH), or the concept that each and every ionization increases the risk for cancer. Even if this were true, it is important to recognize that the increased risk is very small at low doses and cannot be detected. This paper demonstrates the large number of assumptions and extrapolations needed when using the LNTH to estimate low-dose cancer risk. The manuscript provides information at every level of biological organization suggesting that many of these linear assumptions do not hold. While the initial damage may be produced linearly with dose, the processing of that damage is very non-linear. Finally, the paper provides the unique prospective on radiation-induced cancer, demonstrating that it takes large amounts (total energy) of radiation delivered to large populations to detect an increase in cancer frequency. These observations are supported by both theoretical calculations and examples based on past human radiation exposure.

Keywords: LNTH, cancer risk, total energy

INTRODUCTION

There is a public misconception regarding the relationship between radiation and cancer. This is the belief that any amount of radiation can cause cancer. This radio-phobia is unjustified since the real risk for radiation-induced cancer is very low. It takes a very large amount of radiation to cause cancer.

The biological damage that can be caused by high doses of ionizing radiation, including increased cancer, is well documented and justifiably feared (Hall 2000). However, the public perception of the ability of radiation to induce cancer is much greater than is supported by scientific data (Slovic 2000).

WHERE IS THE RADIATION-INDUCED CANCER?

If cancer is readily caused by every ionization of radiation, it should be possible to detect. However, radiation-induced cancer is difficult to detect. There are three major reasons for this. Variable background radiation dose makes increased cancer risk from small exposures impossible to detect. Cancer rate and cancer mortality are highly variable in differ-

Address correspondence to Professor Antone L Brooks, Washington State University Tri-Cities, Richland, WA 99354-1671. Tel: +509-372-7550; fax: +509-372-7552; e-mail: tbrooks@tricity.wsu.edu

ent human populations making it very difficult to pinpoint excess radiation-induced cancer. At the present time there are no specific biological markers for radiation-induced cancer so they cannot be identified or assigned a cause.

WHY IS CANCER ATTRIBUTED TO RADIATION EXPOSURE?

The public accepts the perception promulgated and enforced by the linear-no-threshold hypothesis which states that there is an increase in cancer risk for every unit of radiation exposure, or that any amount of radiation may cause cancer (NCRP 2001; BIER 2005). This suggests that there is no "safe level" of radiation and all radiation exposure must be avoided.

The basis for this hypothesis is the extrapolation of risk from cancers produced by high doses into low dose regions where no significant increase in radiation-induced cancer can actually be detected. By suggesting that there is a "firm" link between dose and cancer, regardless of the total dose, it becomes possible to multiply small radiation doses delivered at low or high dose rates to very large populations and calculate an "excess" in cancers for any radiation exposure. However, this link is not "firm" because of the multiple extrapolations that are needed to go from measured changes in cancer frequency to predicted cancers which are extrapolated to exist following very low doses of radiation.

Multiple extrapolations are needed to move data from one scenario to another. This makes the extrapolated numbers of excess cancers uncertain, since they are not based on measured cancer frequency. The fact that the risk estimates from the LNTH are based on multiple extrapolations compounds the problems associated with uncertainty. The increased cancers are calculated numbers rather than real disease, and must be regarded as such.

EXTRAPOLATION FROM HIGH TO LOW DOSE

The extrapolation of biological effects over large dose ranges are not applicable. At low doses of radiation, many cell and molecular switches are activated which involve gene expression, DNA repair, cell death and cell transformation. Each of these biological processes modifies the shape of the dose-response curve (Brooks 2005). These biological processes make a linear extrapolation across even one order of magnitude of dose (10-100 mSv) biologically unacceptable.

EXTRAPOLATION FROM HIGH TO LOW DOSE-RATE

The linear extrapolation of dose-rate from the A bomb survivors to environmental exposures is over more than 7 orders of magnitude! Assuming linearity over such a wide range of dose-rates is not reasonable.

To accommodate this dramatic dose-rate extrapolation, the LNTH model uses a dose-dose-rate effectiveness factor (DDREF) of 1.5-2.0.

EXTRAPOLATION FROM WHOLE BODY TO PARTIAL BODY RADIATION EXPOSURES

There is extensive literature on the influence of internally deposited radioactive materials in experimental animals (Stannard 1988). The effectiveness of these protracted exposures to limited numbers of organs for the production of cancer is reduced relative to that following whole body acute exposure. Careful experimental animal studies have demonstrated that the risk to an organ per unit of dose from single acute whole body exposure is higher than the same dose delivered only to that organ (Thompson 1989).

EXTRAPOLATION ACROSS LEVELS OF BIOLOGICAL ORGANIZATION

At every level of biological organization there are many non-linear dose relationships that have been shown to exist. To ignore all the non-linear data that has been derived at every level of organization and assume that the extrapolation between dose and biological response is linear is not acceptable.

Molecular effects

At the molecular level, for example, it has been demonstrated that the initial interaction of radiation with cells to produce DNA damage as detected with γH2AX is linear over a wide range of doses (Rothkamm and Lobrich 2003). However, the processing and repair of DNA damage and the cellular and molecular responses that result from this initial DNA damage are very non-linear. The response to the radiation is dependent on both exposure and biological factors, so that at a low dose rate, the frequency of γH2AX foci decreased to background levels (Ishizaki *et al.* 2004). Studies comparing high and low dose radiation response have demonstrated that the number (Yin *et al.* 2003) and the type of genes activated (Ding et al. 2005) change as a function of dose. The results of these studies suggest that low-dose IR may activate protective and reparative mechanisms as well as depressing signaling activity (Yin *et al.* 2003).

Cell and tissue effects

There are also unique responses for different doses at the cell and tissue level. It has been possible to demonstrate that at low doses, cell killing is greater per unit of dose than at higher doses. This "hyper radiation sensitivity" seems to be related to the ability of the cells to have an "induced radiation resistance". This is similar to an adaptive response (Joiner *et al.* 1996).

An "adaptive response" has also been demonstrated for cells and tissues. This occurs when low doses of radiation precede a high dose, and

the response is less than predicted from the high dose given alone. In addition, it has been shown that low doses of radiation reduce the background rate of a biological response. Both of these phenomena are called an adaptive response. Adaptive responses have been demonstrated for the induction of chromosome aberrations (Wolff 1996; Wolff 1998) and radiation-related cell transformation (Redpath *et al.* 2001). Research has been conducted to determine the genes and pathways that are involved in the induction of the adaptive response. These involve DNA repair, stress response, cell cycle control and apoptosis" (Coleman *et al.* 2005).

Matrix effects

Cells and their sub-cellular matrix can also be modified by radiation exposure. Extensive research has demonstrated that these responses are related to the whole tissue (Bracellos-Hoff 2001). These observations suggest that "it takes a tissue to make a cancer". This intercellular and cell-matrix communication is critical for all forms of physiological function (Griffith and Swartz 2006).

Whole animal effects

Low doses of radiation alter the response at the whole animal level. It has been demonstrated that radiation can prolong the latent period before cancer, and modify the frequency of some types of cancer in mice (Mitchel *et al.* 1999, Mitchel *et al.* 2003).

Human population effects

In large human population studies, where a radiation exposed population is compared to a non-exposed population, there is a wide range of responses reported as a function of radiation exposure. For radiation workers, for example, studies have shown either "healthy worker effects" (Howe *et al.* 2004), or an increase in cancer rate in the radiation workers (Cardis *et al.* 2005). This range of responses highlights some of the difficulties for conducting epidemiological studies at low doses.

EXTRAPOLATION BETWEEN DIFFERENT HUMAN POPULATIONS

The final extrapolation that is used in the A-bomb data is to extrapolate between different populations and ethnic groups, for example from Japanese to the U.S. population. Studies must attempt to control all other exposures and confounding factors and limit the differences between the selected populations to the difference in radiation exposure. In reality, this is almost impossible and therefore, divergent conclusions may often be drawn from the same data, depending on how the populations are defined.

All these extrapolations suggest that it is not possible to establish a linear link between dose and cancer. Using the LNTH, which suggests a

"firm" link between dose and cancer risk makes it possible to multiply small radiation doses delivered at low or high dose rates to any exposed population and calculate "excess" cancers for any radiation exposure. These calculations may or may not reflect real risk.

HOW MUCH RADIATION IS REQUIRED TO INCREASE CANCER INCIDENCE?

Using the LNTH, it is possible to extrapolate or calculate the number of "excess" cancers in any exposed population without any data on cancer frequency. We have discussed several of the difficulties associated with extrapolation of cancer frequency to determine the amount of radiation required to produce a cancer.

In many studies the "exposed" population has less cancer than the controls. To quote from BEIR VII (2005), "In most of the nuclear industry workers studies, death rates in the worker populations were compared with national or regional rates. In most cases, rates for all causes and all cancer mortality in the workers were substantially lower than in the reference populations. Possible explanations include the healthy worker effect and unknown differences between nuclear industry workers and the general population". However, when the cancer frequency is higher in the "exposed" population, risk estimates for radiation exposure are calculated even though an "unhealthy worker effect" or other unknown differences between the exposed and control population may be responsible for the increased cancer frequency seen in the exposed population. Thus, a causative link between cancer and radiation dose has not and can not be established following low doses.

Many people argue that just because a cancer increase cannot be detected in a population doesn't mean that an excess in radiation-induced cancer doesn't exist. This is theoretically true, but if you cannot detect an increase in cancer, the risk has to be relegated to a lower level of concern relative to other environmental insults such as life style, diet, smoking or asbestos where clear cut cancer increases can be demonstrated. BEIR VII (2005) acknowledges that cancer risk following low doses is small. However, it is important to expand this observation to determine just how much radiation is required to produce an excess in total cancer in a population.

To illustrate the amount of radiation that is required to produce a cancer, two tables have been prepared. In these tables, the exposure has been assumed to be an acute whole-body exposure to low-LET radiation. The data for the tables comes from the BEIR VII (2005) committee and relates the background cancer frequency, not mortality, to radiation doses. These tables use the data for "solid cancers" and the "conservative" Linear-No-Threshold model. However, as illustrated in this paper, there is a large body of scientific data that suggest that at low doses of low-LET

radiation the response to radiation is less than predicted by the LNTH model (Rossi 1999; Redpath *et al.* 2001; Mitchel *et al.* 2003; Brooks 2005). The LNT hypothesis is used in these tables to illustrate the point that, even with the conservative LNTH, very large amounts of radiation are required to produce a calculated excess in the cancer incidence.

AMOUNT OF RADIATION TO INCREASE CANCER FREQUENCY: RADIATION IN THE POPULATION HELD CONSTANT AND THE AMOUNT IN THE INDIVIDUAL VARIED

In Table 1, the total amount of low LET-radiation delivered acutely to a population is held constant at 700 joules. The sum of the amount of radiation (energy in joules) delivered to each individual provides the best dose metric to estimate the cancer risk to a population (Bond 2005). This amount of radiation was selected as a starting point to illustrate that when 700 joules of radiation are delivered to a single 70 Kg man it results in a lethal dose of 10 Gy. Without medical intervention 100% of the people exposed to this large amount of radiation die of acute radiation sickness. Therefore, because this is a high "dangerous" individual dose, it is often assumed by the public that if this same amount of radiation, 700 joules, were delivered to a population it must cause a great deal of death and cancer. If this same large amount of radiation (700 J) were distributed to 10 people, it would result in a high dose of 1.0 Gy per person, and no acute radiation deaths would be expected (Hall 2000). If 700 J were distributed to increasing numbers of people, as seen in Table 1, increased cancer risk, rather than death, becomes the major concern. Using the LNT hypothesis and the data from the BEIR VII (2005) report, if 100 people were exposed to 700 J, the dose to each individual would be 0.1 Gy or 100 mGy. Using these most conservative estimates, one extra cancer is predicted in this exposed population in addition to the 42 cancers normally observed without radiation. Because of linearity, one extra cancer

TABLE 1: The total amount of radiation held constant at a level that results in 100% lethality when given to one person (700 J or about 10 Gy) and the population size increased.

Number of People	Dose/ Person (Gy)	Amount/ Person (J)	Amount (J)	Background Cancer	Excess Cancer
1	10	*700	700	.42	0.0
10	1	70	700	4.2	1.0
100	0.1	7	700	42	1.0
1,000	0.01	0.7	700	420	1.0
10,000	**0.001	0.07	700	4,200	1.0
100,000	0.0001	0.007	700	42,000	1.0

*This is a large lethal amount of radiation given to one person. Cancer can never be detected with this amount of radiation regardless of population size!

** Background low LET dose/person

would be predicted in any population size given this amount of radiation energy. If this amount of radiation was distributed to 10,000 people the level of dose to each person would be similar to the amount received from low-LET background radiation in one year or if the dose and risk from background is added over a life time the risk would be $1/70^{th}$ of that from background radiation. It can be seen from this table, that this large, lethal amount of radiation can not produce a statistically significant or detectable increase in cancer frequency, regardless of the population size exposed.

AMOUNT OF RADIATION TO INCREASE CANCER FREQUENCY: AMOUNT OF RADIATION IN EACH INDIVIDUAL HELD CONSTANT AND THE AMOUNT IN THE POPULATION VARIED

Table 2 shows the results if each and every person is assumed to be exposed to a constant, acute exposure of radiation, 7.0 J or 0.1 Gy. This amount of radiation per person is twice the exposure allowed per year for radiation workers. As the number of people exposed to this amount of radiation increases, the amount of energy in the whole population becomes very large. Since the population is the unit measured to detect cancer, the amount of radiation energy in the whole population is assumed to be the important variable (Bond *et al.* 2005). The table shows the background cancer rate and the predicted (BIER 2005) excess cancer from the radiation exposure. The table illustrates, as has been previously published (Brenner *et al.* 2003), that it requires a very large population, each with this 7.0 J of radiation, to be able to detect an increase in cancer. If 10,000 people each get 7.0 J of radiation energy the total amount

TABLE 2: The amount of radiation/person held constant at a level that results in a calculated 1% increase in cancer frequency (7 J/person or about 0.1 Gy).

Number of People	Dose/ Person (Gy)	Amount/ Person (J)	Amount (J)	Background Cancer	Excess Cancer
1	0.1	7	7	.42	0.01
10	0.1	7	70	4.2	0.1
100	0.1	7	700	42	1
1,000	0.1	7	7,000	420	10
10,000	0.1	7	70,000	4,200	100
*22,506	0.1	7	158,000	9,450	increased
**86,611	0.14	10	894,557	10,127	572
100,000	0.1	7	700,000	42,000	1000

Amount of energy per person and the population size are below the level to detect cancer

*Cancer is detectable in this range of population, dose, and total energy

**Total amount of radiation, A-bomb and observed response

*The population size and the total amount of radiation (J) required to detect a change in cancer frequency.

in the population would be 70,000 joules. However, the number of spontaneous cancers also increases as the population size increases. Since the frequency of radiation-induced cancers is small at this population size and level of radiation, it would still not be possible to detect an increase in the cancer frequency above the background level of cancer.

Using statistical methods, it can be calculated that it would require 22,606 people each exposed to 7.0 J to detect an increase in cancer frequency (with a confidence level of 5% false negatives and 5% false positives). This would result in deposition of more than 158,000 joules into the population. A quantity of 700 J delivered as an acute exposure to single person results in 100% lethality. This illustrates how much total radiation energy is required (158,000 J) to produce a significant increase in cancer frequency. From this discussion, it is obvious that although large amounts of radiation energy delivered to a single person are lethal, distribution of that amount over a large population is not lethal and doesn't produce a detectable increase in cancer frequency. Only after very large amounts of radiation is it possible to detect excess cancer. This highlights the fact that radiation is a very good cell killer, (this is why we use it in radiation therapy), but that it is a poor carcinogen.

REAL LIFE EXAMPLES

Although it is true that the extrapolations at the heart of public radiophobia are based on real life examples, the perception of the radiation risk is much greater than the real risk (Slovic 2000). The risk estimates used in the previous tables comes from extrapolation of the data from the A-bomb survivors. In contrast to calculations, the next section reports the raw numbers of cancers. These may or may not be radiation-induced, but they are the excess cancers in the exposed populations compared to carefully selected controls. The use of these numbers help to put the perception of risk and the real risk into perspective so that the public can make their own decisions on the acceptability of radiation risk.

A-Bomb data

The A-bombs were the most terrible radiation events in the history of the world and each of these bombs killed about 100,000 people from blast, burn and radiation-induced sickness. The impact of these nuclear weapons must never be trivialized. Of those that survived the bomb in 1945 (60 years ago), there has been a large follow-up study to determine the cause of death in the 86,611 people that were exposed to graded doses of radiation from the bomb. As of 2004, 47,685 of these people have died, leaving about 45% of the exposed population alive for future studies (Pierce *et al.* 2000; Preston *et al.* 2004). This is a very important population that must continue to be evaluated until their death. However, it

can be seen from the survival in this group (45%) and the number of cancers induced (572 in a background cancer frequency of 10,127) that if an individual did not die from the blast, burns and acute radiation exposures, the risk for cancer induction is small and for most of the population the individuals will live out normal life spans. Of course, if a serious radiation catastrophe occurs (atomic bomb) where there will be very high levels of radiation exposure delivered to large populations, there will be large numbers of people killed by the bomb and there will be excess cancer produced. However, cancer should not be the primary concern for this catastrophe. Instead of thinking that each and every ionization results in cancer the reality is that large amounts of radiation can be delivered to human populations and result in very little, or no detectable increase in cancer.

Chernobyl

The exposure to the radiation from the A-bomb was delivered over a very short time. Most environmental radiation exposures are delivered at a low dose-rate protracted over long periods of time. These low dose-rate exposures come from natural background, fallout from atomic bomb tests, nuclear accidents, nuclear waste clean-up or other types of accidents involving radioactive material. These exposures involved both external radiation and radiation from inhaled or ingested radioactive materials which result in very low radiation dose-rates.

With this in mind, it is useful to review the worst nuclear accident in history. In 1986 there was an explosion in Chernobyl's number four reactor that resulted in wide distribution of radioactive materials which contaminated the entire northern hemisphere. More than 600,000 people involved in trying to control the event and in the clean-up receiving varied and high levels of exposure (IAEA 2006). Most of these that received high doses were reactor staff, emergency and recovery personnel. The very high doses resulted in 50 deaths after the accident from acute radiation syndromes. There were very high doses to the thyroid glands of children who drank milk from cows that had eaten grass contaminated with radioactive iodine. This resulted in high doses to the thyroid glands which have produced an excess of about 4,000 thyroid cancers. To date there have been 9 deaths from these cancers. Therefore, in a population of several million exposed people there are to date a total of 59 deaths from this accident. Using the linear-no-threshold extrapolation and the calculated doses to this large population, it can be postulated that a 3,490 additional people will die from cancer as the result of this exposure. This can be related to the 252,000 cancers that will occur spontaneously in a population of this size or to the 5000 known deaths from coal mining accidents that occur each year or 100,000 since Chernobyl.

Chernobyl is a worst case example of a "dirty bomb". The Chernobyl data are useful in estimating the impact of a terrorist radiation dispersal device where the amount of radiation involved, the population exposed, the radiation doses and thus, the cancer outcome would be much, much less than observed at Chernobyl.

FALLOUT

A prime example of extrapolation from high doses to low doses is seen in estimating "excess" cancers from radioactive fallout from Nuclear Weapons (Simon *et al.* 2006). In this manuscript the authors multiply small doses times the linear risk per unit dose times a huge population and generate a predicted number of "excess cancers". Using fallout doses and the LNTH, the frequency of "excess" leukemia in the United States was calculated to be 1,800. Even using the LNTH, which may not be true for leukemia, calculated leukemia frequency is a very, very small fraction of the spontaneous frequency (1,500,000) in this population.

This helps us to understand that these are indeed calculations and very large extrapolations. Such small changes in cancer frequency relative to the very high cancer background can never be detected. The use of the words, "might eventually occur" (Simon *et al.* 2006), could be replaced with "will never be detected" and demonstrate that this calculated excess risk is a very small public health concern.

CONCLUSION

This paper does not focus on calculated risk associated with radiation (Kennedy 2005; Simon *et al.* 2006), but on detectable statistically significant increases in cancer frequency and the amount of radiation (energy in Joules) required to produce these changes regardless of the population size exposed. The risks for radiation-induced cancer are low relative to other potential causes of cancer. This paper has demonstrated that it takes a very large amount of radiation to produce an increase in cancer incidence, in contrast to the LNTH, which promotes the public misconception that any amount of radiation causes cancer.

Data from A-bomb, Chernobyl and fallout can and should be used by the scientific community to construct models, make risk estimates and predict cancer frequency. However, these calculations need to be complemented with the available clearly understandable raw data. When this is done it is obvious that it takes a lot of radiation to make cancer and that excess cancers are not the prime concern from a nuclear event.

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REFERENCES

Barcellos-Hoff MH. 2001. It takes a tissue to make a tumor: epigenetics, cancer and microenvironment. J Mamm Gland Biol Neo 6: 213-221

BIER VII-Phase 2, Health risks from exposure to low levels of ionizing radiation, Committee to assess health risks from exposure to low levels of ionizing radiation, National Research Council (National Academy of Sciences, Washington, D.C.), USA 2005

Bond, VP, Sondhaus CA, Couch LA and Brooks AL. 2005. The requirement for energy imparted in radiation protection practice. Int J Low Rad 1: 452-462

Brenner DJ, Doll R, Goodhead DT, Hall EJ, Land CE, Little JB, Lubin JH, Preston DL, Preston RJ, Puskin JS, Ron E, Sachs RK, Samet JM, Setlow RB and Zaider M. 2003. Cancer risks attributable to low doses of ionizing radiation: Assessing what we really know. PNAS USA 100: 13761-13766

Brooks AL. 2005. Paradigm shifts in radiation biology: Their impact on intervention for radiation-induced disease. Rad Res 164: 454-461

Cardis E, Vrijheid M, Blettner M, Glibert E, Hakama M, Hill C, Howe G, Kaldor J, Muirhead CR, Schubauer-Berigan M, Yoshimura T, Bermann F, Cowper G, Fix J, Hacker C, Heinmiller B, Marshall M, Thierry-Chef I, Utterback D, Ahn Y-O, Amoros E, Ashmore P, Auvinen A, Bae J-M, Bernar Solano J, Biau A, Combalot E, Deboodt P, Diez Sacristan A, Eklof M, Engels H, Engholm G, Gulis G, Habib R, Holan K, Hyvonen H, Kerrekes A, Kurtinaitis J, Malker H, Martuzzi M, Mastauskas A, Monnet A, Moser M, Pearce MS, Richardson DB, Rodriguez-Artalejo F, Rogel A, Tardy H, Telle-Lamberton M, Turai I, Usel M and Veress K. 2005. Risk of cancer after low doses of ionising radiation: retrospective cohort study in 15 countries. BMJ 333: 77

Coleman MA, Yin E, Peterson LE, Nelson D, Sorensen K, Tucker JD and Wyrobek AJ. 2005 Low-dose irradiation alters the transcript profiles of human lymphoblastoid cells including genes associated with cytogenetic radioadaptive response. Rad Res 164: 369-382

Ding L-H, Shingyoji M, Chen F, Hwang J-J, Durma S, Lee C, Cheng J-F and Chen DJ, 2005. Gene expression profiles of normal human fibroblasts after exposure to ionizing radiation: A comparative study of low and high doses. Rad Res 164: 17-26

Griffith LG and Swartz MA. 2006. Capturing complex 3D tissue physiology in vitro. Nature Rev/Mol Cell Biol 7: 211-223

Hall EJ. Radiobiology for the Radiobiologist. Fifth edition. Lippincott.Williams & Wilkins, New York, USA, 2000.

Howe GH, Zablotska LB, Fix JF, Egel J. and Buchananb J. 2004. Analysis of the mortality experience amongst U.S. nuclear power industry workers after chronic low-dose exposure to ionizing radiation. Rad Res 162: 517-526

IAEA (International Atomic Energy Agency). 2006. Environmental Consequences of the Chernobyl Accident and their Remediation: Twenty Years of Experience. Report of the Chernobyl Forum Expert Group 'Environment'. 2006, Vienna.

Ishizaki K, Hayashi Y, Nakamura H, Yasui Y, Komatsu K and Tachibana A. 2004. No induction of p53 phosphorylation and few focus formation of phosphorylated H2AX suggest efficient repair of DNA damage during chronic low-dose-rate irradiation in human cells. J Radiat Res 45: 521-525

Joiner MC, Lambin P, Malaise EP, Robson T, Arrand JE, Skov KA and Marples B. 1996. Hypersensitivity to very low single radiation doses: its relationship to the adaptive response and induced radio-resistance. Mut Res 358: 171-183

Kennedy D. 2005. Editorial: Risks and Risks. Science 309: 2137

Mitchel REJ, Jackson JS, McCann RA and Boreham DR. 1999. The adaptive response modifies latency for radiation-induced myeloid leukemia in CBA/H Mice. Rad Res 152: 273-279

Mitchel REJ, Jackson JS, Morrison DP and Carlisle SM. 2003 Low Doses of Radiation Increase the Latency of Spontaneous Lymphomas and Spinal Osteosarcomas in Cancer-Prone, Radiation-Sensitive Trp53 Heterozygous Mice. Rad Res 159: 320-327

NCRP National Council on Radiation Protection and Measurements, 2001. Evaluation of the Linear-Nonthreshold Dose-response Model for Ionizing Radiation. NCRP Report No. 136. Issued July 4, 2001. National Council of Radiation Protection and Measurements. Bethesda, Maryland

Pierce DA and Preston DL. 2000. Radiation-Related Cancer Risks at low doses from atomic bomb survivors. Rad Res 154: 178-186

Preston DL, Pierce DA, Shimizu Y, Cullings HM, Fujita S, Funamoto S and Kodama K. 2004. Effect of recent changes in atomic bomb survivor dosimetry on cancer mortality risk estimates. Rad Res 162: 377-389

Redpath JL, Liang D, Taylor TH, Christie C and Elmore E. 2001 The shape of the dose-response curve for radiation-induced neoplastic transformation in vitro. Evidence for an adaptive response against neoplastic transformation at low doses of low-LET radiation., Rad Res 156: 700-707

Rossi HH. 1999. Risks from less than 10 millisievert. Rad Protect Dosimetry 83: 277-279

Rothkamm K and Lobrich M. 2003. Evidence for a lack of DNA double-strand break repair in human cells exposed to very low x-ray dose. PNAS USAdemy of Science. U.S.A 100: 5057-5062

Simon SL, Bouville A and Land CL. 2006. Fallout from Nuclear Weapons Tests and Cancer Risks. American Scientists 94: 48-57

Slovic P. The Perception of Risk. London, Earthscan Publications Ltd, London and Sterling, VA. 2000.

Stannard JN. Radioactivity and Health, A. History, DOE/R1/01/1830-T59, DE88013791, UC-408, Office of Scientific Information, Pacific Northwest National Laboratory, National Technical Information Services, Springfield, Virginia, USA. 1988.

Thompson RC. 1989. Life-span Effects of Ionizing Radiation in the Beagle Dog. Pacific Northwest Laboratory, Richland, Washington

Wolff S. 1996. Aspects of the adaptive response to very low doses of radiation and other agents. Mut Res 358: 135-142

Wolff S. 1998. The adaptive response in radiobiology: evolving insights and implications. Environmental Health Perspectives 106: Supp 1: 277-283

Yin E, Nelson DO, Colman MA, Peterson LE, Wyrobeck AJ. 2003. Gene expression changes in mouse brain after exposure to low-dose ionizing radiation. Int Radiat Biol 79: 759-775.