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***Chapter 6***

# DOSE RATE PROBLEMS IN EXTRAPOLATION OF HIROSHIMA-NAGASAKI ATOMIC BOMB DATA TO ESTIMATION OF CANCER RISK OF ELEVATED ENVIRONMENTAL RADIATION IN FUKUSHIMA

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## ABSTRACT

Problems in evaluating the cancer risk in the Fukushima environment caused by radioactive contamination following the nuclear accidents are discussed, with special concern given to the dose-rate effects in relation to their application to the cancer data from the atomic bomb (A-bomb). Determination of the A-bomb radiation dose rate itself requires evaluation of the exposure time of the A-bomb radiation which consists of multi-complex components. By taking 1 μsec at minimum and 5 sec as median for the exposure time for survivors on the ground, the dose rate of A-bomb radiation was estimated to be in the range between $6 \times 10^5$ and $6 \times 10^8$ Gy/min, or 0.12 and 120 Gy/min, respectively, in contrast to $10^{-9} - 10^{-8}$ Gy/min in environmental radiation. From analysis of non tumor doses as a function of the dose rate of radiation, the dose rate effectiveness factor to extrapolate the A-bomb data to the cancer risk of environmental radiation was estimated as 16.5.

**Keywords**: Radiation, dose rate, cancer risk, non tumor dose, DDREF

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## INTRODUCTION

The environmental contamination by radioactive nuclear fission products that were released by the explosion of the nuclear reactor buildings that occurred in Fukushima, Japan, after the tsunami in March, 2011 [1], created a number of social problems, including the evacuation of residents from the contaminated areas in accordance with strict radiation protection regulations. These regulations are based upon the risk estimated from the cancer data on Hiroshima-Nagasaki A-bomb survivors. However, there is a large difference in the magnitude of radiation cancer risk between A-bomb and environmental radiation cases for the same dose. The main factor for this difference is the dose rate of radiation.

The effect of the dose-rate on cancer induction was shown in experimental animals in early studies by Upton and coworkers [2] and this effect was extensively surveyed with special concern given to the effect of low dose radiation by the United Nations Scientific Committee [3,4]. The International Commission of Radiological Protection (ICRP) recommended the value 2 for the dose and dose-rate effectiveness factor (DDREF) [5]. However, this factor was obtained within the dose-rate range of the A-bomb radiation at very high dose rates, whereas the dose rate of environmental radiation is at the level of $10^{-9}$ Gy/min. Obviously, the current DDREF value cannot be applied to the environmental radiation. Its application to the estimation of cancer risk in the Fukushima environmental cases creates an overestimation of the risk.

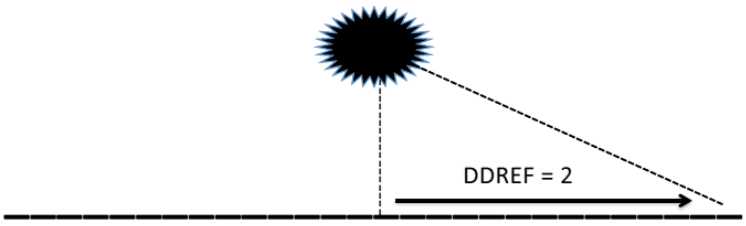
As an approach to revise the DDREF value, the dose-rate effect data on radiation-induced cancers were reviewed in previous articles [6,7]. The non tumor dose, $D_{nt}$, was defined as the highest dose at which no statistically significant increase of cancer incidence was observed above the control level, and these values surveyed in the literature were analyzed as a function of dose rate. The present article is an extension of the previous studies and further provides a method to extrapolate the A-bomb cancer data to the Fukushima situation.

## 1. EXPOSURE TIME AND DOSE RATE OF A-BOMB RADIATION BASED ON DS86

The dose of A-bomb radiation received by survivors depends on the distance from the hypocenter of the explosion (Figure 6-1). In estimating DDREF for cancer risk by ICRP [5], A-bomb cancer data were divided into two dose rate groups according to the low and high doses given in the same exposure time. The ratio of the two dose-response lines was 2, and this value was taken as DDREF. In this estimation, the difference of the dose rate between the two groups is considered to be 10, according to the difference of the dose range, 0-1 Gy and 1-10 Gy with the same exposure time. However, estimation of the exposure time of A-bomb radiation itself involves many problems.

Extensive revision of the dose of A-bomb radiation has been made by the US-Japan joint assessment DS86 [8] and DS02 [9]. A-bomb radiation includes various components: prompt γ rays, prompt neutrons, prompt secondary γ rays, delayed γ rays, delayed neutrons, and delayed secondary γ rays. The timing of radiation dose delivery was extensively analyzed in Chapter III of the DS86 study [10]. Among those, primary fission γ rays (exposure time, 1

μsec), prompt secondary γ rays (exposure time < 0.1 sec) and delayed γ rays (exposure time < 30 sec) contribute to the main part of the absorbed dose and hence to the major biological effects.




| Exposure time used for calculation | Dose rate for 0.01-10 Gy dose range Gy/min |
|---|---|
| 1 μsec[a] | $6 \times 10^5 - 6 \times 10^8$ |
| 5 sec[b] | 0.12 – 120 |
| Natural background | $2.3 \times 10^{-9}$ |

Figure 6-1. Dose and dose rate of A-bomb radiation received on the ground level.The distance from the hypocenter is a major determining factor for dosimetry in cancer mortality analysis. a. Exposure time was taken from the time duration of the nuclear fission chain reaction. b. Exposure time was taken from the median value of the time interval of the dose delivery, involving delayed γ rays, estimated in the DS86 study [10]. The value 2 for DDREF was estimated by ICRP within the A-bomb dose rate range [5].

For delayed γ rays, an exposure rate is almost at the same level up to 10 sec after the chain reaction according to the measurement in the Nevada study, while it increases with time, reaches a peak at 5 sec and decreases to zero level after 20 sec at a distance of 2779 m from the hypocenter [10]. Therefore, A-bomb radiation includes different components of the dose rate within 20 sec after the explosion even at a fixed distance. As an overall estimation of the exposure time, the minimum limit is considered to be 1 μsec and a median value to be 5 sec. By applying this exposure time, the dose rate for A-bomb survivors was estimated by dividing the received dose, 0.01-10 Gy, by the exposure time, yielding $6 \times 10^5 - 6 \times 10^8$ Gy/min for the exposure time of 1 μsec and 0.12– 120 Gy/min for the exposure time of 5 sec. Accordingly, the dose rate varies over a wide range and the estimation of the dose-rate effect is not a simple task. Moreover, the dose-rate range of A-bomb radiation is far higher than the dose-rate of γ radiation in the natural environment, 1.2 mGy/yr or $2.3 \times 10^{-9}$ Gy/min, or 3.8 mSv/yr including other sources of radiation in the daily life of humans.

Compared with the time scale of the biological clock, including cell cycle, DNA replication and repair, and other biochemical reactions, the exposure time of A-bomb radiation is very short and the dose rate effect appears unlikely to occur within this exposure time. The dose rate effect is thought to appear at much lower dose rates below the A-bomb dose rate.

## 2. LEUKEMIA AND SOLID CANCERS IN A-BOMB SURVIVORS

Leukemia data on A-bomb survivors are primarily important in assessing cancer risk of ionizing radiation, since leukemia is induced in the early stage of the post-exposure period with a high frequency [11], compared with solid cancers [12]. Solid cancers are a combination of various types of cancers that appear in the relatively late stage of the post-exposure period with a relatively low individual frequency compared with that of leukemia. For solid cancer mortality, 100 mGy was thought to be the detectable limit. However, the position of ICRP is that the cancer risk of radiation exists at any small dose that can be extrapolated by the linear non-threshold (LNT) model. The problem as to whether the undetectable risk should be incorporated as an existing risk into radiation protection regulations or be approved as a tolerable level of radiation is a currently important problem that needs to be argued. At least, the magnitude 2 for DDREF proposed by ICRP seems too small for extrapolation of A-bomb data to the Fukushima environmental cases.

## 3. DOSE RATE OF ENVIRONMENTAL RADIATION AND CANCER RISK

Natural background radiation includes external $\gamma$ radiation from the ground and cosmic rays, and internal radiation from $^{40}$K $\beta$ rays and $\alpha$ rays from radon and its decay products. It should be noted that ground $\gamma$ rays, cosmic ray protons and muons, and $^{40}$K $\beta$ rays exert whole body low LET radiation, whereas $\alpha$ rays from radon and its decay products exert partial body high LET radiation to the lung. In addition, medical radiation exerts a considerably high dose of partial body low LET radiation. The contribution of these components to the overall cancer risk should be analyzed separately as discussed later.

Compared with the multi component character of A-bomb radiation, the elevated $\gamma$ radiation level in the high natural background radiation areas provides more precise information on the dose-rate of radiation from a well-defined source. Epidemiological studies have been conducted in areas with elevated $\gamma$ radiation backgrounds in Yanjiang, China [13] and in Kerala, India [14] in parallel with dosimetry. The level of the dose rate of $\gamma$ radiation from the ground is 3 and 7 fold of the natural level respectively, that contribute to the dose rate to residents $4.05 \times 10^{-9}$ and $7.55 \times 10^{-9}$ Gy/min, respectively. An increase of the radiation level from the ground contaminated by radioactive cesium has been detected and its level as of September, 2014, is 5 $\mu$Sv/hr, i. e., $8.3 \times 10^{-8}$ Gy/min, at the Namie/Iitate district with the highest level outside the 20 km zone from the nuclear reactor according to the Fukushima Prefecture Radioactivity Measurement Map released on line. To evaluate the cancer risk of this level of radiation, the cancer data on the high natural radiation background areas are directly applicable.

The whole figure of various exposure conditions, including whole body low LET, whole body high LET, partial body low LET, and partial body high LET radiations, is schematically shown with a dose-rate range from the A-bomb radiation level down to an environmental level (Figure 6-2).

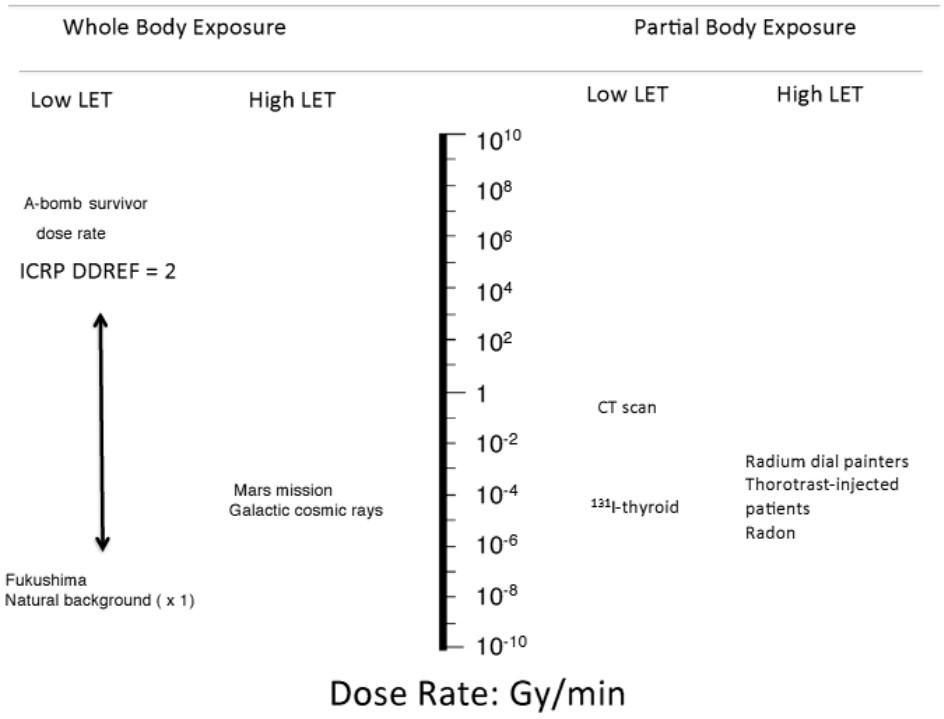



Figure 6-2. Dose rate range for radiation in human environment. Exposure conditions were classified as whole body low LET exposure, whole body high LET exposure, partial body low LET exposure, and partial body high LET exposure.

## 4. Application of the Non Tumor Dose Concept for Estimation of Cancer Risk

The shape of the dose-response curve varies from linear to non-linear, depending on the dose rate of radiation. Although ideally a complete set of dose response curves is desirable for different dose rates, the number of available data showing such a relation is limited, especially those at a low dose range where tumors start to increase with the increasing dose above the control level.

To get an indication on how much dose is necessary to induce cancer or is tolerable to the host, the data on non tumor dose ($D_{nt}$) were surveyed on experimental animals and humans in the literature (Figure 6-3b) [6,7]. The data on the whole body low LET radiation are listed in Table 6-1 with special attention to compare with A-bomb data [2, 11-14,15-29].

### 4.1. External Whole Body Exposure Data

Besides A-bomb cancer data, epidemiological data on cancer mortality in residents in a high natural radiation background area represent human cases with a lifetime exposure to external whole body radiation with increased dose rates. Despite the fact that the dose-

response relation is not available because of the limit of life span, these data provide important information on how much an increase in background radiation humans can tolerate.

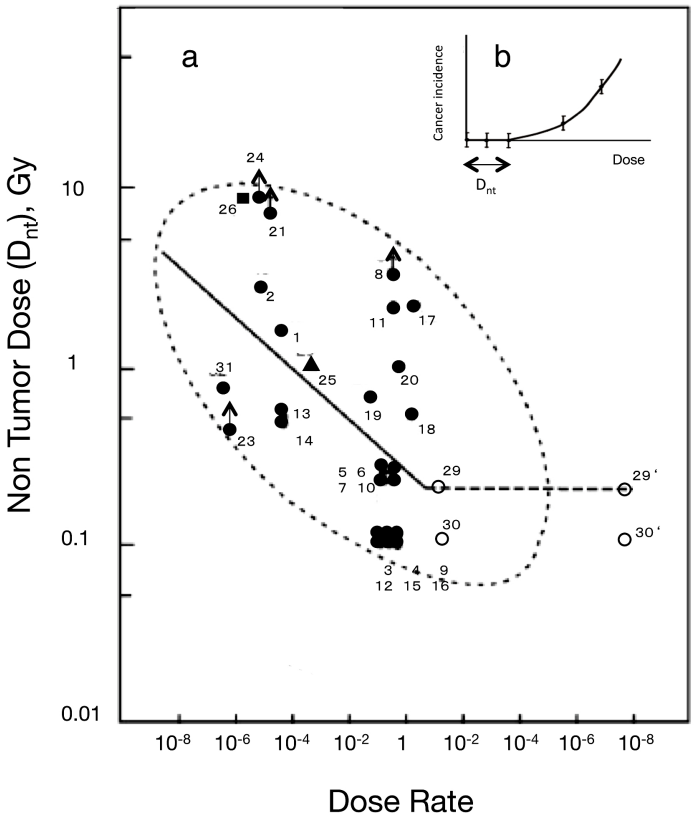



Figure 6-3. Non tumor dose, $D_{nt}$, plotted as a function of dose rate (Gy/min) of radiation for the whole body low LET exposure cases (a) and definition of non tumor dose (b). Attached are data numbers listed in Table 1. (●) mouse, (▲) rat, (■) dog, and (○) human; 29 and 30: A-bomb leukemia and solid cancers, exposure time 5 sec assumed; 29' and 30': exposure time 1 μsec assumed. Arrows indicate that $D_{nt}$ is higher than these values and not used for calculating the regression line.

Laboratory experiments with animals provide substantial information with accurate dose and dose rate with well-defined source of radiation. Most of the early data were contributed by Ulrich et al, then at Oak Ridge National Laboratory. Since the dose rate range covered by each laboratory experiment is limited to a relatively narrow range, the whole range of dose rate extending to the environmental level is constructed by combination of separate experimental results.

A few animal experiments were designed to observe cancer incidence during the lifespan with radiation at very low dose rates. C57BL mice irradiated continuously at a dose rate of 2 x $10^{-5}$ mGy/min for the lifespan showed no tumors even when a cumulative dose reached 7.2 Gy [24], while mice irradiated with 4 repeats of acute dose with the same total dose 7.2 Gy, as the original regimen of Kaplan and Brown [30], showed a 90% incidence of thymic lymphoma. The Institute for Environmental Sciences, Japan, conducted a large scale experiment with B6C3F1 mice irradiated continuously for 22 h a day with graded dose rates

up to 20 mGy/day, 400 fold of the environmental radiation level, with a total dose of 8 Gy. No detectable increase of tumor incidence was observed in the mice irradiated, although the multiplicity of tumors was increased [25]. If these results are compared with the estimated value using the LNT model from 0.5% cancer increase with 100 mSv with DDREF =2, the discrepancy is obvious. Mice irradiated with 8 Gy are expected to develop tumors with a frequency of 20%, contrary to the experimental results.

## 4-3. Internal Whole Body Exposure Data

Internal radiation from radioactive cesium and iodine is also of great concern after the Fukushima accident. Radioactive cesium incorporated in the body is uniformly distributed in the body, a case of whole body low LET exposure. Since the dose-response relationship for cancer from internally deposited radioactive cesium is not available, a series of precise experiments with mice orally administered with radioactive tritiated water by Yamamoto et al. [28] is most valuable for assessing the cancer risk of whole body low LET radiation from internal emitters. They demonstrated the $D_{nt}$ = 700 mGy at an estimated dose rate of 6.4 x $10^{-7}$ Gy/min for thymic lymphoma induction. Yamamoto et al. proposed the idea of a zero equivalent point (ZEP) where the dose rate of tritium β rays exerts zero effect in cancer induction.

Radioactive iodine deposits in thyroid, a target organ. This case is fitted to the category of partial body low LET radiation, and cannot be directly compared with the whole body exposure from A-bomb radiation. Briefly, radioactive iodine injected to rats induced thyroid adenomas in a non-linear dose-response manner with $D_{nt}$ = 3.3 Gy for dose rate of 1.7 x $10^{-4}$ Gy/min [29]. From internal high LET exposure experiments with beagle dogs by Raabe and Lloyd et al. [31, 32], the idea of a practical threshold was presented. From internal low LET exposure experiments, Brooks et al. proposed the value 20-35 for the dose-rate effectiveness factor [33]. Other human data of the dose response relation for partial body exposure were obtained for bone tumors in radium dial painters [34], liver cancers in thorotrast- administered patients [35], and secondary soft tissue sarcomas in patients after radiation therapy [36]. All of them showed a non linear and threshold-like dose response for cancer induction. These cases should be analyzed separately from whole body exposure cases. Moreover, it should be noted that the dose rate effect exists even for high LET radiation at low dose rates.

## 4-4. Non Tumor Dose and DDREF as a Function of Dose Rate

Focusing on whole-body exposure to low LET radiation to simulate A-bomb radiation, the non tumor dose was surveyed in human and experimental data and listed together with the corresponding dose rate in Table 6-1. A plot of $D_{nt}$ against dose rate on the logarithmic scale gives the relation between $D_{nt}$ and dose rate (Figure 6-3a).

**Table 6-1. Whole body low LET exposure data for non tumor dose versus dose rate of radiation surveyed in literature**

| Exposure condition | Data Number | Subject | | Radiation | Tumor | Dose rate, Gy/min | Non tumor dose, $D_{nt}$, Gy | Reference |
|---|---|---|---|---|---|---|---|---|
| External whole body exposure | 1 | Mouse | RFM/Un male | γ ray | myeloid leukemia | $3 \times 10^{-5}$ | 1,5 | Upton et al. [2] |
| | 2 | " | female | " | " | $5 \times 10^{-6}$ | 2,5 | [2] |
| | 3 | " | RFM/Un | " | thymic lymphoma | 0,45 | 0,1 | Ulrich et al. [15] |
| | 4 | " | " | " | Harderian tumor | 0,45 | 0,1 | "..[15] |
| | 5 | " | " | " | uterine | 0,45 | 0,25 | " [15] |
| | 6 | " | " | " | mammary | 0,45 | 0,25 | " [15] |
| | 7 | " | " | " | myeloid leukemia | 0,45 | 0,25 | " [16] |
| | 8 | " | " | " | reticulum cell sarcoma | 0,45 | > 3 | " [15, 16 ] |
| | 9 | " | " | " | ovarian | 0,45 | 0,1 | " [15, 17 ] |
| | 10 | " | " | " | pituitary | 0,45 | 0,25 | " [15, 17 ] |
| | 11 | " | " | " | lung adenoma | 0,45 | 2 | " [15, 17 ] |
| | 12 | " | " | " | thymic lymphoma | 0,45 | 0,1 | " [18] |
| | 13 | " | " | " | thymic lymphoma | $5.8 \times 10^{-5}$ | 0,5 | " [18] |
| | 14 | " | " | " | ovarian | $5.8 \times 10^{-5}$ | 0,5 | " [18] |
| | 15 | " | BALB/c | " | lung adenoma | 0,4 | 0,1 | " [19] |
| | 16 | " | " | " | ovarian | 0,4 | 0,1 | " [19] |
| | 17 | " | " | " | thymic lymphoma | 4 | 2 | Maisin et al. [20] |
| | 18 | " | BC3F1 | X ray | hepatocellular carcinoma | 1,3 | 0,5 | Di Majo et al. [21] |
| | 19 | " | " | " | solid tumor | $6 \times 10^{-2}$ | 0,64 | Covelli et al. [22] |
| | 20 | " | CB17 | γ ray | thymic lymphoma | 0,5 | 1 | Ishii-Ohba et al. [23] |
| | 21 | " | C57BL/6 | " | " | $2 \times 10^{-5}$ | > 7.2 | Ina et al. [24 ] |
| | 22 | " | B6C3F1 | " | no tumor increase | $3.8 \times 10^{-8}$ | > 0.02 | Tanaka III et al. [25] |
| | 23 | " | " | " | " | $7.7 \times 10^{-7}$ | > 0.04 | " |
| | 24 | " | " | " | " | $1.5 \times 10^{-5}$ | > 8 | " |
| | 25 | Rat | WAG/Rij | " | mammary carcinoma | $4 \times 10^{-4}$ | 1 | Bartsra et al. [26] |
| | 26 | Dog | Beagle | " | myeloproliferative disease | [a] $2 \times 10^{-6}$ | 8,6 | Thompson [27] |
| | 27 | Human | Yangjiang, China | " | no tumor increase | [a] $4.05 \times 10^{-9}$ | > 0.15[b] | Wei et al. [13] |
| | 28 | " | Kerala, India | " | no tumor increase | $7.55 \times 10^{-9}$ | > 0.28[b] | Nair et al. [14] |
| | 29 | " | Hiroshima-Nagasaki | A–bomb γ ray + (neutron) | leukemia | (0.12-120)[c] ($6 \times 10^{5}$-$6 \times 10^{8}$)[d] | 0,2 | Shimizu et al [11] |
| | 30 | " | " | " | solid cancer | " | 0,1 | Preston et al. [12] |
| Internal whole body exposure | 31 | Mouse | BC3F1 | Tritium β ray, oral | thymic lymphoma | $6.4 \times 10^{-7}$ | 0,71 | Yamamoto et al. [28] |
| Internal partial body exposure | 32 | Rat | Long-Evans | $^{131}$I β ray, injected | thyroid adenoma | $1.7 \times 10^{-4}$ | 3,3 | Lee et al. [29] |

[a] The increase of radiation from the ground was incorporated in total dose.

[b] Exposure time: 70 years.

[c] Exposure time assumed to be 1 μsec.

[d] Exposure time assumed to be 5 sec.

A-bomb data were well fitted on the regression line when the dose rate of A-bomb radiation was estimated from the median exposure time of 5 sec. The figure shows an inverse relation between $D_{nt}$ and dose rate, i. e., the lower the dose rate the higher the $D_{nt}$ level and provides a measure of the cancer risk or the tolerance level corresponding to the dose rate. Regression line fitted to the data is:

$D_{nt} = 0.258X^{-0.141}$, $R^2 = 0.320$ for whole body low LET exposure,

where $D_{nt}$ is non tumor dose in Gy and X is dose rate between $10^{-9}$ and 1 Gy/min [7].

From this equation, $D_{nt}$ values can be calculated for the corresponding dose rate. The ratio of $D_{nt}$ values between A bomb radiation (0.258 Gy) and environmental radiation (4.26 Gy) is 16.5. Therefore, the DDREF value is 16.5 for application of the cancer risk of A-bomb radiation to environmental radiation.

For other exposure conditions, regression lines are given by the previous analysis [7],

$D_{nt} = 0.0207X^{-0.0733}$, $R^2 = 0.781$ for whole body high LET exposure
$D_{nt} = 2.69X^{-0.0857}$, $R^2 = 0.147$ for partial body low LET exposure
$D_{nt} = 0.0439X^{-0.167}$, $R^2 = 0.303$ for partial body high LET exposure.

The above four equations cover all possible exposure conditions and cancer risks of radiation.

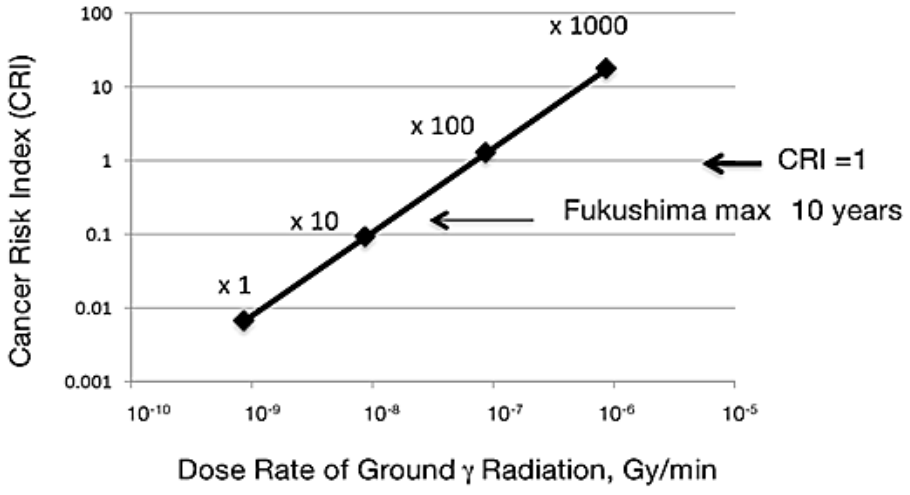



Figure 6-4. Cancer risk index, CRI, defined as the ratio of total dose of radiation to the non tumor dose, versus dose rate. The graph shows how much increase of radiation from the contaminated ground approaches the threshold of cancer risk.

## 4.5 Cancer Risk Index

Although $D_{nt}$ values can be used as a measure of the cancer risk of radiation, the ratio of $D_{nt}$ to a total dose of radiation received by the subject provides a clearer index and is defined

as cancer risk index (CRI) [37]. Figure 6-4 is a plot of CRI against a dose rate of γ radiation from the ground, assuming that low LET radiation is received for 70 years for calculation of total dose. Figure 4 shows that CRI reaches 1 when γ radiation from the ground increases 100 fold. The highest level of contamination in the Namie/Iitate area outside the restricted zone in Fukushima is 5 μSv/h.The procedure to evaluate the CRI value for this condition is illustrated in Table 6-2, such as 1) classify exposure condition: whole body low LET exposure, 2) estimate dose rate in Gy/min, 3) estimate total dose for exposure time (10 years taken for calculation), 4) estimate $D_{nt}$ from the dose rate by the equation, and 5) divide total dose by $D_{nt}$ to obtain CRI. In the Fukushima case, CRE is 0.17. However, if the exposure time is 70 years, CRI comes close to 1. On the contrary, calculation from the LNT model with DDREF = 2 and 0.5% cancer increase with 100 mSv gives 1.2% cancer increase for 10 years, or 8.4% for 70 years in Namie/Iitate if the residents lived there.

**Table 6-2. Practice to estimate cancer risk index (CRI) in Fukushima**

| Maximum dose rate level in Namie/Iitate, Fukushima | Non tumor dose[a] Gy | (A) Total dose, 10 yr Gy | (B) CRI (B/A) |
|---|---|---|---|
| 5 μSv/hr[b] | 2.57 | 0.44 | 0.17 |

[a] Non tumor dose, $D_{nt}$, was calculated by the equation $D_{nt} = 0.258\ X^{-0.141}$ for whole body low LET exposure.

[b] Maximum radiation level outside the 20 km zone in Fukushima in September, 2014.

## 5. FURTHER PROBLEMS

This chapter focused on the topic on whole body low LET radiation with attention given to the applicability of A-bomb data to other radiation exposure cases. Even in this category, the radiation cancer risk varies in a wide range depending upon the dose rate of radiation. Furthermore, the dose rate problem extends to other exposure categories, i. e., whole body high LET radiation such as heavy particles in galactic cosmic rays in space travel, partial body low LET radiation such as medical radiation in cancer therapy and diagnosis, and partial body high LET radiation such as heavy charged particles in internal exposure to radon, radium, and thorotrast α rays. The cancer risk of radiation should be assessed separately in each category. Further experimental data corresponding to each exposure condition are needed to obtain the whole scheme of cancer risk from radiation.

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## REFERENCES


[1] Tanaka S (2012) Accident at the Fukushima Dai-Ichi nuclear power stations of TEPCO-Outline & lessons learned. *Proceedings of Japan Academy of Science*, Ser. B 88: 471–484.

[2] Upton AC, Randolph ML, Conklin JW (1970) Late effects of fast neutrons and gamma-rays in mice as influenced by the dose rate of irradiation: *Induction of neoplasia*. *Radiation Research* 41: 467-491.

[3] United Nations Scientific Committee on the Effects of Atomic Radiation (UNCEAR) (1993) Influence of dose and dose-rate on stochastic effects of radiation. In: Sources and Effects of Ionizing Radiation. Report to the General Assembly, Annex F. New York: United Nations.

[4] United Nations Scientific Committee on the Effects of Atomic Radiation (2000) Biological effects at low radiation doses: Models, mechanisms and uncertainties. In: Sources and Effects of Ionizing Radiation: Genetic and Somatic Effects of Ionizing Radiation. Report to the General Assembly, Annex I. New York: United Nations.

[5] International Commission on Radiological Protection (1991) 1990-Recommendation of the International Commission on Radiological Protection. Publication 60. *Annals of the ICRP*. Oxford: Pergamon Press.

[6] Tanooka H (2001) Threshold dose-response in radiation carcinogenesis: an approach from chronic β-irradiaiton experiments and a review of non-tumour doses. *International Journal of Radiation Biology* 77: 541-551.

[7] Tanooka H (2011) Meta-analysis of non-tumour doses for radiation-induced cancer on the basis of dose-rate. *International Journal of Radiation Biology* 87: 645-652.

[8] Roesch WC, editor (1987) US-Japan Joint Reassessment of Atomic Bomb Radiation Dosimetry in Hiroshima and Nagasaki, DS86. *Radiation Effects Research Foundation*. Hiroshima: Radiation Effects Foundation.

[9] Young RW, Kerr GD editors (2005) Reassessment of the Atomic Bomb Radiation Dosimetry for Hiroshima and Nagasaki (DS02) vol. 1 and vol. 2. Hiroshima: *Radiation Effects Research Foundation.*

[10] Kerr GD, Pace III JV, Mendelsohn E, Loewe WE, Kaul DC et al. (1987) Transport of initial radiations in air over ground. In: Roesch WC editor, US-Japan Joint Reassessment of Atomic Bomb Radiation Dosimetry in Hiroshima and Nagasaki. Chapter III. Vol. 1. Hiroshima: *Radiation Effect Research Foundation*.

[11] Shimizu Y, Kato H, Schull WJ (1990) Studies of the mortality of A-bomb survivors. Mortality, 1950-1985: Part 2: Cancer mortality based on the recently revised doses (DS86). *Radiation Research* 121: 120-140.

[12] Pierce DA, Preston DL (2000) Radiation-related cancer risks at low doses among atomic bomb survivors. *Radiation Research* 154: 178-186.

[13] Chen D, Wei LX (1991) Chromosome aberration, cancer mortality and hormetic phenomena among inhabitants in areas of high background radiation in China. *Journal of Radiation Research* 32 suppl. 2: 46-53.

[14] Nair MK, Nambi KSV, Amma NS, Gangadharan P, Jayalekshmi P et al. (1999). Population study in the high natural background radiation area in Kerala, India. *Radiation Research* 152: S145-148.

[15] Ullrich RL, Jernigan MC, Cosgrove GE, Satterfield LC, Bowles ND et al. (1976) The influence of dose and dose-rate on the incidence of neoplastic disease in RFM mice after neutron irradiation. *Radiation Research* 68: 115–131.

[16] Ullrich RL, Storer JB (1979) Influence of γ-irradiation on the development of neoplastic disease in mice. I. Reticular tissue tumors. *Radiation Research* 80: 303–316.

[17] Ullrich RL, Storer JB (1979) Influence of γ-irradiation on the development of neoplastic disease in mice. II. Solid tumors. *Radiation Research* 80: 317–324.

[18] Ullrich RL, Storer JB (1979) Influence of γ-irradiation on the development of neoplastic disease in mice. III. Dose-rate effects. *Radiation Research* 80: 325–342.

[19] Ullrich RL (1983) Tumor induction in BALB/c mice after fission neutron or γ-irradiation. *Radiation Research* 93: 506–515.

[20] Maisin JR, Wambersie GB, Gerber GB, Guelette J, Mattelin G et al. (1983) The effects of a fractionated gamma irradiation on life shortening and disease incidence in BALB/c mice. *Radiation Research* 94: 359–373.

[21] Di Majo V, Coppola M, Rebessi S, Bassani B, Alati T et al. (1986) Radiation-induced mouse liver neoplasms and hepatocyte survival. *Journal of National Cancer Institute* 77: 933–939.

[22] Covelli V, Coppola M, Di Majo V, Rebessi S, Bassani B et al. (1988) Tumor induction and life shortening in BC3F1 female mice at low doses of fast neutrons and X rays. *Radiation Research* 113: 362–374.

[23] Ishii-Ohba H, Kobayashi S, Nishimura M, Shimada y, Tsuji H et al. (2007) Existence of a threshold-like dose for γ ray induction of thymic lymphomas and no susceptibility to radiation-induced solid tumors in SCID mice. *Mutation Research* 619: 124–133.

[24] Ina Y, Tanooka H, Yamada T, Sakai K (2005) Suppression of thymic lymphoma induction by life-long low dose-rate irradiation accompanied by immune activation in C57BL/6 mice. *Radiation Research* 163, 153-158.

[25] Tanaka IB III, Tanaka K, Ichinohe K, Matsushita S, Matsumoto T et al. (2007). Cause of death and neoplasia in mice continuously exposed to very low dose rates of gamma rays. *Radiation Research* 167: 417-437.

[26] Bartsra RW, Bentvelzen PAJ, Zoetelief J, Mulder AH, Broerse JJ et al. (2000) The effects of fractionated gamma irradiation on induction of mammary carcinoma in normal and estrogen-treated rats. *Radiation Research* 153: 557–569.

[27] Thompson RC (1989) Life-span effects of ionizing radiation in the beagle dog. A summary account of four decades of research funded by the US Department of Energy and its predecessor agencies. *Pacific Northwest Laboratory Report* PNL-6822 UC-408. pp. 1–323.

[28] Yamamoto O, Seyama T, Itoh H, Fujimoto N (1998) Oral administration of tritiated water (HTO) in mouse. III. Low dose-rate irradiation and threshold dose-rate for radiation risk. *International Journal of Radiation Biology* 73: 535–541.

[29] Lee W, Chiacchierini RP, Shleien B, Telles NC (1982) Thyroid tumours following $^{131}$I or localized X irradiation to the thyroid and pituitary glands in rats. *Radiation Research* 92: 307-319.

[30] Kaplan HS, Brown MB (1952) A quantitative dose-response study of lymphoid-tumor development in irradiated C57 black mice. *Journal of National Cancer Institute* 13: 185–208.

[31] Raabe O (2011) Toward improved radiation safety standards. *Health Physics* 101: 84-93.

[32] Lloyd RD, Taylor GN, Fisher DR, Schlenker RA, Miller SC (2000) Effective thresholds for induction of skeletal malignance by radionuclides. *Health Physics* 79: 722-727.

[33] Brooks AL, Eberlein PE, Couch LA, Boecker BB (2009) The role of dose-rate on risk from ineternally-deposited radionuclides and the potential need to separate dose-rate effectivensee factor (DREF) from the dose and dose-rate effectiveness factor (DDREF). *Health Physics* 97: 458-469.

[34] Rowland RE, Stehney AF, Lucas HF (1978) Dose-response relationships for female radium dial workers. *Radiation Research* 76: 368–383.

[35] Anderson M, Storm HH (1992) Cancer incidence among Danish thorotrast-exposed patients. *Journal of National Cancer Institute* 84: 1318–1325.

[36] Tubiana, M. Diallo, I. Chavaudra, J, Lefkopoulos D, Bourhis J et al. (2011) A new method of assessing the dose-carcinogenic effect relationship in patients exposed to ionizing radiation. A concise presentation of preliminary data. *Health Physics* 100: 296-299.

[37] Tanooka H (in press) Dose Rate: A Critical Factor in Determining the Cancer Risk of Radiation at an Environmental Level. In Mishra KP editor, Radiation Exposure: Monitoring Systems, Long-Term Health Effects and Methods for Protection. New York: *Nova Scientific*.