

H. Kuni, Marburg<sup>1</sup>

## Dose-Response Relationship of Low and High LET Radiation <sup>2</sup>

### Abstract

The dose-response relationships of the various types of leukaemia are completely different. Analysing the leukaemia incidence in the atomic bomb survivors the results of the relative risk model looks more plausible. A significant dose response is missed in adult T-cell leukaemia, endemic in Nagasaki. Estimations of the relative risk summarising all types underestimate the risk of types with risks higher than the mean as CML and ALL. The dose-response curves show a decline in the high dose range after a maximum due to cell killing effect depending from the type. The maximum of CML is seen at lower doses (two to three Gray) than that of AML (three to four Gray). Risk estimates neglecting the cell killing give to low risk factors. The RBE of the atomic bomb neutrons is 23.6 for ALL, 161 for AML, and 46 for CML (reference radiation: 250 kVp X-ray). The linear component of the dose-response function of ALL in the age below 15 years shows a doubling dose of 12.5 mGy for atomic bomb gamma-rays, equivalent to 3.5 mGy X-ray.

In the radium cases an elevated leukaemia risk was missed. The leukaemia risk in the Thorotrast cases is markedly lower compared with exposure to low LET-radiation, supposed the dose calculations and radiation weighting factors are true. The relative incidence of MDS and erythroleukaemia (M<sub>6</sub> FAB) is increased after exposure to alphanradiation. The assumption of cell killing effect of high alpha doses and diminished effectiveness of high alpha dose rate as causes of false low leukaemia incidence are supposed by epidemiological results of increased leukaemia incidence after low dose exposure to alpha radiation, for example by radium contamination of drinking water or radon exposure.

The occupational life time dose of flight personnel with increased leukaemia incidence (mostly AML), calculated using the radiation weighting factors recommended by ICRP, must be multiplied by about twenty for explaining quantitatively the observed elevated relative risk.

---

<sup>1</sup> Horst Kuni, MD, university professor retired, Clinical Nuclear Medicine, Medical Centre of Radiology, Philipps-university Marburg

<sup>2</sup> Marburg 2008: 2nd revised edition of a paper, originally presented at the International Workshop 'Radiation Exposures by Nuclear Facilities, Evidence of the Impact on Health', University of Portsmouth, GB, 1996, In: Schmitz-Feuerhake, I., Schmidt, M. (Ed.): Radiation Exposures by Nuclear Facilities, Evidence of the Impact on Health, Proceedings International Workshop, University of Portsmouth, GB, 1996, Thomas Dersee, Strahlentelex, Berlin, 1998, p. 20-34.

## Introduction

Beginning with a short historic overview we have to remember that as early as in the second decade after the discovery of X-rays and radioactivity Jacig reports in 1911 leukaemia on five radiation workers [18]. In a listing of 14 milestones in radiation carcinogenesis by Mossman we recognise leukaemia as one of the most impressive malignancies observed in humans exposed to ionizing radiation, listed in seven items.

It is remarkable that the first systematic reports by Henshaw and Hawkins 1944 concern the consequences of an occupational handling of X-rays and evaluate facts which are public to everybody who read the weekly published death notices in the Journal of the American Medical Association [9]. US physicians died 1.7 times more frequently of leukaemia than the general population and the US radiologists significantly more often than other physicians.

Thus the look was sharpened for the recognition of the impressive wave of leukaemia in the atomic bomb survivors only few years after the bombings. The victims of Hiroshima and Nagasaki and patients treated with X-rays because of such dubious indications as thymus hyperplasia demonstrate the exceptionally high sensitivity of children. However, the important discovery of Stewart and co-workers in 1958 [23], an enhancement of childhood leukaemia following diagnostic X-ray pictures during pregnancy, listed as historic milestone by Mossman also, has provoked a deep controversy. Their findings were an impressive support of the postulated linear non-threshold relationship for leukaemia. Furthermore, the hypothesis of radiogenic mutation of the genes causing not only leukaemia but also malignancies of all other tissues, on principle, was corroborated by a vast number of studies until today.

The exceptional position of the leukaemia is underlined by the fact that nine of twelve studies in a compilation of Boice demonstrate a significant risk [4].

In the incidence study on the atomic bomb survivors leukaemia shows the most prominent attributable risk in comparison to all cancers following the whole body exposure (ref. tab. 1, p. 3).

Table 1: Attributable risk, excess relative risk and absolute excess over expectation of radiation-induced cancers after whole body exposure. Data from the atomic bomb survivors. (After Thompson et al. [25])

Organ	Attributable Risk %	Excess Relative Risk / Gy	Absolute Excess / 10 <sup>4</sup> PY-Gy
Leukaemia	50	4.37	2.7
Breast	32	1.6	6.7
Thyroid	26	1.2	1.6
Skin	24	1.0	0.84
Lung	19	1.0	4.4
Ovary	18	1.0	1.1
Urinary Bladder	16	1.0	1.2
Colon	14	0.72	1.8
Liver	11	0.49	1.6
Stomach	6.5	0.32	4.8

However, in spite of the enormous excess relative risk of leukaemia, about four times and more than that of other sites, the absolute number of excess cases is not so prominent because of the relatively low background rate of this disease.

Today, the fact is that during our century the incidence of leukaemia was doubled, in a period that add about the same radiation dose to the population by technical sources as it was exposed to natural sources. But, the conclusion suggesting itself of a radiogenic nature of most leukaemia and a doubling dose in the order of natural radiation is refused, e.g. by Jacobi and Chmelevsky, attributing only about ten per cent of the spontaneous leukaemia to background radiation [13]. Their calculations are based on the excess relative risk values observed on leukaemia mortality of the atomic bomb survivors reported by Shimizu and coworkers [21]. The observations on the cohort of the atomic bomb victims are used as golden standard, a procedure, as you know, in which my previous speaker was involved also.

## The A-bomb Survivors and Dose-Response Relationships

Therefore, following this brief introduction I will focus on the data of the atomic bomb survivors. The dose revision DS86<sup>3</sup> has greatly diminished the so called city effect by lowering the neutron and increasing the photon doses in Hiroshima. The last evaluation of risk figures by the RERF uses a dose

<sup>3</sup> Abbreviations: ALL: acute lymphatic leukaemia; AML: acute myeloid leukaemia; ATL: adult T-cell leukaemia; BEIR: Committee on the Biological Effects of Ionizing Radiations; CASTOR: cast for storage of radioactive material; CLL: chronic lymphatic leukaemia; CML: chronic myeloid leukaemia; DS 86: Dosimetry System 1986; E: number of expected cases; EAR: excess absolute risk; ERR: excess relative risk; FAB: French American British classification of leukaemia; ICD International classification of disease; ICRP: International Commission on Radiological Protection; MDS myelodysplastic syndrome; O: number of observed cases; RBE: relative biological effectiveness; RERF: Radiation Effect Research Foundation Hiroshima; SIR standardized incidence ratio; PY person year ; SMR: standardized mortality ratio

independent RBE of the neutrons of ten and the absolute risk model [19]. The diagnoses of about two thirds of the leukaemia were revised according to the FAB-classification. Doses of more than four Gray were excluded. The best result fitting all types of leukaemia combined was a quadratic dose response function.

About ten per cent of the diseases were ATL, adult T-cell leukaemia, an infectious disease, endemic in Nagasaki, without a significant dose response. The dose response of the other entities is strongly modulated by diagnosis, sex, age at exposure, city and time to onset.

After the dose revision Shimizu and coworkers calculated a RBE of  $52 \pm 60$  using a linear model both for neutrons and photons [21]. A linear-quadratic model for photons and a linear one for neutrons shows a markedly inverse dose relationship with a RBE of 27 at 1 Gy, 60 at 100 mGy and 149 at 10 mGy. Such high values of RBE have little acceptance, obviously, because of enormous consequences in the daily practice of radiation protection. As an example I remember on the public discussion of the transport of high radioactive waste in Germany using the CASTOR casts.

Zaider does not hesitate publishing a RBE of  $70 \pm 50$  for solid tumours [29]. Fitting the data of Shimizu and coworkers of relative mortality risk of leukaemia he was able to reduce the parameter to a quadratic component for the dose of both kinds of radiation and a negative parameter for an exponential concave-downward shape of the dose response curve attributed to cell killing. The parameter of cell killing by neutrons was about 14 times greater than that by photons.

The following analysis deals with all kinds of myeloid leukaemia and acute lymphatic leukaemia without chronic lymphatic leukaemia (CLL). CLL is very seldom in Japan. In the atomic bomb survivors in Nagasaki CLL was observed in one case, only [19]. In newer classification systems, CLL will be classified as a kind of malignant lymphoma. I have used the Leukaemia Incidence File HAEMA87.DAT provided by RERF with creation date 9 September 1994 calculating the parameters of the formula

$$\eta(D) = \rho(D) * \zeta(D)$$

with

$$\rho(D) = (\alpha_g D_g + \alpha_n D_n + \beta (D_g + D_n)^2)$$

and

$$\zeta(D) = \exp(-\gamma_g D_g - \gamma_n D_n - \delta (D_g + D_n)^2)$$

D is Dose in Gray in each dose class, weighted by person years (PY); g and n mean gammarays and neutrons.

In the relative risk model to the result  $\eta(D)$  (ERR) one is added, to calculate the relative risk, and the result is multiplied by the background incidence per 10,000 PY (b) and by the person years of each dose class (PY(D)) for calculation of the number of expected cases in each dose class (E(D)). The person years of risk are adjusted to migration. For comparison with the observed cases in each dose class (O(D)) a modified chi-square value was calculated after Stewart and Kneale [22].

$$E(D) = (\eta(D) + 1) * b * PY(D)$$

$$\chi^2 = (O(D) - E(D))^2 / (O(D) + 2)$$

In the absolute risk model to the result  $\eta(D)$  (EAR) the background incidence is added and the sum is multiplied by the person years of each dose class for calculation of the number of expected cases.

$$E(D) = (\eta(D) + b) * PY(D)$$

Table 2: Parameters of dose-response relationships of ALL, AML and CML (all age groups together).

	ALL		AML		CML	
	EAR	ERR	EAR	ERR	EAR	ERR
background	0.0691	0.0687	0.298	0.295	-0.0997	0.095
$\alpha_g$	0.12	2.23	0	0.423	0.416	5.05
$\alpha_n$	16.7	189.55	83.2	244.494	86.112	833.25
RBE	139	85	-	578	207	165
$\beta$	0.275	4.15	0.693	2.32	0	0
$\gamma$	0.005	0	0	0	0.367	0.345
$\delta$	0.034	0.0344	0.079	0.076	0	0
$\chi^2$	4.87	4.86	8.69	9.13	17.3	17.41

Table 3: Parameters of dose-response relationships (relative risk model only) of ALL, AML and CML (mean age less than 15 years).<sup>4</sup>

	ALL		AML		CML	
	age <15	all ages	age <15	all ages	age <15	all ages
background	0.0159	0.0687	0.067	0.295	0.058	0.095
$\alpha_g$	78.6	2.23	0	0.423	0	5.05
$\alpha_n$	78.6	189.55	0	244.494	0	833.25
RBE	1	85	-	578	-	165
$\beta$	0	4.15	40.9	2.32	20.3	0
$\gamma$	0.13	0	0	0	0.3	0.345
$\delta$	0	0.0344	0.37	0.076	0	0
$\chi^2$	1.93	4.86	3.36	9.13	2.84	17.41

<sup>4</sup> CML, age <15: with  $\delta = 0.05$  instead of a  $\gamma$ -value:  $\beta = 14$  and  $\chi^2 = 2.88$

All parameters, including the figure of background, were changed iteratively minimising the sum of chi-square over all dose classes. With both models, relative and absolute risk, similar chi-square values can be obtained (cf. tab. 2, p. 5), but the results of the relative risk model look more plausible.

The absolute risk model gives a negative value for background in CML of all age groups and ALL of younger people. Also, the relative risk model is compatible to the observation of new incidence cases of AML up to the eighties. Therefore, the parameters of the age group less than 15 years are calculated using the excess relative risk model only (cf. tab. 3, p. 5.). A positive  $\beta$  parameter for a quadratic concave-upward shaped curve was always combined with a negative  $\delta$  parameter for a quadratic component of cell killing effect. There are remarkable high values of RBE of 85 for ALL, 578 for AML and 165 for CML.

Before comparing these values of RBE with the quality factors and radiation weighting factors, recommended on radiation protection, we have to consider the new declaration of the energy of the photons of the atomic bombs by Straume [24]. He has indicated an energy of about 3 MeV and a biological effectiveness of about 3.6 times smaller than that of orthovoltage X-rays of 250 kVp. Using X-rays as reference radiation the RBE will be diminished to 23.6 for ALL, 160.6 for AML and 45.8 for CML.

For ALL and AML the cell killing effect seems to be smaller in comparison to CML. AML shows a quadratic parameter, which was also seen in the results of Preston and co-workers [19] in a similar figure. Because of nearly 50 percent of the atomic bomb survivors of the atomic bomb survivors of the atomic bomb survivors with radiation related leukaemia has suffered from AML, it is not surprising that dose-response-curves for all types of leukaemia combined shows a quadratic component as calculated by the BEIR-committee using the relative risk model, too [3].

Fig. 1 (p- 7) shows the results for AML. Please, pay attention to the contribution of the cell killing effect on the shape of the dose response area in the high dose range of  $\gamma$ -dose.

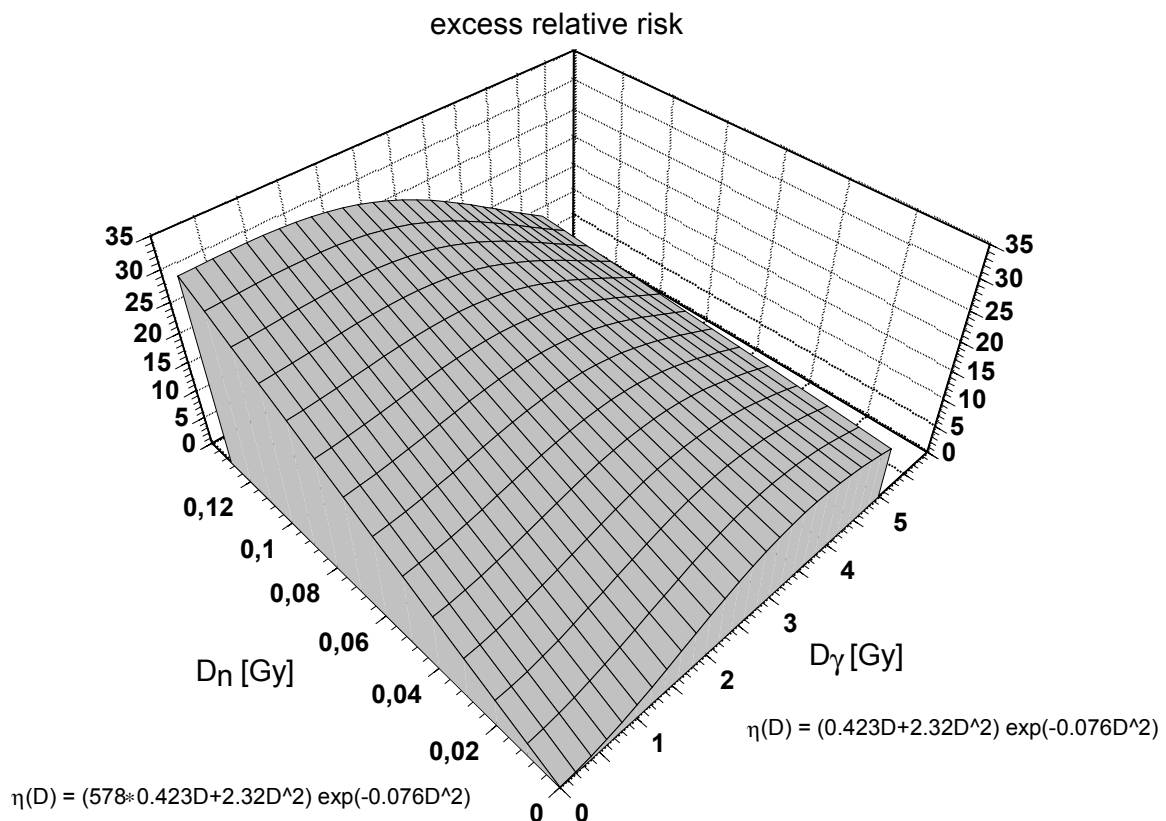


Fig. 1: Dose-response area of AML, relative risk model, all ages.

Limiting the calculation to classes with a mean age at exposure of less than 15 years, we get quite another result (cf. tab. 3, p. 5). AML and CML lose the linear component for both kinds of radiation. In the case of ALL we see a very steep linear component and no quadratic parameter. The  $\alpha$ -value of 78.6 means a doubling dose of 12.7 mGy of the atomic bomb radiation and of 3.5 mGy equivalent to 250 kVp X-rays. These risk factors describe the mean risk of the time 5-37 years after the exposure. Because of the strong time since exposure effect of the incidence of leukaemia after exposure in the first period after the latency period, the risk factor will be markedly higher.

Getting a better impression of the consequence of the cell killing effect we take a look at the dose response curve of the low LET radiation exclusively. In AML and CML the curves show a maximum in the range of three to four Gray, that of CML at a lower value than that of AML (cf. fig. 2, p. 8). We recognise, that in the range of high dose AML is the diagnosis with the most prominent ERR. Contrarily in the low dose range a higher ERR of CML than AML can be expected (cf. fig. 3, p. 8). In childhood ALL shows the greatest ERR (cf. fig. 4, p. 9).

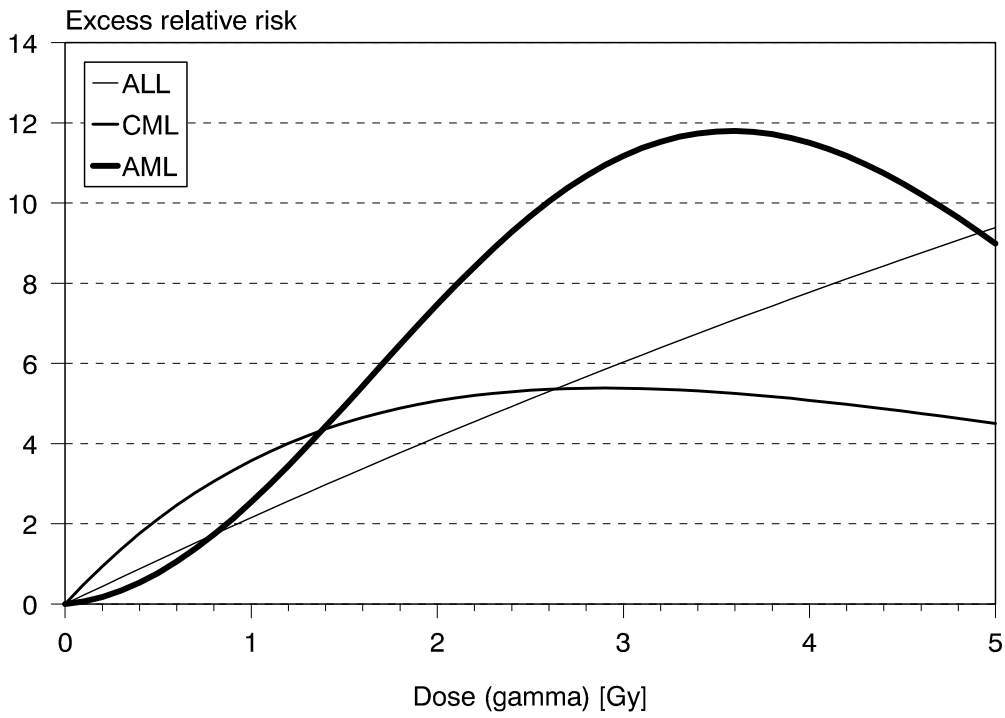


Fig. 2: Dose-response curve for atomic bomb gamma radiation, relative risk model, all ages.

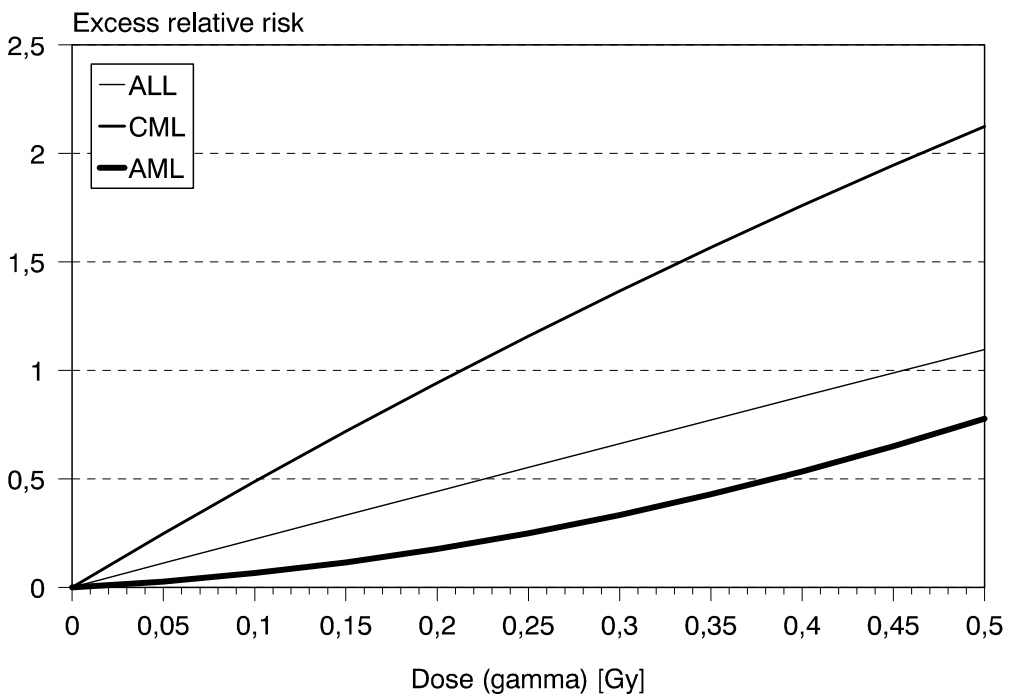


Fig. 3: Same as fig. 2, low dose region <100 mGy.



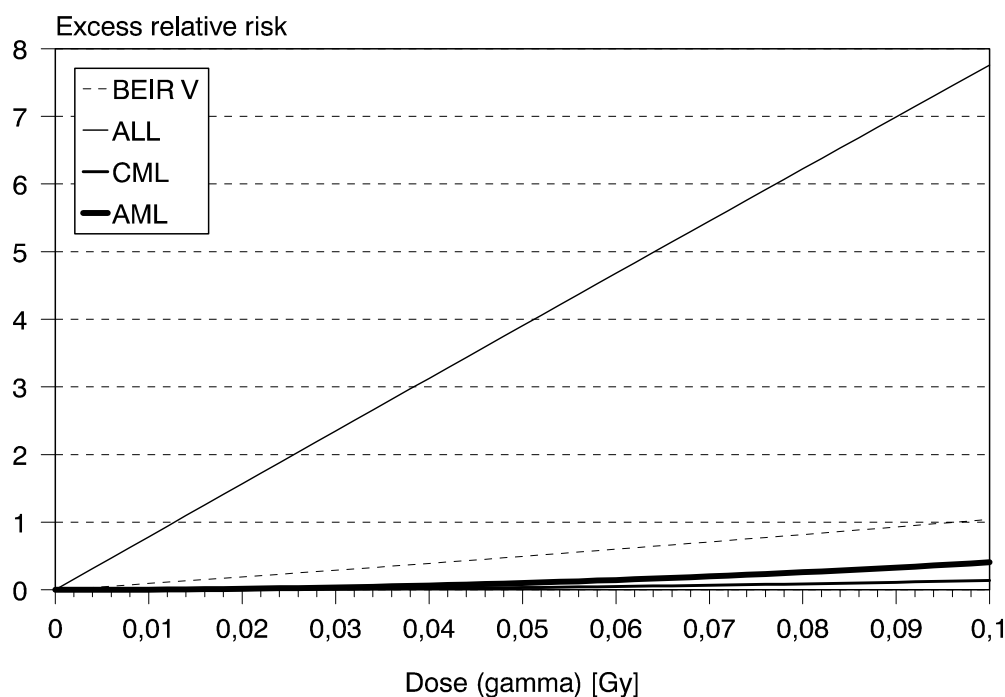


Fig. 4: Dose-response curve for atomic bomb gamma radiation, relative risk model, age <14 years.

This result is important concerning the controversy about the increased leukaemia incidence in the neighbourhood of the German atomic power plant Krümmel. The hypothesis of a radiogenic cause of the increased relative risk of childhood ALL and adult CML was rejected with the argument, the typical kind of radiation induced leukaemia should be AML [7]. A higher absolute number of excess cases of AML can be combined with a higher relative risk of CML.

The risk factors presented here are remarkable greater than that estimated by BEIR and ICRP. The calculation of these committees includes all diagnoses (ICD 204-207), also kinds of leukaemia like the ATL (adult T-cell Leukaemia) without any dependence from radiation exposure. The main cause of the difference will be the exclusion of cases with a dose of more than four Gray without allowance for a cell killing effect.

Proving the plausibility of a cell killing effect and the method of estimation the dose-response relationship, presented above, the prediction of a dose-response relationship to doses of radiation therapy shall be compared with the results of a case-control study of leukaemia mortality after radiation therapy for cervix cancer [5]. The analysis of the leukaemia incidence of the atomic bomb survivors was restricted to females older than 35 years (cf. Table 4, p. 10). For each dose class the distribution of doses in the compartments of bone marrow, used by Boice et al., was calculated. The excess relative risk in each compartment was weighted by the relative amount of bone marrow in this compartment.

Table 4: Parameters of dose-response relationships of ALL, AML and CML, females &gt;35y.

	ALL	AML	CML
background	0.0798	0.34	0.165
$\beta$	6.1	5.92	98
$\delta$	0.047	0.065	4.51
$\chi^2$	0.93	3.49	4.41

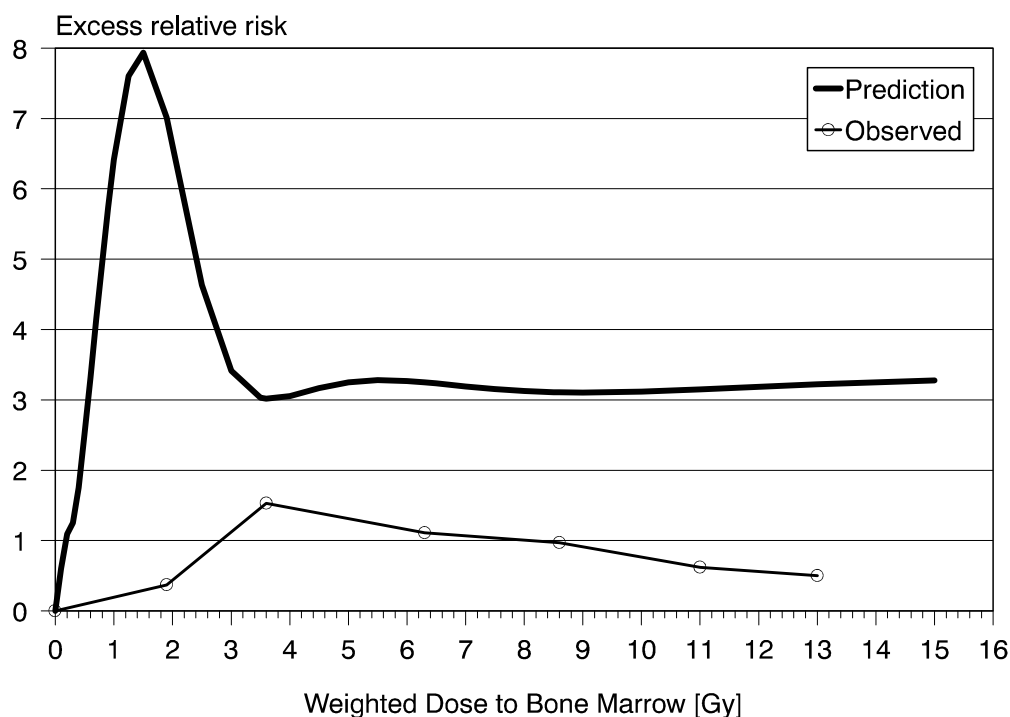


Fig. 5: Prediction of the dose response-curve for radiation therapy of cervix carcinoma (parameter cf. tab. 4, p. 10) and observations (data: Boice et al. [5] )

The shape of the observed dose-response curve is characteristic for the existence of a cell killing effect (cf. fig. 5, p. 10). But there is a difference of about a factor of three between the quantitative level of the observed and calculated curves. The absence of the peak calculated in the low dose region may be caused by the reason, that the minimal therapeutic dose was higher than the narrow region of the peak. The quantitative difference can be due to many causes, e.g. specific sensitivity of a collective special selected by medical reasons, differences in the follow up time and life expectancy. Above all, in mortality statistics many leukaemia are missed, which are dying with due to bleeding (thrombocytopenia), infectious complications (granulocytopenia), aplastic anaemia as symptoms of bone marrow insufficiency in the aleukaemic stage of an acute leukaemia or of a myelodysplastic syndrome (MDS) before transformation to an overt leukaemia. If these kinds of development of

leukaemia have specific dose-response curves, not only a cohort study, but also a case-control study may be influenced.

The possibility has to be discussed that target cells with a genom transformed for expressing a leukaemia have an increased sensibility for being killed by the next exposure during fractionation of radiation therapy.

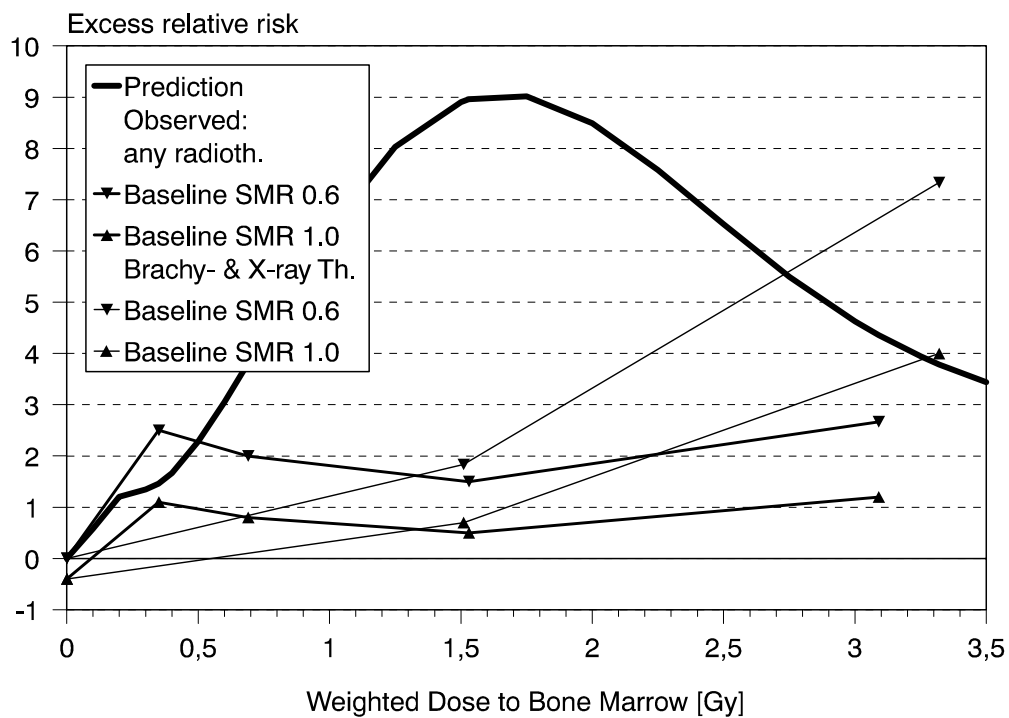


Fig. 6: Prediction of the dose response-curve for pelvic radiation therapy of benign diseases (parameter cf. tab. 4, p. 10) and observations (data: Inskip et al. [12]). For the group „brachytherapy and external-beam X-ray therapy“ combined (Brachy- & X-ray Th.) the dose distribution of the total group „any radiotherapy“ (Any radioth.) was used. The SMR of the group „No radiotherapy“ was corrected to 0.6 because of the one case of leukaemia found in this group by the revision of doses (Observed four instead of three cases, expected 6.30). The mean dose in the interval „201-1100 cGy“ of the group „Any radiotherapy“ was set as 309 cGy instead of the value of table VI (209 cGy) because of the value in Fig. 3 and the values of the means in this interval of the other groups.

The comparison with the results of a cohort study of women treated with ionizing radiation [12] for benign pelvic diseases gives a better agreement in the lowest and highest dose regions, but the calculated peak of incidence is missed again (cf. fig. 6, p. 11). The radiation doses in this modality of therapy were nearly one order of magnitude lower than in the study before. Most frequently brachytherapy was used with lower doses in the surrounding bone marrow avoiding cell killing effect. The cell killing effect becomes visible above a weighted dose of more than 0.5 Gy, which corresponds

to a bone marrow dose of the pelvis of 1.3 Gy. The gradient of the first part of the dose-response curve in the low dose region below 0.5 Gy is comparable with the predicted course, especially in the cases with radium therapy (cf. fig. 7, p. 12). This is an important finding because the dose rate was in the range of only some centigrays per hour, more than one order of magnitude lower comparing with radiation therapy by external beams of X- or gammarays. As in the survivors of the atomic bomb the mostly elevated relative risk was seen in CML. Additionally, the CML shows a marked time course with a very early and high peak after a time of three years since irradiation.

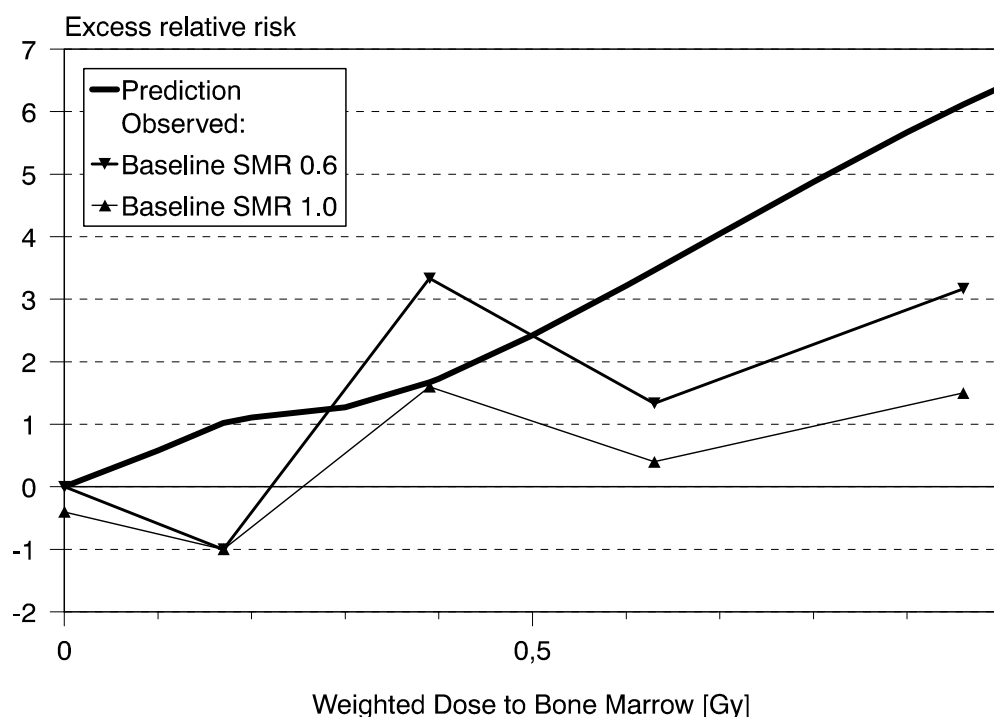


Fig. 7: Same comparison as Fig. 6 (p. 11), but for brachytherapy only.

As next example I compare the parameters derived by my method with the study on the leukaemia mortality after X-ray treatment for ankylosing spondylitis [28]. The analysis was restricted to the ages 20-60 years (cf. tab. 5, p. 13). For each dose class the distribution of doses in the compartments of bone marrow, used by Weiss et al., was calculated. The excess relative risk in each compartment was weighted by the relative amount of bone marrow in this compartment. A relation of male to female 83.5:16.5% was used. The excess relative risk was calculated against the baseline value of the zero dose group with a relative risk of 0.57 and of 1.00 in comparison to the national mortality register.

Table 5: Parameters of dose-response relationships of ALL, AML and CML, 20-60y <sup>5</sup>

	ALL		AML		CML	
	female	male	female	male	female	male
background	0.0479	0.116	0.283	0.765	0.1	0.281
$\beta$	6.75	4.62	6.79	2.06	142	8.21
$\delta$	0.037	0.167	0.146	0.055	4.61	0.147
$\chi^2$	1.64	2.07	6.50	4.95	4.84	6.38

The observed excess relative risk is in the same order of magnitude as expected (cf. fig. 8, p. 13). But, the shape of the dose response curve is less well fitted. The enormous fluctuation of the observed risk figures is warning against an overinterpretation. But the observed figures are well compatible with models respecting the cell killing effect, as stated by the authors, too.

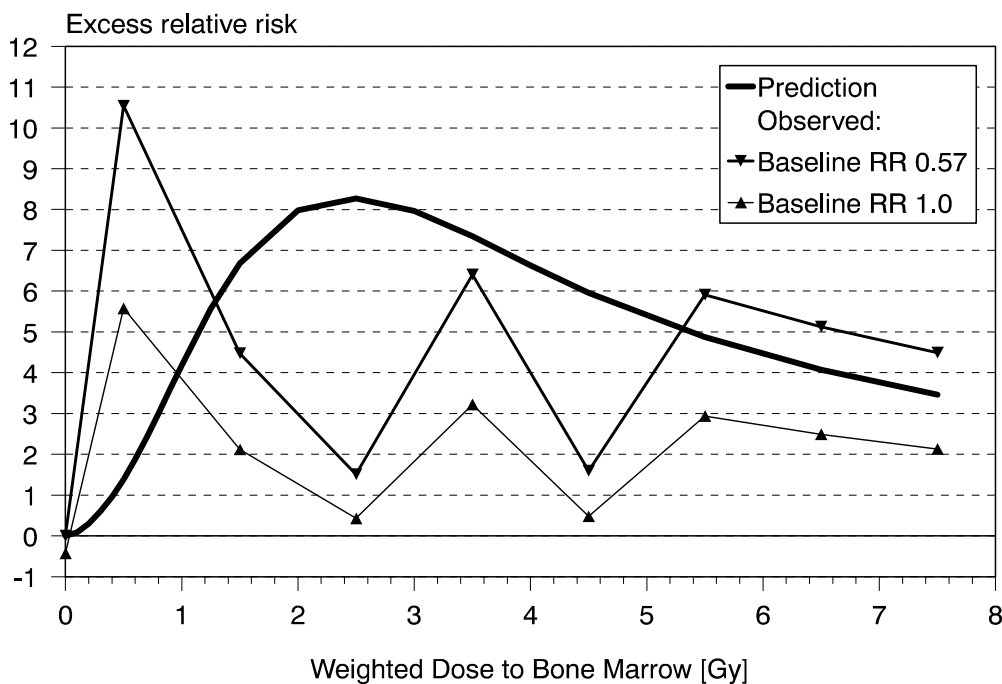


Fig. 8: Prediction of the dose response-curve for radiation therapy of ankylosing spondylitis (parameter cf. tab. 5, p. 13) and observations (data: Weiss et al. [28])

Before finishing this chapter a remark on the results of the fitting method used is necessary. The fitting of the data of CML of males was particularly difficult and ambiguous. This seems to be similarly in the

<sup>5</sup> in case of CML male better fitting with  $\chi^2 = 5.91$ :  $\alpha_n = 753$ ,  $\delta = 0.089$  ( $\alpha_\gamma, \beta, \gamma = 0!$ )

results of the calculations of Thompson et al. [25]. They presented significantly different background values of CML for Hiroshima and Nagasaki, a city effect without any apparent explanation. Therefore in the calculations presented above, a background value of both cities together was used. Not only the background incidence is different in both cities, the incidence of CML of males is very seldom in Nagasaki after the exposure to radiation, too. Therefore the fitting method used here isolates the neutron dose, which is the much important difference of the radiation field, as the most prominent cause of radiation induced CML. This and, perhaps in part or totally, the very high RBE-values may be an artefact due to other causes of the city effect.

Remarkably is the very different expression of the parameters depending from the age at the time of the bombings. Only fitting the younger ages below 20 years or the inclusion of this age group gives an  $\alpha$ -parameter for a linear dose-response function. The older age groups show a  $\beta$ -parameter for a quadratic function exclusively. This observation induces the speculative question, if targets, which lead to induction of leukaemia by one single hit, are such sensible, that the natural radiation dose acquired in the first two decades of life was sufficient to change all of them to leukaemic cells.

## High LET Radiation

Not only after radiation therapy, but also after exposure to high LET radiation the appearance of leukaemia in some studies was seen seldom, e.g. in the radium cases an increased mortality on leukaemia was missed. Mole has interpreted this fact as false negative finding [16]. He supposed early death of the radium victims by infections during MDS (Myelodysplastic Syndrome) or aleukaemic or early phases of overt leukaemia before diagnosis.

However, the mortality statistics of the Thorotrast cases exhibit elevated risk figures of leukaemia [1, 17, 27]. Although, the risk figures are lower by about one order of magnitude calculating the doses as equivalent dose using the quality factor of twenty for alpha particles and much more if we use the risk parameters derived for neutrons in the calculation above and if the dose calculations, very difficult for alpha particles indeed, are true. In the Danish patients a highly significant relationship between the estimated mean bone marrow dose and the standardised incident rate of leukaemia compared with the figures of the cancer register was observed [1]. However, within the group of Thorotrast patients in all studies no significant influence of injected volume of Thorotrast has been seen. In a multivariate analysis a nonsignificant parameter of 0.276 times cumulative dose was estimated [1]. The incidence rate was strongly related to the natural incidence, rising sharply with increasing age, but also to the combined effect of dose rate and the exposure time.

The Thorotrast victims exhibit some special features. MDS is very frequently seen. The relation to all myeloid leukaemia is 4:6, whereas in the atomic bomb survivors the relation is only 1:10. [6]

A very seldom kind of AML is the erythroleukaemia, classified by FAB as subgroup  $M_6$  with a spontaneous occurrence of two per cent of AML. In the atomic bomb victims, where all  $M_6$  were counted in the low dose group, the frequency was elevated about three times to 6.6 per cent. The Thorotrast patients show a sevenfold increased proportion of 14 per cent.

The observation of a low biological effectiveness of alpha particles for induction of leukaemia stands in a strong contrast to the hypothesis of Honcho and co-workers assuming a relative biological effectiveness comparing to the atomic bomb radiation in the range of 20-180. [8]

This discrepancy can be the result of many causes:

According to the hypothesis of Schmitz-Feuerhake a chronic exposure to a high dose rate will be increasingly ineffective because of the limitation by growing again of mutations in the genom causing enhanced radiation sensitivity [20].

A cell killing effect cannot be excluded but more important seems to be the special microscopic geometry between source cells and specific target cell e.g. for initiation of MDS or  $M_6$ -AML.

Therefore I assume that it is impossible to extrapolate from the very high dose rate in the order of 100 mGy per year as in the Thorotrast cases to the very low dose rate in the range of 10  $\mu$ Gy per year, to conclude from one kind of alpha-emitter to the other and in no way to compare with photon radiation. Good bye, equivalent dose principle.

Some other epidemiological observations support a high risk of leukaemia after exposure to low dose alpha radiation. Lyman et al. report an association of leukaemia with radium groundwater contamination [15]. A cluster of childhood leukaemia in the neighbourhood of a uranium processing plant could be attributed to contamination of the drinking water with radium [10, 11].

Finally, the correlation found by Henshaw and co-workers may be in part a pseudocorrelation in that sense that the doses of other kinds of radiation are correlated indirectly to the mean radon concentration, too. For example, the radon concentration exhibits a strong dependence from the geographic latitude as it is true for the neutron dose rate of cosmic radiation, at sea level also [26]. The impression of a very little contribution of neutrons to the natural radiation field is faked by the mistake of identifying the weighting factors of radiation recommended in radiation protection with real RBE. But, the weighting factor for neutrons is not corrected for the difference of biological effectiveness between X-rays, the reference radiation of RBE, and the high energy atomic bomb gammaradiation and does not take into account the inverse dose and dose rate effect of neutrons.

Therefore, ending my presentation, I come back to the relative biological effectiveness of neutrons. I compare the life time dose of flying personal necessary to explain the significant elevated incidence of

leukaemia by the risk figures of the BEIR committee and the equivalent dose calculated with the radiation weighting factors recommended by ICRP 60.

Band et al. have observed in a cohort of 2,740 Air Canada Pilots nine incident cases of leukaemia (5.47 cases expected, SIR = 1.65) [2]. The SIR of myeloid leukaemia (O/E 7/2.39, SIR = 2.93) and of AML (O/E 6/1.27, SIR = 4.72) were significantly elevated ( $p = 0.01$  resp. 0.002). The mean dose rate of occupational radiation exposure was estimated with 6 mSv per year respecting the elevated geomagnetic latitude. With a mean working time of 20,8 years an occupational life time dose of 124.8 mSv results. The authors had evaluated the ERR for all leukaemia without CLL respecting the age distribution of the cohort and using the risk coefficients of BEIR V with a result 0.04 for the dose rate of 6 mSv/y, this means a  $ERR_{1\text{Sv}}$  of 32. The SIR of 1.88 for these diseases corresponds to a biological equivalent occupational life time dose of 2,777 mSv. The discrepancy between the life time doses amounts to a factor of 22. This underlines my suggestion to revise the weighting factors of neutrons [14].

## Acknowledgement

This report makes use of data obtained from the Radiation Effects Research Foundation (RERF) in Hiroshima, Japan. RERF is a private foundation funded equally by the Japanese Ministry of Health and Welfare and the U.S. Department of Energy through the U.S. National Academy of Sciences. The conclusions in this report are those of the authors and do not necessarily reflect the scientific judgement of RERF or its funding agencies.

## References

1. **Andersson, M., Carstensen, B., Visfeldt, J.:** Leukemia and Other Related Hematological Disorders among Danish Patients Exposed to Thorotrast, *Radiat. Res.* 134 (1993), 224-233
2. **Band, P.R., Le, N.D., Fang, R., Deschamps, M., Coldman, A.J., Gallagher, R.P., Moody, J.:** Cohort Study of Air Canada Pilots: Mortality, Cancer Incidence, and Leukemia Risk, *Am. J. Epidemiol.* 143 (1996), 137-143
3. BEIR V, Committee on the **B**iological **E**ffects of **I**onizing **R**adiations: Health Effects of Exposure to Low Levels of Ionizing Radiation, National Academy Press, Washington DC, 1990
4. **Boice, Jr., J.D.:** Risk Estimates for Radiation Exposures, In: Hendee, W.R., Edwards, F.M. (Eds.): *Health Effects of Exposure to Low-Level Ionizing Radiation*, Institute of Physics Publishing, Bristol and Philadelphia, 1996, pp. 237-268



5. **Boice Jr., J.D., Blettner, M., Kleinerman, R.A., Stovall, M., Moloney, W.C., Engholm, G., Austin, D.F., Bosch, A., Cookfair, D.L., Kremenz, E.T., Latourette, H.B., Peters, L.J., Schulz, M.D., Lundell, M., Petterson, F., Storm, H.H., Bel, C.M.J., Coleman, M.P., Fraser, P., Palmer, M., Prior, P., Choi, N.W., Hislop, T.G., Koch, M., Robb, D., Robson, D., Spengler, R.F., von Fournier, D., Frischkorn, R., Lochmüller, H., Pompe-Kirn, V., Rimpela, A., Kjoerstad, K., Pejovic, M.H., Sigurdsson, K., Pisani, P., Kucera, H., Hutchison, G.B.:** Radiation Dose and Leukemia Risk in Patients Treated for Cancer of the Cervix, *J. Natl. Cancer Inst.* 79 (1987), 1295-1311
6. **Carter, R.L., Bennett, J.M., Pisciotta, A.V., Finch, S.C.:** Differential Effects of Atomic Bomb Irradiation in Inducing Major Leukemia Types: Analyses of Open-city Cases Including the Life Span Study Cohort Based upon Updated Diagnostic Systems and the Dosimetry System 1986 (DS86), Radiation Effects Research Foundation, Hiroshima, Technical Report Series, RERF TR 9-91, 1991
7. **Gaßmann, W.:** Personal Communication, 1995
8. **Henshaw, D.L., Eatough, J.P., Richardson, R.B.:** Radon as a Causative Factor in the Induction of Myeloid Leukaemia and Childhood Cancer, *Lancet* i (1990), 1008-1012
9. **Henshaw, P.S., Hawkins, J.W.:** Incidence of Leukaemia in Physicians. *J. Natl. Cancer Inst.* 4 (1944), 339-346 (cited after Mossman]
10. **Hoffmann, W.:** Inzidenz Maligner Erkrankungen bei Kindern und Jugendlichen in der Region Ellweiler, Rheinland-Pfalz, Anwendung der Biologischen Dosimetrie zur Ermittlung möglicher Belastungspfade, Inauguraldissertation Marburg, 1993
11. **Hoffmann, W., Kuni, H., Artmann, S., Bahr, A., Götz, A., Herrwerth, C., Schmitz-Feuerhake, I., Schubert, F.:** Leukämiefälle in Birkenfeld und Umgebung: Eine erste Bestandsaufnahme, In: Köhnlein, W., Kuni, H., Schmitz-Feuerhake, I. (Hrsg: Niedrigdosisstrahlung und Gesundheit, Medizinische, rechtliche und technische Aspekte mit dem Schwerpunkt Radon, Springer Verlag, Berlin, Heidelberg, New York, London, Paris, Tokyo, Hongkong, Barcelona, 1990, S. 175-181
12. **Inskip, P.D., Kleinerman, R.A., Stovall, M., Cookfair, D.L., Hadjimichael, O., Moloney, W.C., Monson, R.R., Thompson, W.D., Wactawski-Wende, J., Wagoner, J.K., Boice, Jr., J.D.:** Leukemia, Lymphoma, and Multiple Myeloma after Pelvic Radiotherapy for Benign Disease, *Radiat. Res.* 135 (1993), 108-125
13. **Jacobi, W., Chmelevsky, D.:** Possible Age-specific Leukaemia Rate from Natural Radiation, In: Michaelis, J. (Ed.): *Epidemiology of Childhood Leukaemia*, Medizinische 6, Akademie der Wissenschaften und Literatur, Mainz, G. Fischer Verlag, Stuttgart, Jena, New York, 1993, pp. 81-95
14. **Kuni, H.:** Die Bewertung von Alpha- und Neutronenstrahlen bei der Berechnung der Äquivalentdosis, In: Lengfelder, E., Wendhausen, H. (Hrsg.): *Neue Bewertung des Strahlenrisikos, Niedrigdosis-Strahlung und Gesundheit*, MMV Medizin Verlag, München, 1993, S. 19-27
15. **Lyman, G.H., Lyman, C.G., Johnson, W.:** Association of Leukemia with Radium Groundwater Contamination, *JAMA* 254 (1985), 621-626
16. **Mole, R.H.:** Alpha-particle Irradiation and Human Leukaemia, In: Taylor, D.M., Mays, C.W., Gerber, G.B., Thomas, R.G (Eds.): *Risks from Radium and Thorotrast*, BIR Report 21, British Institute of Radiology, London, 1989, pp. 153-158

17. **Mori, T., Kato, Y., Aoki, N., Hatakeyama, S.:** Statistical Analysis of Japanese Thorotrast-Administered Autopsy Cases-1980, *Health Phys.* 44 (1983), Suppl. 1, 281-292
18. **Mossman, K.L.:** A Brief History of Radiation Bioeffects, In: Hendee, W.R., Edwards, F.M. (Eds.): *Health Effects of Exposure to Low-Level Ionizing Radiation*, Institute of Physics Publishing, Bristol and Philadelphia, 1996, pp. 1-26
19. **Preston, D.L., Kusumi, S., Tomonaga, M., Izumi, S., Ron, E., Kuramoto, A., Kamada, N., Dohy, H., Matsui, T., Nonaka, H., Thompson D.E., Soda, M., Mabuchi, K.:** Cancer Incidence in Atomic Bomb Survivors, Part III: Leukemia, Lymphoma and Multiple Myeloma, 1950-1987, *Radiat. Res.* 137 (1994), S68-S97
20. **Schmitz-Feuerhake, I.:** Der Wandel im Erkenntnisstand über stochastische Strahlenwirkungen im Niedrigdosisbereich, In: Otto Hug Strahleninstitut (Hrsg.): *Strahlenexposition und -risiko sowie Sicherheit bei der sog. 'schadlosen Verwertung' von bestrahlten Brennelementen im Ausland*, Gutachten erstellt im Auftrag der Freien und Hansestadt Hamburg, Bonn, 1990, S. VIII-1-VIII-29
21. **Shimizu, Y., Kato, H., Schull, W.J.:** Life Span Study Report 11, Part 2. Cancer Mortality in the Years 1950-85 Based on the Recently Revised Doses (DS86), Technical Report, Hiroshima, RERF TR 5-88, 1988
22. **Stewart, A., Kneale, G.W.:** Radiation Dose Effects in Relation to Obstetric X-rays and Childhood Cancers, *Lancet* i (1970) 1185-1188
23. **Stewart, A., Webb, J., Hewitt, D.:** A Survey of Childhood Malignancies, *BMJ* i (1958), 1495-1508
24. **Straume, T.:** High-Energy Gamma Rays in Hiroshima and Nagasaki: Implications for Risk and  $w_R$ , *Health Phys.* 69 (1995), 954-956
25. **Thompson, D.E., Mabuchi, K., Ron, E., Soda, M., Tokunaga, M., Ochikubo, S., Sugimoto, S., Ikeda, T., Terasaki, M., Izumi, S., Preston, D.L.:** Cancer Incidence in Atomic Bomb Survivors. Part II: Solid Tumors, 1958-1987, Technical Report, Hiroshima, 1992, RERF TR 5-92, *Radiat. Res.* 137 (1994), S17-S67
26. **UNSCEAR: United Nations Scientific Committee on the Effects of Atomic Radiation, Sources, Effects and Risks of Ionizing Radiation, UNSCEAR 1993 Report to the General Assembly, with Scientific Annexes, United Nations, New York, 1993**
27. **van Kaick, G., Muth, H., Kaul, A., Immich, H., Lieberman, D., Lorenz, D., Lorenz, W., Lührs, H., Scheer, K.E., Wagner, G., Wegener, K., Wesch, H.:** Recent Results of the German Thorotrast Study - Epidemiological Results and Dose Effect Relationships in Thorotrast Patients, *Health Phys.* 44 (1983), Suppl. 1, 299-306
28. **Weiss, H.A., Darby, S.C., Fearn, T., Doll, R.:** Leukemia Mortality after X-Ray Treatment for Ankylosing Spondylitis, *Radiat. Res.* 142 (1995) 1-11
29. **Zaider, M.:** Evidence of a Neutron RBE of 70 ( $\pm 50$ ) for Solid-Tumor Induction at Hiroshima and Nagasaki and its Implications for Assessing the Effective Neutron Quality Factor, *Health Physics* 61 (1991), 631-636