공학석사 학위논문

Study on the Allometric Scaling of Animal Data for Assessing Human Risk of Low-dose Radiation Exposure

저선량 방사선 피폭에 따른 인체위해도 평가를 위한 동물실험자료의 알로메트릭 스케일링 연구

2020년 2 월

서울대학교 대학원

에너지시스템공학부

이 희 찬

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이 논문을 공학석사 학위논문으로 제출함
2020 년 1 월

서울대학교 대학원
에너지시스템공학부
이 희 찬

이희찬의 공학석사 학위논문을 인준함
2019 년 12 월

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Abstract

While the effect of high dose radiation on humans is well established, the effect of low dose radiation is still controversial. This analysis such as the derivation of DDREF is conducted mainly on epidemiological studies. However, since epidemiological analysis has inherent flaws that it is hard to know the exact exposed dose. Moreover, the increased risk with low dose radiation is hard to be distinguished because of the low increase of risk compared to the background risk. For these reasons, additional radiation exposure experiments to cells and animals have been conducted to supplement epidemiological investigations.

Several studies on low dose radiation such as BEIR VII were conducted with human epidemiology and animal studies. These studies analyzed different sources with the same dose scale to derive DDREF. However, some studies indicate that the reaction of humans from radiation is different from that of other species. Species specificity of toxic chemicals has been studied for a long time and it is relatively well established by the name of allometry.

In this study, I suggested and verified a new dose scaling method with reflecting the difference in the weight of the animal species and conducted an analysis of mouse exposure data from ERA and Janus using BEIR VII's method. With the allometric method, the new dose range for the mouse that I used as a corresponding dose range of 0−1.5 Gy for the human is 0−11Gy based on'3/4 Rule'.

Radiation exposure data of mouse in the dose range of 0−11Gy fits better on the LQ model than the linear model. Besides, the tendency of the results and derived DDREF distributions showed similar to those of humans.

In view of these points, it is thought that the dose standard applied to humans should not be applied to animal exposure data and allometric scaling methods from weight comparison would be a good option for the application of animal radiation exposure data to humans.

Keywords : Low dose radiation, Linear-Quadratic model, DDREF, Animal studies, Allometry
Student Number : 2018-21273

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Chapter 1 Introduction

Radiation effects on health have been one of the main concerns of the public for decades after atomic bombs and several radiation-related accidents. However, unlike high dose exposure, the effects of low dose exposure or low dose-rate exposure are relatively were not well analyzed yet and their relationship is still controversial[1].

The relatively small excess risk from a low dose or low dose-rate radiation exposure makes assessing the relation between risk and exposure dose from epidemiologic data difficult. To get estimates with the same statistical power and significance level, about 100 times larger samples are needed for 1/10 dose level[2].

Despite these difficulties, it is essential to research the effects of low dose radiation. Since most people are exposed to low dose radiation, low dose radiation is more closely related to public health. With the accurate analysis of low dose radiation exposures, the assessment of the cancer risk from radiation exposure would be accurate and would reduce a lot of social costs associated with radiation[3].

For these reasons, several methods and sources have been tried for accurate analysis of low dose radiation exposure. In addition to epidemiologic studies, various animal experiments and cell experiments have been conducted to investigate the relationship between risk and exposure dose[4].

Several institutes have tried to analyze and estimate the low dose effect of radiation and a few of them analyzed with both epidemiological and experimental data. One of them was described in BEIR VII[5], however, an analysis of BEIR VII was conducted with the limited animal data source. For this reason Haley et al.[6]

wondered how the results would be different if analyzed with additional data. The extended analysis was conducted with data of European Radiation Archives(ERA) [7] and Janus Tissue Archive [8,9] through BEIR VII's method.

In this study, I tried to review the result and method of BEIR VII and Haley et al.'s work. Furthermore, I questioned the direct application of animal data to humans without alteration and wanted to review existing methods of similar fields and make suggestions on what would be the best way to estimate humans' radiation risk from animal experiment data.

Chapter 2 Backgrounds and advance studies

2.1 Backgrounds

2.1.1 Risk models of low dose radiation exposure

Multiple mathematical models explain the risks of cancer from exposure to low-LET radiation. In the early 1900s, the main model that explains the risks of radiation was the threshold model[10,11]. According to the threshold model, radiation exposure below a certain threshold dose has no effect on the human body. However, after the H. J. Muller's experiments and several epidemiological studies of atomic bomb survivors, the linear no-threshold (LNT) model was started to be supported[10,12,13]. However, the LNT model has weak points that epidemiologic data of low-dose radiation are limited and have inherent volatility. To be specific, while risk increase of high dose radiation is large enough to get the relationship, risk increase of low dose radiation is too small to get an accurate relationship and the exact exposure dose of individuals is also hard to be figured.

As it is hard to confirm the cancer risk of low dose radiation through epidemiologic studies, studies of low dose radiation have been conducted through cell and animal experiments. The results of these experiments differed from the LNT model[14-16]. Several effects such as bystander effect, hormesis, hyper-radiosensitivity were observed in the low dose exposure experiments. The bystander effect is an effect that irradiated cells affects other neighbor unirradiated cells[17]. Hormesis, a phenomenon that observed widely in toxicology, is a process that low doses of toxic can have a good effect on cells or organisms[15]. Hyper-radiosensitivity is an

effect that the tendency of risk increase in particular low dose exposure shows different from that of other dose exposure[18].

Based on these experimental results, various models of the radiation response have been claimed including supra-linear model, linear-quadratic model (LQ model), linear threshold model, and radiation hormesis model[19].

Among these models, two of the most supported models are the LQ model and the LNT model. LNT model has a strength that it is quite simple to use and good for conservative risk assessment. On the other hand, the LQ model explains the observed difference of risk increase per dose from various exposure conditions in experiments and epidemiologic studies. Some researchers or organizations use the LNT model for the basic model and adopt a new concept of factor, Dose and Dose-rate Effectiveness Factor (DDREF), which modifies the difference of risk increase. With this concept, the strengths of the two models can be achieved[20].

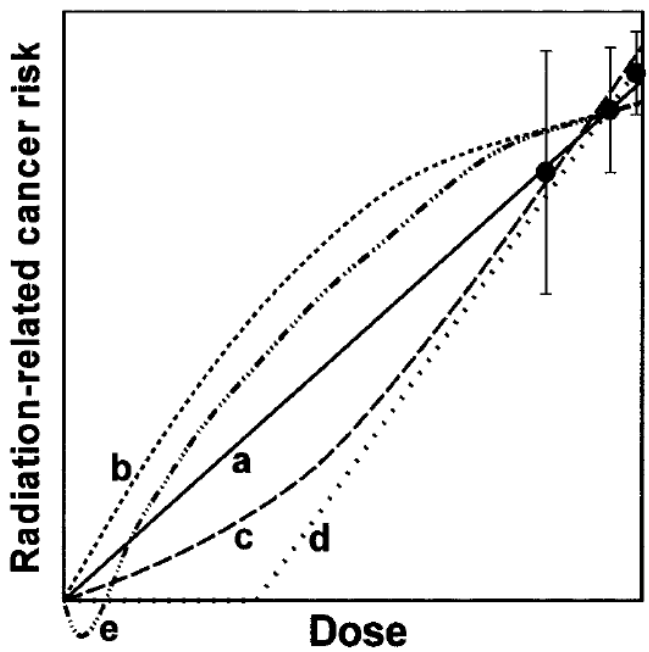

Figure 2.1 Schematic representation of different possible extrapolations of measured radiation risks down to very low doses Curve a, linear extrapolation; curve b, downwardly curving (decreasing slope); curve c, upwardly curving (increasing slope); curve d, threshold; curve e, hormetic[19].

2.1.2 Linear quadratic model & DDREF

The linear-quadratic model (LQ model) has a prominent feature that is different from other models. This model represents a smaller increase of risk in low dose range than an increase of risk in the high dose range. The LQ model can be expressed by the equation below.

$$R = \alpha D + \beta D^2$$

where R means risk from radiation exposure, D means exposure dose, α and β refer to linear and quadratic coefficients respectively.

DDREF (Dose and Dose rate Effectiveness Factor) is a correction factor that modifies the estimated risk of low dose or low dose-rate exposure which can be higher than the actual risk. DDREF which was first introduced in ICRP 60[20] is an integrated concept of LDEF and DREF which had been widely studied before the DDREF was used. LDEF is the concept focusing on the low dose radiation and DREF is the concept focusing on the low dose rate radiation[21]. Since the LQ model shows the difference of risk per dose between low dose or low dose-rate exposure and high dose or high dose-rate exposure, DDREF is usually derived from the LQ model.

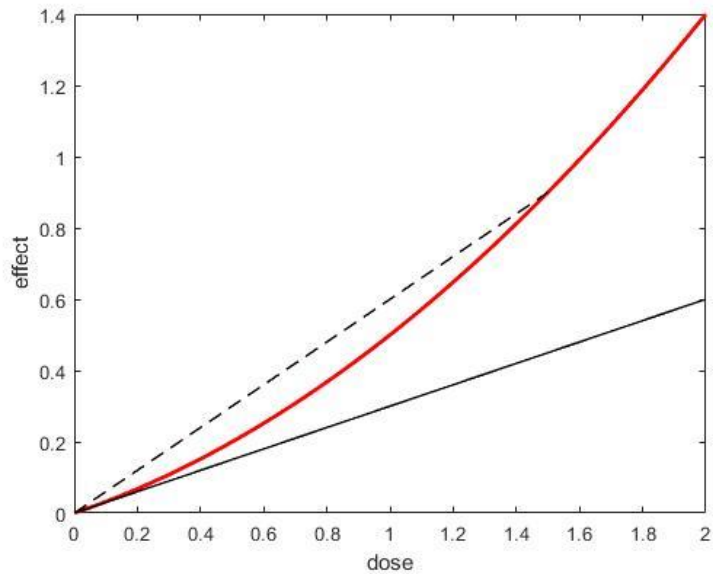

Figure 2.2 Concept of LDEF

The red line refers to a linear-quadratic curve, the slope of a black dotted line refers to an estimated or observed risk increase per unit dose of high dose exposure, and the slope of a black solid line refers to an estimated or observed risk increase per unit dose of low dose exposure.

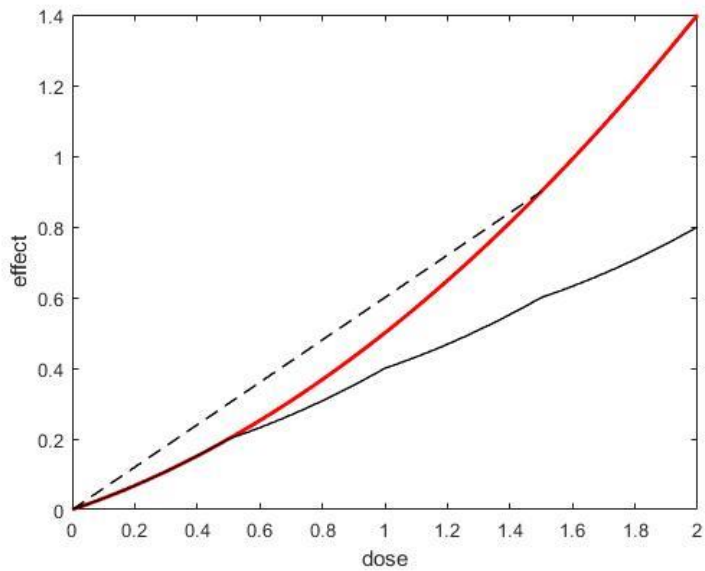

Figure 2.3 Concept of DREF

The red line refers to a linear-quadratic curve, the slope of a black dotted line refers to an estimated or observed risk increase per unit dose of single high dose and high dose-rate exposure, and a black bumpy solid line refers a risk increase of fractional exposures.

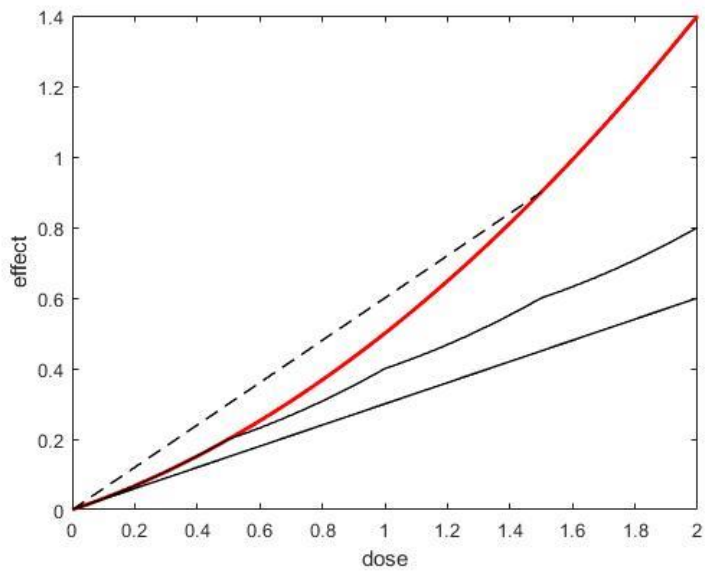

Figure 2.4 Concept of DDREF

The red line refers to a linear-quadratic curve, the slope of black dotted line refers to an estimated or observed risk increase per unit dose of single high dose and high dose-rate exposure, the slope of black straight solid line refers to an estimated or observed risk increase per unit dose of low dose exposure, and black bumpy solid line refers to a risk increase of fractional exposures. If the number of fraction is large enough, the slope of two black solid lines would be almost the same.

2.1.3 Derivation of DDREF

DDREF can be derived in two ways. One is a derivation from the concept of LDEF and the other is a derivation from the concept of DREF. By using the LQ model, the risk of radiation exposure can be expressed as below.

$$R = \alpha D + \beta D^2$$

Then the risk per unit dose in the low dose range and the high dose range can be expressed as αD/D and (αD+ βD^2)/D. Therefore, the LDEF (or DDREF) can be expressed as

$$DDREF = 1 + \frac{\beta}{\alpha} D_H$$

where D_H is a criteria dose for high dose exposure and usually used as 1 Gy.

LDEF can be also derived from a comparison between the excess risk per dose of high dose exposure and the excess risk per dose of low dose exposure. LDEF (or DDREF) can be also expressed as

$$DDREF = \frac{\alpha_L}{\alpha_{LQ}}$$

α_L is a fitted risk per unit dose in the linear model and α_{LQ} is a value of α in the LQ model. Thus, α_L and α_{LQ} represent the risk in low dose range and high dose range.

DDREF can be also derived by comparing the risk in the low dose-rate and the high dose-rate. This concept is originated from DREF (Dose Rate Effectiveness Factor). Usually, DREF (or DDREF)

can be expressed as below.

$$DDREF = \frac{ERR/_{Gy} \ \ at \ \ high \ \ dose \ \ rate}{ERR/_{Gy} \ \ at \ \ low \ \ dose \ \ rate}$$

ERR represents Excess Relative Risk from radiation exposure.

With these methods, DDREF has derived from two types of sources. One is epidemiologic studies of human and the other is animal radiation studies[4]. There are pros and cons of assessing the risk of low dose radiation from each source. Since exposure to humans is hard to be controlled, epidemiologic studies of humans have inherent errors. However, animal radiation studies have weak points that response to radiation can be different from human and other animals[22].

Various studies estimated the distribution of DDREF. Some of them such as Kocher et al. derived DDREF from only human epidemiologic studies, while others like the BEIR VII committee derived DDREF from both human and animal exposure data[5,23].

2.2 Advance studies

2.2.1 DDREF derivation from various human epidemiological data: Kocher et al. [23]

One of the recent research on developing DDREF by integrating epidemiological data from different sources is the paper of Kocher et al. It describes the way to develop a distribution of the DDREF.

They calculated the LDEF and the DREF from different epidemiologic studies. The coefficients from each study were fitted in Weibull distributions. They estimated 50^{th} percentile and 90% CIs (Confidence Intervals) of LDEF and DREF by using fitted distributions and Monte Carlo uncertainty propagation techniques. Then, each value of LDEF and DREF were integrated with assigned weights.

In order to derive the LDEF, the data of cancer incidence and cancer mortality were needed. They derived LDEF from each study. After that, each LDEF for cancer incidence and cancer mortality was developed by integrating corresponding derived LDEF with assigned weights. LDEF for cancer incidence and LDEF for cancer mortality were integrated with the weight of 2:1 to obtain LDEF. DREF was derived in the same way with LDEF.

These finalized LDEF and DREF were combined by assigning equal weight to develop DDREF. After that, values of less than 0.2 and more than 20 were removed to obtain a more preferable distribution of DDREF since the range of 0.2−20 is not credible for DDREF.

Table 2.1 Summary of probability distributions of LDEF, DREF, and DDREF for all solid cancers calculated using stepwise procedures for combining probability distributions of LDEF and DREF from epidemiological studies to obtain preferred DDREF distribution.(Table 5 of Kocher et al.(2018)) [23]

Step in procedure	Type of combined estimate	Percentile of probability distribution				
		2.5th	5th	50th	95th	97.5th
Step 1	LDEF for cancer incidence	0.89	0.96	1.4	2.2	2.4
	LDEF for cancer mortality	0.92	0.97	1.5	5.2	7.0
	DREF for cancer incidence	0.31	0.41	1.2	5.2	8.8
	DREF for cancer mortality	0.26	0.31	0.72	3.1	5.4
Step 2	LDEF for cancer incidence and mortality combined, with relative weights of 2:1 assigned to incidence− and mortality−based distributions	0.90	0.96	1.4	3.0	4.5
	DREF for cancer incidence and mortality combined, with relative weights of 2:1 assigned to incidence− and mortality−based distributions	0.28	0.36	1.0	4.7	7.7
Step 3	DDREF obtained by combining LDEF and DREF distributions from Step 2, with equal weight assigned to each distribution	0.36	0.44	1.3	3.8	6.1
Step 4	Preferred DDREF distribution obtained by truncating distribution from Step 3 by removing values <0.2 and >20	0.39	0.47	1.3	3.6	5.6

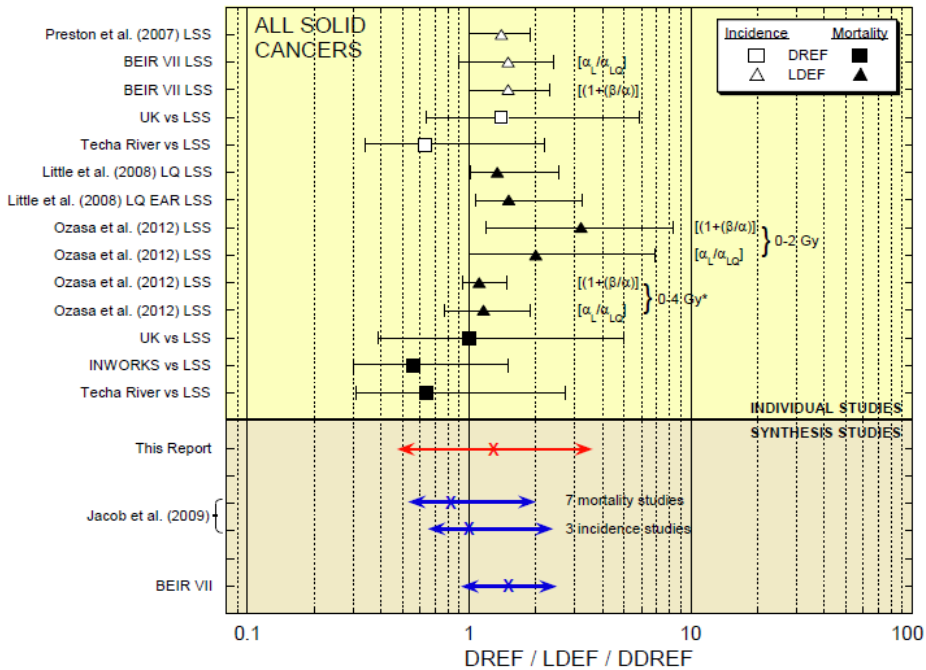

Figure 2.5 Estimates of 50th percentile and 90 % CIs of DREFs and LDEFs for solid cancer of various studies

This Report in synthesis studies section refers to Kocher et al.(2018) [23]

2.2.2 DDREF derivation from various human epidemiological data and animal studies: BEIR VII[5]

DDREF derivation of BEIR VII is a representative example of DDREF derived from epidemiological data and animal studies. BEIR VII used the LSS cohort of atomic bomb survivors and mouse data. Both LSS data and mouse data were analyzed over the dose range of 0−1.5 Gy.

Among these data, two types of mouse data were used, cancer data and life−shortening data. For cancer data, data were classified with 11 conditions and they were fitted to LQ models to get estimates of DDREF. For life−shortening data, they were processed to derive DDREF. The BEIR VII committee assumed the risk from radiation exposure as the reciprocal of mean life length. The details of this process are described in the method section.

The final distribution of DDREF was derived by combining the possible distribution of DDREF from LSS data and mouse data. The combined estimates of DDREF announced in BEIR VII are 1.5 and its 95% CIs are (1.1, 2.3).

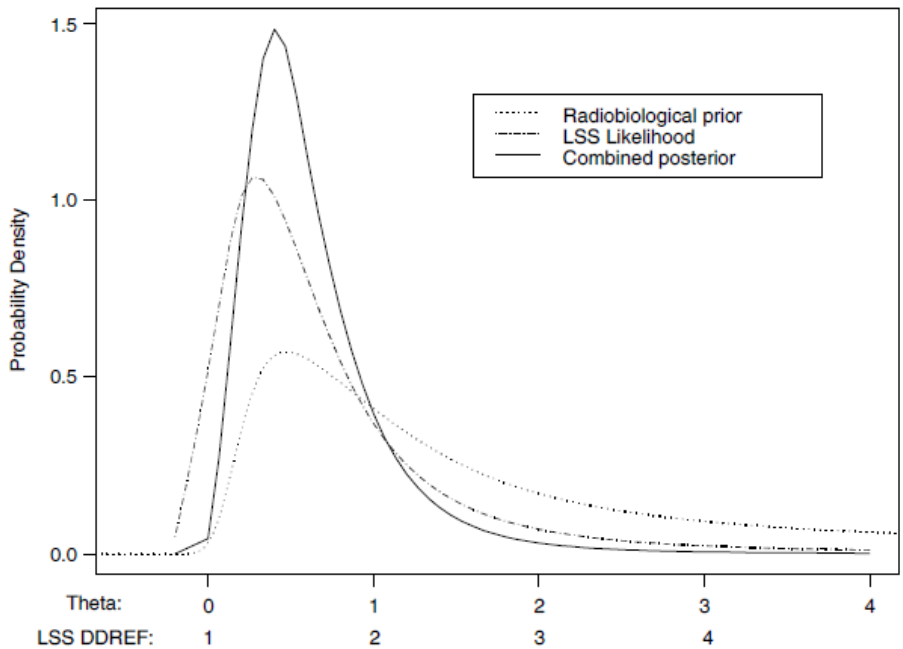

Figure 2.6 The probability density curves of theta and DDREF in BEIR VII

Radiobiological prior curve was drawn with animal data, LSS likelihood curve was drawn with atomic bomb survivors' data, and combined posterior curve was made by combining the two probability density curves[5].

2.2.3 Radiation animal studies

Among the two types of experiments, cell experiments and animal experiments, that assist epidemiological investigations in low dose radiation effect analysis, animal experiments have greater advantages in that they reflect the mechanisms in the body. In this sense, the data from animal studies can be considered suitable for direct application to humans.

As lots of studies were done with human epidemiology, a large amount of animal experiments were also done largely especially in the 1970s and 1980s. Exposure experiments of various conditions were done to diverse animals such as mice, rats, dogs, and monkeys and many of them are archived in ERA[7]. Therefore, researches are being conducted using these archived data. Two of the recent studies done with the data are conducted by Haley et al.[6] and Tran and Little[24].

Haley et al.[6] analyzed additional animal experiment data not covered in BEIR VII with its method. They identified the methods BEIR VII used by recreating the results of BEIR VII from data BEIR VII used. They made further analysis of the archived data in ERA or Janus with BEIR VII's method. According to their results, the analysis of data didn't follow the LQ model and they suggested a new model called 'linear−linear model'.

Tran and Little[24] analyzed exposed groups of the full dose range and under 5 Gy(gamma) or 0.1 Gy(neutron) and the results of the analysis were summarized in the paper.

However, studies comparing the differences between species were also conducted. Liu et al.[22] raised the possibility of radiation toxicities differences between species. Even though Mus

musculus and Peromyscus leucopus share physical similarities, th ey show different responses to radiation. In this respect, applyin g the result from data of animal studies to the reaction of human s to radiation might be controversial.

2.2.4 Equivalent dose across animal species: Chemical Toxin

While the study on toxicities of radiation has not been deeply researched, the study on toxicities of chemicals has been deeply studied for a long time. One of the studies that summarized the difference of toxicity between species is the work of Chappell[25]. He introduced the allometric method for calculating the equivalent dose of species. Allometry means the study of the relation between body size, weight or other various physical characters[26]. According to his study, the response to doses of chemicals is not proportional to animals' weight. On the other hand, the dose that shows the same response is proportional to 0.6−0.8 power of weight. In the past, this relationship was considered as the result of the difference of each species body surface. However, with more recent studies, it seems that the metabolic rate is the main factor for the relationship. Although there are some disputes about the law, after the studies of Kleiber[27], '3/4 Rule' is widely used for estimating the metabolic rate of animals. With a higher metabolic rate, each individual can quickly get rid of toxic substances in the body and this difference makes the difference of response to chemicals.

From this approach, the dose per weight of chemical toxin that shows the same response is proportional to −0.25 power of weight. In other words, smaller species can be seen as more resistant to toxicity.

2.2.5 Equivalent dose across animal species: Radiation

Although the exact process of radiation damages the organisms and their cells, one of the theories that radiation damages them is generation of ROS (reactive oxygen species) [5]. As ROS is a type of chemicals, the effects of chemicals and radiation can be seen similar. In this point of view, it is possible to infer the species difference of radiation toxicity from that of chemical toxicity.

As the equivalent dose (mg/kg) of chemicals are larger for the animals of smaller weights (or higher metabolic rate per body mass), it can be predicted that the smaller animals would show larger radiation resistivity. In the work of Liu et al.[22] on comparing the radiation toxicities across species, the observed resistivity of Mus musculus was larger than that of Peromyscus leucopus. According to the Human Ageing Genomic Resources[28,29], the average adult weight of Mus musculus (20.5 g) was smaller than that of Peromyscus leucopus (23 g) and this is consistent with the results inferred from the toxic reactions of chemicals.

Chapter 3 Methods

3.1 BEIR VII's LQ model[5]

BEIR VII expressed the relative risk from K exposures by following equation.

$$RR_{total} = \alpha D + \beta D^2/K$$

Since it is hard to get raw data of experiments, BEIR VII used reciprocal of mean survival time as an approximated relative risk.

$$1/mean(lifespan) = \alpha D + \beta D^2/K + \gamma$$

γ of this equation refers to the estimated survival time of non-exposed individuals. In the general case of analyzing directly from relative risk, γ should be 0, but in this case, there is a remainder since reciprocal of mean survival time was used instead of relative risk.

I used the same equation for fitting the additional animal experiment data by using R[30]. I used the function of glm, ddply, lrtest from the library of plyr[31], dplyr[32], lmtest[33].

The results of BEIR VII fitting the data of Storer et al. to the LQ model are shown in figure 3.1(figure 10B-3 in BEIR VII). Referring to this figure and work of Haley et al.[22], I tried to reproduce the result and I found out the results I made were consistent with previous studies.

In this process, weighting for the fitting was conducted with the number of samples. Among two common ways for weighting, inverse

variance method and sample size method[34], the reason why I chose this way is that the size of the sample is primary statistical value and can be easily processed and obtained.

Moreover, to compare with the LQ model and linear model I made an analysis of the linear model. This linear model was based on the LNT model.

$$1/mean(lifespan) = \alpha D + \gamma$$

Analysis of the linear model was conducted in a similar way to the LQ model. This was also analyzed by using library plyr[31], dplyr[32], and lmtest[33] of R[30] and the same weighting method was used.

Through the analysis, estimates, standard errors, and p-values of each coefficient were obtained.

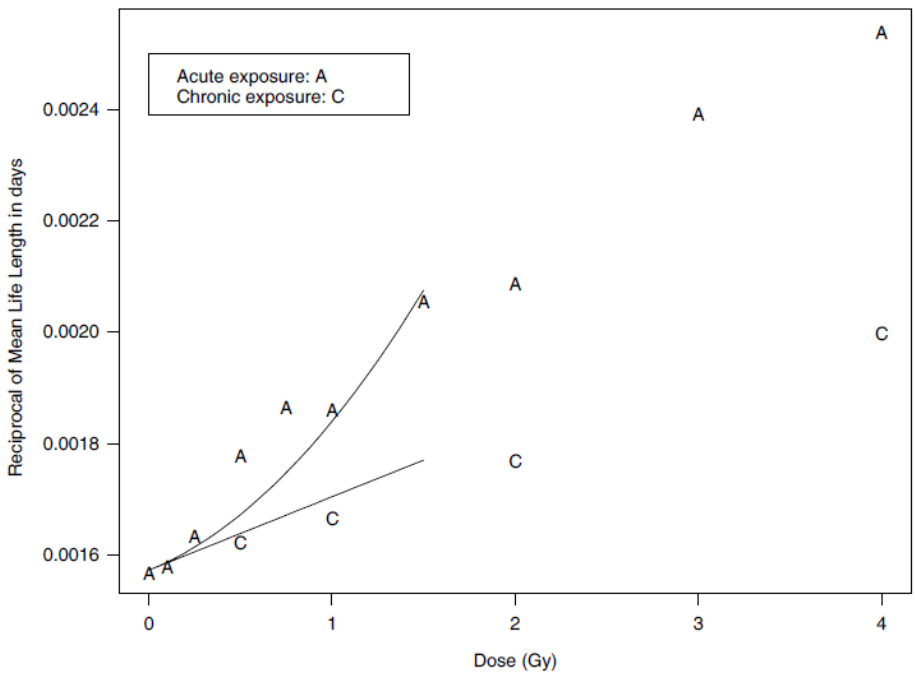

Figure 3.1 Life shortening data from storer et al. and their fitted curves in BEIR VII

Symbol A and symbol C mean acutely exposed groups and chronically exposed groups respectively and both curves are fitted to the 0–1.5Gy dose range[5]

3.2 Selection of dose range

BEIR VII[5] analyzed the Life shortening of RFM female mice from Storer et al.[35] with the subjective dose range of 0−1.5 Gy. It seems that the reason why the committee chose the range is that they also analyzed human LSS data with the range of 0−1.5 Gy.

However, since the radiosensitivity to human and mouse might be different[22], the range of analysis should be different. As the equivalent dose of chemicals is approximately proportional to −0.25 power of body weight, I assumed this relationship also applies to radiation exposure.

Using the average adult weight of a human (62.035 kg) and Mus musculus (0.0205 kg)[28], 1.5 Gy radiation exposure for a human might be equivalent to 11 Gy radiation exposure for Mus musculus. For these reasons, I chose the range of 0−11 Gy for analysis.

3.3 Selection of data

There are a variety of experimental data in ERA. These data were classified and grouped by sex, exposed age, and species. Grouped data were selected by the following selection standard which was referred to the Haley et al.[6]. Data that cannot be confirmed in the published literature or data with nonsense numbers or defects were excluded from the analysis.

- Whole body gamma or X-ray exposure with no other additional treatments
- At least one of 6-11 Gy exposed group
- Can be confirmed in the published literature
- Data that have serious flaws

Groups that were selected by the standard were filtered by the following criteria

- Subject dead before the first exposure
- Groups of same exposed dose with less than 10 subjects

Exceptionally, data of study ID 1003 were analyzed using that of Janus instead of ERA. Following these criteria, there were 7 groups of data in 5 experiments. In addition to these 7 groups, even though they don't meet the standard, data from Storer et al.[35] that was used in BEIR VII were also analyzed.

Table 3.1 Groups of data concerned in this study

Serial Number	source	Sex	Age of first exposure[1]	Strain	Dose range[2]	Number of samples	Radiation type
1	3.3[3][7,36]	M	92	CBA	0-7	294	X-ray
2	3.5[3][7,37]	M	92	BC3F1	0-7	869	X-ray
3	3.5[3][7,37]	M	580	BC3F1	0-7	451	X-ray
4	9.5[3][7,38]	M	84	C57BL	0-6	1806	Cs-137 gamma
5	9.6[3][7,39]	M	84	C57BL	0-6	2712	Cs-137 gamma
6	Janus[8,9]	M	113	B6CF1	0-10.7	8726	Co-60 gamma
7	Janus[8,9]	F	113	B6CF1	0-10.6	9159	Co-60 gamma
8	Storer[35]	F	NA	RFM	0-4	23381	Cs-137 gamma

[1]Days [2]Gy [3]study Id in ERA

3.4 Kocher et al.'s DDREF derivation[23]

Among DDREF derivation methods, DDREF derivation from the concept of LDEF was considered for DDREF derivation in this study. DDREF derivation with the concept of DREF is not suitable for this study since DREF derivation is usually conducted without considering the LQ model.

Kocher et al.'s LDEF derivation method were used for this study since derived LDEFs from human mortality data were described in the paper and the methods they used are described in detail.

To reproduce and verify this method, LDEF and confidence intervals were derived using the same references and their coefficients that Kocher et al. used. As a result, it was confirmed that the same values and confidence intervals with a slight difference were derived and decided to use this method in this study.

Derivation of DDREF from estimated coefficients was conducted in the process below and this process is referred from Kocher et al.'s description.

- 50^{th} percentile and confidence intervals of coefficients are fitted into the Weibull distributions
- Possible coefficients were randomly sampled with the fitted probability density function
- Each sampled coefficients are paired with the following methods
  - For derivation from $1+(\beta/\alpha)D$, α and β were assumed as negatively correlated(correlation coefficient$=-1$) and paired with each other, arranged in ascending order and in descending order.

- For derivation from α_L / α_{LQ}, α and β were assumed as uncorrelated and paired randomly.

- With the paired samples of coefficients, LDEF was calculated and the 50^{th} percentiles and 90 % confidence intervals were derived.

Analysis for confirmation of the Kocher et al.'s method and its application on DDREF derivation from animal studies were conducted with MATLAB.

Table 3.2 Comparison of derived LDEFs for cancer mortality between Kocher et al. and this study

Reference	Method of calculation	Dose range[1]	LDEF[2] of Kocher et al.[23]	LDEF[2] in this study
Little et al.[40]	$1+(\beta/\alpha)D$	0–4	1.34(1.01, 2.53)	1.35(1.01, 2.53)
Little et al.[40]	$1+(\beta/\alpha)D$	0–4	1.51(1.07, 3.26)	1.51(1.07, 3.25)
Ozasa et al.[41]	$1+(\beta/\alpha)D$	0–2	3.2(1.2, 8.3)	3.2(1.2, 8.3)
Ozasa et al.[41]	α_L/α_{LQ}	0–2	2.0(1.0, 6.8)	2.0(1.0, 6.9)
Ozasa et al.[41]	$1+(\beta/\alpha)D$	0–4	1.11(0.94, 1.48)	1.11(0.94, 1.48)
Ozasa et al.[41]	α_L/α_{LQ}	0–4	1.16(0.77, 1.90)	1.16(0.78, 1.90)

[1]Gy [2]50th percentile and 90% confidence intervals

Chapter 4 Results

4.1 Fitting experiment data up to 11 Gy

8 groups of data were fitted in the BEIR VII's LQ model and linear model by using R. Estimates, standard error, p-values of each coefficient are summarized in the following tables and fitted curve with estimated coefficients are shown in the following figures.

4.1.1 BEIR VII's LQ model

Among eight groups, three of the groups (group 1-3) showed negative α_{LQ} or $\beta_{LQ,}$ while the other five groups (group 4-8) showed positive α_{LQ} and β_{LQ}.

The fitted curve of group 1 is convex up, fitted curve of group 2 is almost linear, and the fitted curve of group 3 shows hormetic relation. However, since p-values of the coefficients from these three groups are far larger than 0.05, the meaningful tendency of a quadratic form cannot be found from these data.

The fitted curve of group 5 through 8 shows linear-quadratic relationships. As p-values of the coefficients from these five groups are far lower than 0.05, these experimental results can be considered to follow the LQ model.

4.1.2 Linear model

On the other hand, in the results from the linear model, except for one group (group 3), the coefficients of most groups showed p-values lower than 0.05. All of αL showed the positive value and it seems reasonable to mortality risk from radiation also follows the

linear model and the risk from radiation exposure increases as the exposure dose increases.

Although the LQ model and linear model both appear to be grounded for the analysis in the range of 0–11 Gy, there are additional points to be discussed and I described these on the discussion section.

Table 4.1 Parameters' estimates of the LQ model for mice mortality risk in the range of 0−11 Gy

	1	2	3	4	5	6	7	8
α_{LQ}	1.24E−04	3.29E−05	−1.53E−05	6.93E−05	4.28E−05	2.25E−05	2.46E−05	1.12E−04
±SE	2.81E−05	1.69E−05	2.41E−05	1.02E−05	1.31E−05	2.80E−06	3.17E−06	2.44E−05
p−value	0.047	0.100	0.550	<0.001	0.006	<0.001	<0.001	<0.001
β_{LQ}	−1.10E−05	1.87E−07	3.19E−06	8.16E−06	1.58E−05	9.00E−06	1.00E−05	4.75E−05
±SE	3.93E−06	2.66E−06	3.39E−06	2.16E−06	2.74E−06	8.83E−07	8.56E−07	8.07E−06
p−value	0.108	0.946	<0.001	0.004	<0.001	<0.001	<0.001	<0.001
γ_{LQ}	1.38E−03	1.21E−03	1.14E−03	1.29E−03	1.67E−03	1.01E−03	1.03E−03	1.61E−03
±SE	3.72E−05	1.48E−05	3.37E−05	1.68E−05	2.48E−05	9.92E−06	8.17E−06	2.85E−05
p−value	<0.001	<0.001	<0.001	<0.001	< 2E−16	< 2E−16	< 2E−16	< 2E−16

Table 4.2 Parameters' estimates of the linear model for mice mortality risk in the range of 0−11 Gy

	1	2	3	4	5	6	7	8
α_L	4.91E−05	3.40E−05	6.64E−06	9.83E−05	9.76E−05	3.41E−05	4.39E−05	2.20E−04
±SE	1.38E−05	4.04E−06	6.12E−06	1.00E−05	1.66E−05	5.69E−06	7.73E−06	2.87E−05
p−value	0.038	<0.001	0.314	<0.001	<0.001	<0.001	<0.001	<0.001
γ_L	1.44E−03	1.21E−03	1.12E−03	1.28E−03	1.63E−03	1.01E−03	1.03E−03	1.58E−03
±SE	5.57E−05	1.29E−05	2.59E−05	2.43E−05	4.40E−05	2.21E−05	2.33E−05	5.05E−05
p−value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

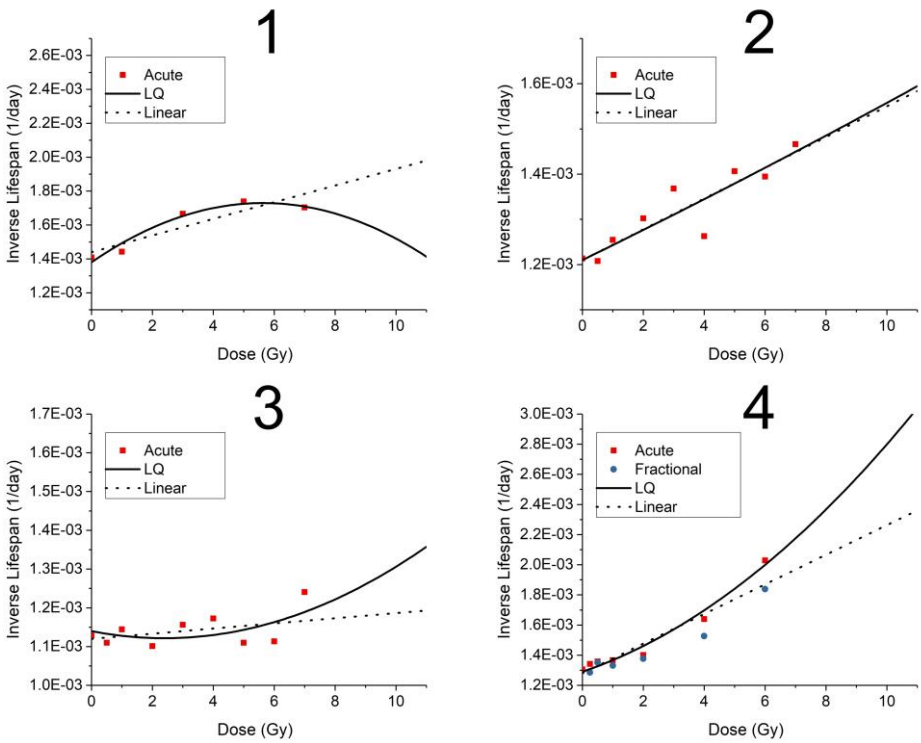

Figure 4.1 BEIR VII's LQ model and linear model fitted to 8 Groups for the dose range of 0–11 Gy(1)

Red square dots refer to acute exposed groups and blue round dots refer to fractional exposed groups. Black solid lines refer fitted linear–quadratic curves and black dotted lines refer fitted linear lines to the data.

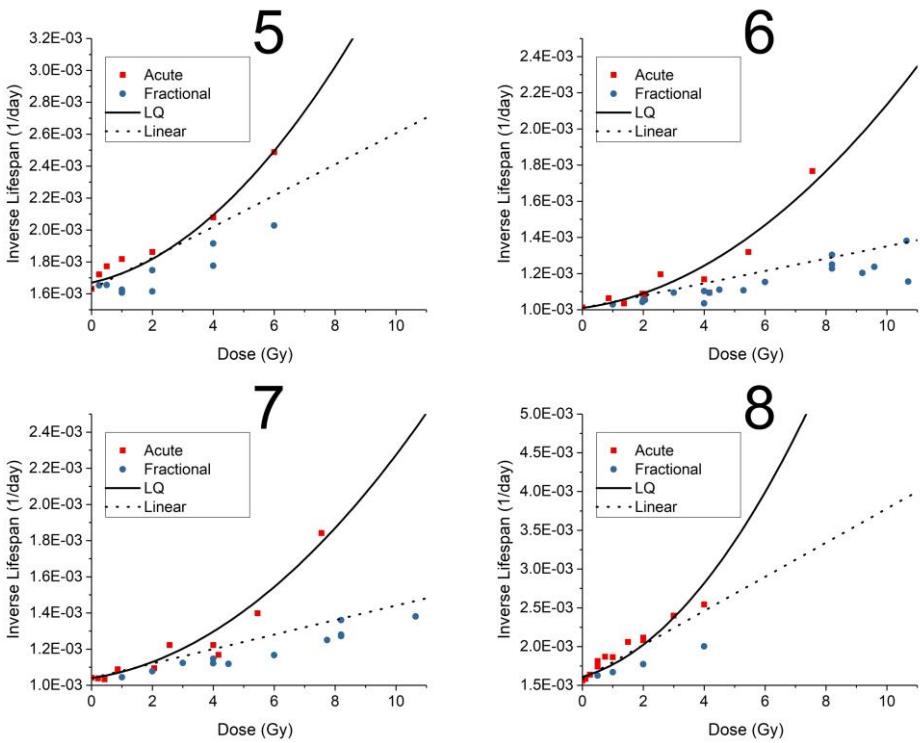

Figure 4.2 BEIR VII's LQ model and linear model fitted to 8 Groups for the dose range of 0–11 Gy(2)

Red square dots refer to acute exposed groups and blue round dots refer to fractional exposed groups. Black solid lines refer fitted linear–quadratic curves and black dotted lines refer fitted linear lines to the data.

4.2 Fitting experiment data up to 1.5 Gy

Among 8 groups, 7 of them except for group 1 have at least 3 treatment groups of exposed to equal or less than 1.5 Gy. Data of these 7 groups were also fitted in the BEIR VII's LQ model and linear model to compare with the result of the new dose range.

4.2.1 BEIR VII's LQ model

Except for only one group (group 8), most groups showed poor regression through BEIR VII's LQ model. Most of the p-values are extremely larger than 0.05, and it means that meaningful quadratic relationships cannot be derived through these data.

4.2.2 Linear model

However, regression through the linear model showed good regression. Except for one group (group 3), the p-values were lower than 0.05. The risk from radiation exposure tends to increase as the exposed dose increase and linear model might be better for explaining relationships in this dose range.

With the small number of treatment groups, analysis in the dose range of 0-1.5 Gy was conducted limitedly. In this analysis, there was no significant quadratic relation between risk and dose, however, the linear relation was found to be meaningful.

Table 4.3 Parameters' estimates of the LQ model for mice mortality risk in the range of 0−1.5 Gy

	2	3	4	5	6	7	8
α_{LQ}	−6.46E−05	−9.07E−05	3.24E−05	−4.05E−05	1.95E−05	1.08E−05	1.24E−04
±SE	NA	NA	3.68E−05	6.60E−05	2.22E−05	8.84E−06	5.33E−05
p−value	NA	NA	0.428	0.566	0.540	0.345	0.049
β_{LQ}	1.06E−04	1.06E−04	2.54E−05	2.08E−04	2.45E−05	6.15E−05	1.43E−04
±SE	NA	NA	3.94E−05	7.61E−05	2.47E−05	1.36E−05	4.14E−05
p−value	NA	NA	0.555	0.041	0.503	0.046	0.009
γ_{LQ}	1.21E−03	1.13E−03	1.31E−03	1.67E−03	1.02E−03	1.03E−03	1.59E−03
±SE	NA	NA	1.45E−05	2.87E−05	8.72E−06	3.06E−06	2.21E−05
p−value	NA	NA	<0.001	<0.001	0.005	<0.001	<0.001

Table 4.4 Parameters' estimates of the linear model for mice mortality risk in the range of 0−1.5 Gy

	2	3	4	5	6	7	8
α_L	3.25E−05	1.59E−05	4.98E−05	8.33E−05	3.46E−05	3.71E−05	2.64E−04
±SE	2.22E−05	3.07E−05	2.35E−05	6.92E−05	1.62E−05	1.83E−05	5.12E−05
p−value	0.381	0.695	0.087	0.274	0.166	0.136	<0.001
γ_L	1.21E−03	1.12E−03	1.31E−03	1.66E−03	1.02E−03	1.03E−03	1.57E−03
±SE	7.47E−06	2.00E−05	1.33E−05	4.09E−05	8.67E−06	8.36E−06	3.16E−05
p−value	0.004	0.011	<0.001	<0.001	<0.001	<0.001	<0.001

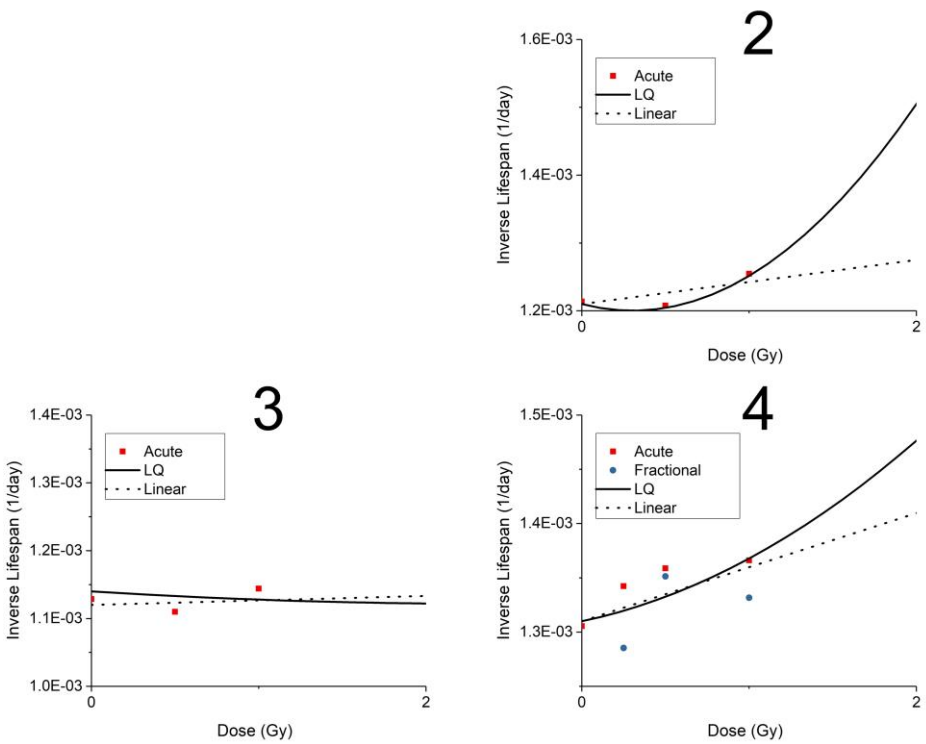

Figure 4.3 BEIR VII's LQ model and linear model fitted to 7 Groups for the dose range of 0−1.5 Gy(1)

Red square dots refer to acute exposed groups and blue round dots refer fractional exposed groups. Black solid lines refer to fitted linear−quadratic curves and black dotted lines refer fitted linear lines to the data. Group 1 was excluded from the analysis since it has less than 3 exposed groups in the dose range.

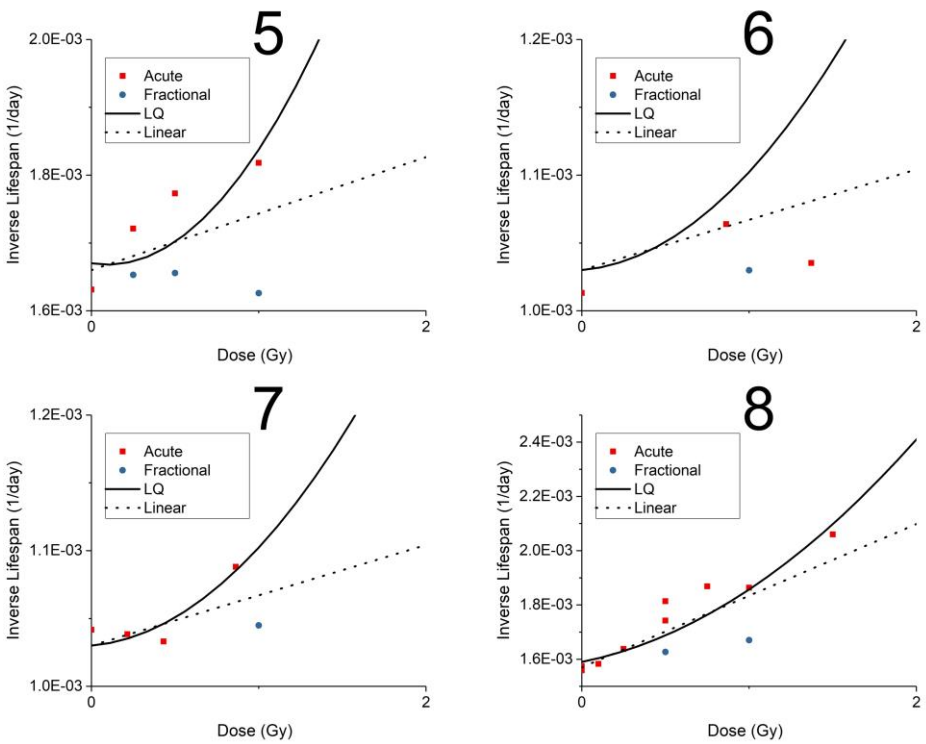

Figure 4.4 BEIR VII's LQ model and linear model fitted to 7 Groups for the dose range of 0–1.5 Gy(2)

Red square dots refer to acute exposed groups and blue round dots refer fractional exposed groups. Black solid lines refer to fitted linear–quadratic curves and black dotted lines refer fitted linear lines to the data.

Chapter 5 Discussion

5.1 Grounds for change of dose range

While the LQ model fits well only in the range up to 11 Gy, the linear model fits well both in the range up to 11 and 1.5 Gy. In these aspects, the linear model might be thought of as a proper model for explanation of low dose effect. However, in the detailed viewpoints, the LQ model could be more supported than the linear model.

5.1.1 Possible reason for poor regression of the LQ model in the dose range of 0−1.5 Gy

Especially for regression in the dose range of 0−1.5 Gy, the LQ model is hard to be supported as a model to explain the low dose radiation effects. However, analysis under 1.5 Gy might have large variability. As mentioned before, the radiation dose to species might not be compatible. According to the assumption that the equivalent dose of each species is proportional to −0.25 power of the body weight, 1.5 Gy for Mus musculus might correspond to 0.2 Gy for humans which is a relatively low dose. As human's risk from exposure of under 0.2 Gy does not make a significant difference from background risk, risk of Mus musculus from exposure below 1.5 also might not make a significant difference. At this point, the observed risk from life−shortening data would have a large error, and it will make difficult to be fitted in the LQ model which is more complex than the linear model.

5.1.2 Advantages of the LQ model over the linear model for explanation of the results: Qualitative advantages

Although the LQ model might be still appropriate despite poor-fitting under 1.5 Gy, this does not indicate the inadequacy of the linear model. However, the LQ model has an advantage that it is easier to explain the observed phenomenon in the experiments.

In all of the exposed groups, the observed risk from single exposure was larger than that of fractional exposure. This can be explained easily with the LQ model. According to the LQ model, risk per dose in high dose exposure is larger than that of low dose exposure. For this reason, the risk from single exposure would be larger than that of fractional exposure, which is the sum of the exposures of a smaller dose.

However, the linear model can't explain it. Although, Haley et al.[6] explained the lower observed risk of fractional exposed groups with a 'linear-linear model', they couldn't suggest a further explanation of the model.

5.1.3 Advantages of the LQ model over the linear model for explanation of the results: Quantitative advantages

The advantages of the LQ model can be also explained with the comparison of deviances from two models. Deviance indicates how much the observed values are different from the regression model[42].

For group 4−8, which are well fitted with low p−value both for LQ and linear model, deviances of two models have significant differences ($p<0.001$). Deviances of each model were calculated with glm function and p−values of the difference of deviances are calculated with lrtest function, which compares regression models with likelihood ratio tests[33].

Since the deviances of the LQ model are significantly smaller, the LQ model explains the results better than the linear model.

Table 5.1 Deviances of LQ model and linear model for well fitted groups

Serial Number	4	5	6	7	8
Deviance of LQ model	2.92E−06	1.12E−05	1.28E−05	7.91E−06	1.35E−04
Deviance of linear model	7.09E−06	3.99E−05	6.59E−05	6.54E−05	4.70E−04
P−value	<0.001	<0.001	<0.001	<0.001	<0.001

5.1.4 Comparison the results with human data

As seen in figure 5.1, the dose-response of higher dose show different aspects. Since risk cannot increase indefinitely as the dose increase, the slope of risk increase above a certain level of dose would decrease. For this reason, data of a larger range of doses will be fitted with the smaller quadratic term. This tendency can be confirmed by various epidemiologic studies of humans.

Ozasa et al.[41] analyzed the mortality of atomic bomb survivors in two dose ranges, full dose range and under 2 Gy. According to their work estimates of linear term and quadratic term of full dose range are 0.36 and 0.038 each while they were 0.22 and 0.18. In the full dose range, the fitted linear model and the LQ model didn't have a significant difference which means the linear model is more plausible.

Comparing these results to our results, since our results showed the relatively significant difference between the linear model and LQ model data fitting with 0-11 Gy of Mus musculus data is more similar with that of 0-2 Gy human data than that of full dose range human data.

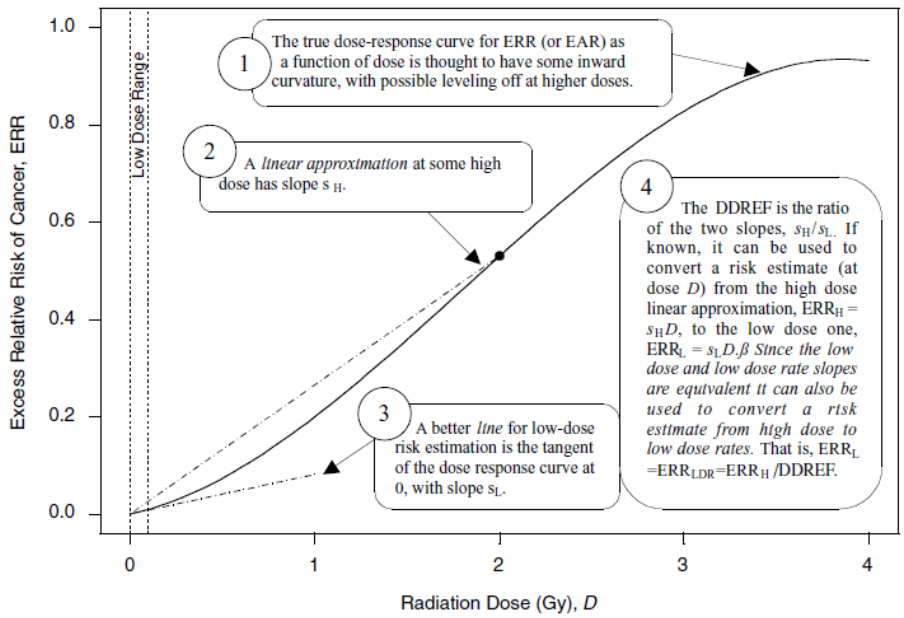

Figure 5.1 A hypothetical dose-response curve [5]

5.1.5 Comparison of DDREFs: mouse vs human mortality data

DDREFs of LSS studies are obtained from the high dose of 1 Gy and this dose should be also changed for the Mus musculus. As 11 Gy for Mus musculus was used as the dose that is equivalent to 1.5 Gy for humans, 7 Gy can be used for Mus musculus as the corresponding to 1 Gy for humans.

Based on this, the expected DDREF with Kocher et al.'s method from each experimental data can be seen between 1.8 and 4, mainly between 3.5 and 4. According to Kocher et al., estimated mortality LDEF derived from Ozasa et al.'s study is 3.2 which is similar to the result of our study.

Admittedly, there is some difference between two DDREF distributions. However, while most of our analysis on Mus musculus data was conducted on dose range under 7 Gy, Kocher et al.'s analysis on the data of Ozasa et al. is conducted on dose range under 2 Gy which is correspondent to about 15 Gy for Mus musculus with our consumption. Considering this difference, this level of deviation is thought to be insignificant[23,41].

Table 5.2 50th percentiles and 90% CIs of DDREF derived from well-fitted groups and atomic bomb survivors with Kocher et al.'s method

Reference	Ozasa et al.	4	5	6	7	8
$1+(\beta/\alpha)D$	3.2 (1.2,8.3)	1.8 (1.4,2.6)	3.6 (2.2,7.8)	3.8 (3.0,5.1)	3.8 (3.0,4.8)	4.0 (2.6,6.9)
α_L/α_{LQ}	2.0 (1.0,6.8)	1.4 (1.1,2.0)	2.3 (1.4,4.8)	1.5 (1.1,2.1)	1.6 (1.1,2.2)	2.0 (1.3,3.2)

5.2 Further studies on animal data

It is not proper to apply the result from animal studies to humans without additional consideration since there is no conviction that the reaction of humans corresponds to the reaction of other species. For example, the primary characteristics of each species such as body weight, body temperature, metabolic rate, and lifespan are different and this different feature can make difference in biological response like the toxic reactions of chemicals[25]. Moreover, cell composition or organ ratios vary slightly from species to species[43]. Due to the different radiation sensitivity of each cell or organ[44,45], radiation-induced response would be varied by the compositions.

The variability from the differences of biological characteristics may not be large, however, in order to use the animal data more accurately, it is necessary to study how the differences of characters affect the radiation response.

I tried a distinct type of analysis concentrating on the weight of animals, however, considering the factors that can affect radiation response, other types of analysis considering various biological characters would be possible.

Chapter 6 Conclusion

Public interest in health is increasing day by day. In particular, there has been a great deal of interest in radiation-induced harm since the Fukushima nuclear accident and the radon mattress scandal in Korea. Low dose radiation exposure is common to the public in various forms, such as radiation therapy, radiation diagnosis, living around the nuclear power plant, radon exposure and boarding an airplane. However, unlike exposure from high dose radiation, the effects of low dose exposure are not yet well established[1].

Since low dose radiation effects are hard to be figured out because of its relatively low-level effects, it is necessary to use various sources of radiation exposure data for analyzing low dose radiation effects. For this reason, animal and cell experiments, as well as human LSS studies, have been conducted.

However, using animal studies for getting information about reaction to humans should be conducted carefully. As the equivalent dose of chemicals to species is applied differently[25], the equivalent dose of radiation also might be applied differently. With this in mind, I conducted a study on the application of animal experimental data to humans for low-dose radiation exposure. The relationship of chemical equivalent dose between species was applied to the relationship of radiation equivalent dose between species.

With the assumption, the LQ model fits animal data in the radiation dose range adjusted by allometric dose scaling. However, the LQ model was hardly fitted to animal data in the radiation dose range commonly used for analysis on human data. Derived distributions of DDREF from animal data with allometric dose scaling were comparable to those from human epidemiology. Given these

positive results of allometric scaling, allometric scaling of dose seems to be a good option for animal radiation. In addition, since data that did not fit the LQ model at lower dose exposure appeared to fit the LQ model in the allometric scaled dose range, the claim [6] that animal mortality data do not follow the linear–quadratic relationship should be changed.

Even though I got positive results through the allometric method, there is no certainty that this method can be applied consistently to other species and it is the sole way to reflect species differences. Nevertheless, I think to apply different standard with the allometric method to each species have grounds to apply in low dose radiation analysis and should be studied further in this point of view.

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국문 초록

저선량 방사선 영향 분서에서 동물실험자료의 효용성 연구

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사람에 대한 고선량 방사선 피폭 효과는 비교적 잘 정립되어 있는 반면, 저선량 방사선 피폭에 대해서는 여전히 논란이 많다. DDREF 도출과 같은 저선량 방사선에 대한 분석은 주로 역학 연구에 의해 진행되어왔는데, 역학 연구는 정확한 피폭 선량을 알기 어렵고 배경 위험도에 비해 방사선 피폭으로 인한 위험도 증가 정도가 작기 때문에 정확한 분석을 알기 어렵다는 내재적 단점이 있다. 이러한 이유로, 역학 연구를 보완하기 위해 동물과 세포에 대한 방사선 피폭 실험이 진행되어왔다.

BEIR VII과 같은 여러 연구에서 사람에 대한 역학조사와 동물실험 자료를 바탕으로 저선량 방사선에 대한 연구가 진행되어 왔다. 이와 같은 연구들은 동물과 사람에 대해 같은 선량 기준을 가지고 분석을 진행하였다. 하지만, 일부 연구에 따르면 방사선으로 인한 사람의 반응과 다른 종의 반응이 다를 가능성이 있기에 이를 같은 기준으로 적용시키는 것이 옳지 않을 것으로 보인다. 이와 유사하게 화학물질에 대한 독성의 종 특이성은 오랜 기간 연구되어 왔고, 이는 알로메트리와 같은 방식으로 비교적 잘 정립 되어있다.

본 연구에서 알로메트리를 이용하여 새로운 선량 스케일링 방법을 제안하고 검증하고자 하였으며, 이 과정에서 BEIR VII의 방법을 사용하여 ERA와 Janus의 쥐 피폭 데이터를 분석하였다. ‘¾법칙’ 을 사용하여 사람에 대한 0~1.5 Gy의 선량 범위에 해당하는 쥐의 선량 범위로

0~11 Gy를 선택하고 분석을 진행하였다.

이와 같은 새로운 선량 범위의 분석에서 LQ모델이 선형모델보다 더 반응을 잘 설명하였고, 분석결과와 도출된 DDREF의 분포가 사람의 것과 유사한 결과를 보였다.

이러한 점을 고려하여, 사람에게 적용되는 선량 기준을 동물 노출 데이터에 그대로 적용시키기 보다는 각 종의 특성에 근거하여 다른 선량 기준을 적용 시켜야 더 정확한 결과를 얻을 수 있을 것으로 생각되고, 그 기준으로 각 종별 무게의 차이를 이용하는 것이 하나의 선택지가 될 수 있을 것이라고 생각한다.

Keywords : 저선량 방사선, 선형이차 모델, DDREF, 동물 실험, 알로메트리
Student Number : 2018-21273

감사의 글

석사 과정을 시작할 때만 하여도 길게만 느껴졌던 2년이 막상 지나고 보니 어떻게 지나간지 모를 정도로 많은 일들이 정신없이 지나간 듯합니다. 시간이 지나고 보니 석사 학위 취득까지 많은 사람들의 도움이 없었다면 불가능했을 것이라는 생각이 가장 먼저 듭니다.

제가 하는 일들을 응원해주시면서 여러 방면에서의 조언을 아끼시지 않아 주신 김은희 교수님께 감사의 말씀 전합니다. 또한, 심사위원장을 맡아 논문의 방향에 대해 여러 조언을 남겨 주신 정경재 교수님과 세세하게 조언을 해 주신 이민호 박사님께도 심사를 맡아 주셔 감사하다는 말씀 전합니다.

또한 연구실에서 연구 방향에 대해 고민을 할 때 많은 조언을 해 주신 지용이형, 잘 모르는 세포실험에 대해 물어 볼때마다 자세히 알려주신 의섭이형, 그 외에도 연구실 생활에 적응하고 진로에 대해 생각하는데 여러가지 도움을 주신 완욱이형, 승희누나, 주희누나, 지원이에게도 감사의 말씀 전합니다. 그리고 연구실 옆자리에서 이런저런 얘기를 나누었던 알리와 같이 석사과정을 시작하여 이번에 같이 졸업하게 되는 동현이에게도 고맙다는 말 전하고 싶습니다. 이 외에도 같이 연구실 생활을 하지는 못하였지만 지금의 연구실을 만든 많은 연구실 선배들 덕분에 무사히 석사과정을 마칠 수 있었던 것 같습니다.

서울대학교 입학 이후 만났던 원자핵공학과의 많은 선후배님들, 11학번 복학생 친구들, 뉴트론즈, 프로톤즈, 학생사회공헌단의 선후배님들과 친구들, 그리고 그 외에도 많은 친구들 덕분에 행복하게 학교를 다닐 수 있었던 것 같아 감사한 마음 항상 간직하고 있습니다. 덕분에 대학교 입학 후 9년동안 큰 스트레스 받지 않고 즐겁게 학업 생활을 이어갈 수 있었던 것 같습니다.

무엇보다도 항상 뒤에서 제 결정을 지지해주시고 큰 도움을 주신 부모님께 가장 큰 감사의 말씀을 전합니다. 27년이 넘는 시간동안 좋은 일이 있을 때나 안 좋은 일이 있을 때나 변함없이 지지해주시고 응원해주신 무한한 사랑 덕분에 어려운 일들을 하나씩 헤쳐 나갈 수 있었습니다. 또한, 미국에서 박사과정을 이어가고 있는 와중에도 여러 도움을 주고 있는 누나와 자형에게도 항상 감사한 마음 가지고 있습니다. 이 외에도 많은 친척들에게 사랑을 받은 덕분에 그간 있었던 여러 어려움을 극복할 수 있었습니다.

다 적고 보니 제가 받아온 사랑에 비하면 제가 베풀었던 것은 한없이 모자란다는 것을 다시 한번 느끼게 되었습니다. 많은 분들의 응원 덕분에 한걸음 또 내딛을 수 있었던 것 같고, 앞으로 제가 받은 사랑을 많은 사람들에게 돌려드리는 삶을 살고 싶습니다. 2년의 석사과정, 그리고 27년 동안 만났던 모든 사람들에게 다시 한 번 감사드립니다.