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ORIGINAL PAPER

**Albrecht M. Kellerer · Linda Walsh · Elke A. Nekolla**

# Risk coefficient for γ-rays with regard to solid cancer

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**Abstract** A previous investigation has uncoupled the solid cancer risk coefficient for neutrons from the low dose estimates of the relative biological effectiveness (RBE) of neutrons and the photon risk coefficient, and has related it to two more tangible quantities, the excess relative risk ($ERR_1$) due to an intermediate reference dose $D_1$=1 Gy of γ-rays and the RBE of neutrons, $R_1$, against this reference dose. With tentatively assumed RBE values between 20 and 50 and in terms of organ-averaged doses – rather than the usually invoked colon doses – the neutron risk factor was seen to be in general agreement with the current risk estimate of the International Commission on Radiation Protection (ICRP). The present assessment of the risk coefficient for γ-rays incorporates – in terms of the unchanged A-bomb dosimetry system, DS86 – this treatment of the neutrons, but is otherwise largely analogous to the evaluation of the A-bomb data for the ICRP report and for the recent report of the United Nations Scientific Committee on the effects of ionizing radiation, UNSCEAR. The resulting central estimate of the lifetime attributable risk (*LAR*) for solid cancer mortality is 0.043/Gy for a working population (ages 25–65),and is nearly the same whether the age at exposure or the attained age model is used for risk projection. For a population of all ages 0.042/Gy is obtained with the attained age model and 0.068/Gy with the age at exposure model. The values do not include a *dose and dose rate effectiveness factor* (*DDREF*), and they are only half as large as the new UNSCEAR estimates of 0.082/Gy (attained age model and all ages) and 0.13/Gy (age at exposure model and all ages). The difference is only partly due to the more explicit treatment of the neutrons. It reflects also the fact that UNSCEAR has converted *ERR* into *LAR* in a way that differs from the ICRP procedure, and that it has summed the overall risk coefficient for solid tumor mortality and incidence from separate estimates for eight solid tumor categories, whereas the present study employs a combined computation for all solid tumors and uses the ICRP procedure for the conversion of *ERR* into *LAR*. The appendix gives results for the solid cancer incidence data.

A.M. Kellerer (✉)
Radiobiological Institute, University of Munich,
Schillerstrasse 42, 80336 Munich, Germany
e-mail: AMK.SBI@LRZ.Uni-Muenchen.de
Tel.: +49-89-5996818, Fax: +49-89-5996840

Institute of Radiobiology
GSF – National Research Center for Environment and Health,
Neuherberg, Germany

L. Walsh · E.A. Nekolla
Radiobiological Institute, University of Munich, Germany

## Introduction

The most recent report [1] of the United Nations Scientific Committee on the effects of ionizing radiation (UNSCEAR) contains, in Annex I, an informative and complete reanalysis of the cancer mortality and incidence data of the A-bomb survivors. Its updated set of risk estimates for sparsely ionizing radiation is going to be widely used in considerations of radiation protection regulations. The present paper deals with a number of aspects that need not change the basic conclusions or alter the risk estimates greatly, but might nevertheless be part of a continued discussion toward their further improvement.

A still unresolved issue is the proper accounting for neutrons in the analysis of the A-bomb data. On the basis of the earlier dosimetry system, *TD65*, for the A-bomb survivors [2] it had been surmised [3, 4] that neutrons were responsible for a substantial fraction of the late health effects observed at Hiroshima. This assumption was abandoned when the current dosimetry system, *DS86*, specified considerably lower neutron doses in Hiroshima [5]. It was then concluded – against some dissenting arguments [6] – that the neutrons are, even in Hiroshima a minor potential contributor to the observed health effects, and that their role, although uncertain, is not critical to risk estimation. In subsequent analyses the neutrons were, therefore, accounted for crudely by a weighting factor 10 applied to their absorbed dose con-

tribution [7, 8]. The sum of the γ-ray absorbed dose and the weighted neutron dose was termed *weighted dose* and was expressed in terms of Sv. This approach was used in the computations that provided the current nominal risk coefficient for photon radiation [9, 10] and it has been equally employed for the new evaluation by UNSCEAR [1].

In contrast to the prevailing assumption, there is evidence that even under the current dosimetry system, DS86, the neutrons have contributed a substantial fraction of the late health effects among the A-bomb survivors [11, 12, 13]. An explicit accounting for the neutrons is thus required in the assessment of the γ-ray risk coefficient, and it will be based here on the unchanged dosimetry system DS86. Various conclusions in a previous article [12] can be referred to without being repeated in detail. These include the considerations on neutron RBE from experimental studies [14, 15, 16, 17] and the relevant dosimetric aspects.

A critical point with major impact on the present computations is the specification of the organ dose that is used in the analysis of the combined data for all solid cancers. In previous studies of the mortality or incidence of all solid cancers combined, reference has been made to the colon dose, i.e. the dose to the deepest lying, most highly shielded organ. This is, of course, an underestimation of the average dose to all relevant organs. For the γ-rays the underestimation is not very critical, because the suitably weighted average organ dose is only somewhat less than 10% larger than the colon dose. However, for neutrons the reference to the colon is unsatisfactory. The averaging – with weighting factors proportional to the risk contribution of individual tumor sites (see [12]) – results in a neutron absorbed dose that is twice as large as the neutron absorbed dose to the colon. As has been done in the preceding article [12], the subsequent considerations will accordingly employ the *organ-averaged dose* that exceeds the colon doses by the factors 1.1 for γ-rays and 2.1 for neutrons.

The present analysis makes use of the same data as UNSCEAR [1], the solid cancer mortality (1950–1990) and incidence data (1958–1987) published by the Radiation Research Effects Foundation (RERF). It is not primarily aimed at the derivation of somewhat modified risk coefficients, but focuses instead on the exploration of certain changes in the modeling calculations that can be employed in future analyses of data from the continued follow-up and results from the current dosimetry revision.

Pierce and Preston [18] have published a first evaluation in terms of extended incidence data (1958–1994) and also in terms of more narrow dose categories. Their work includes a realistic treatment of the neutron RBE in an approach that is employed in the present paper with some modifications. To facilitate the comparison, a notation is used here that parallels largely the notation adopted by Pierce and Preston.

Pierce and Preston also addressed the current reassessment of the dosimetry system, DS86. While DS86 appears to be well supported at intermediate doses of 1 Gy–2 Gy, it is still possible that – apart from a moderate revision of the γ-ray doses – the neutron doses will need to be somewhat increased for Hiroshima at lower total doses [13]. The subsequent analysis utilizes the unchanged DS86.

## The conventional treatment

Realistic modeling of the dose-effect dependence for a mixed field of γ-rays and neutrons must account for the fact that the RBE of neutrons tends to increase with decreasing dose. As long as it was presumed that neutrons contributed little to the excess cancer rates among the A-bomb survivors, it seemed acceptable to disregard this dependence and to account for the neutrons roughly in terms of a constant weight factor, $w$=10, applied to their absorbed dose contribution in the colon. This approach postulates *a priori* a linear dose dependence both for γ-rays and neutrons, an assumption that is at variance with a wide range of radiobiological observations. While the subsequent modeling will utilize a more explicit treatment, computations according to the conventional treatment will be included to facilitate the comparison to previous risk calculations and, especially, the most recent UNSCEAR results.

The excess relative risk is factorized into a dependence on dose, $d$, and a modifying function, μ, that depends on the variables gender, $s$, age at exposure, $e$, or age attained, $a$:

$$ERR(d,s,e,a) = \mu(s,e,a) \cdot \rho(d) \qquad (1)$$

where $d$ is the "weighted dose" defined in terms of the γ-ray absorbed dose, $D_\gamma$, and the neutron absorbed dose, $D_n$:

$$d = D_\gamma + w \cdot D_n$$

The dose dependence $\rho(d)$ has usually been taken to be linear for solid cancers combined, and linear-quadratic for leukemias. The present computations employ the more general linear-quadratic fit in terms of weighted dose:

$$\rho(d) = \alpha \cdot \left(d + \theta \cdot d^2\right) \qquad (2)$$

This is irrelevant for the maximum likelihood results, because they happen to be close to linear dose dependencies, but it is essential because it permits the derivation of the lowest initial slope, i.e. the minimum risk estimate that is compatible with the data in terms of a linear-quadratic dose dependence. Knowledge of this minimum value is necessary for an assessment of the *dose and dose rate effectiveness factor* (*DDREF*) that has been postulated by ICRP [9].

If the fitted data extend to large doses (say >2 Gy), it is common to include an added negative exponential term that accounts for the "bending over", i.e. the re-

duced slope of the dose dependence at higher doses. In the subsequent modeling a low dose cut-off of 2 Gy total absorbed dose will be chosen, and there will, accordingly be no need to include the negative exponential term, nor will there be a need to apply the corrections for random errors in dosimetry [19, 20].

## A modified approach

The linear, linear-quadratic dose dependence

The explicit treatment employs, as has been done before [11, 18], a linear-quadratic dose dependence for the γ-ray dose, $D_\gamma$, and a linear relation for the neutron dose, $D_n$:

$$ERR\left(D_\gamma, D_n, s, e, a\right) = \mu(s, e, a) \cdot \rho\left(D_\gamma, D_n\right) \quad (3)$$

with the dose dependent term:

$$\rho\left(D_\gamma, D_n\right) = \alpha \cdot \left(D_\gamma + \lambda \cdot D_n + \theta \cdot D_\gamma^2\right) \quad (4)$$

As pointed out in previous analyses [7, 8, 11, 18], it is impossible to infer from a fit to the solid cancer or the leukemia data both parameters, α, the linear dose coefficient for γ-rays, and λ, the low dose limit of the neutron RBE. A wide range of values of the limiting RBE of neutrons at low doses, $\lambda = RBE_{max}$, fits the data equally well.

Extraneous information is therefore required, and to this purpose reference has usually been made to the maximum RBE of neutrons. This value, $\lambda = RBE_{max}$, is inferred by extrapolating RBE values from cell or animal studies to *low doses*. To avoid the uncertainty inherent in extrapolating to a limit at low doses, the previous article [12] invoked the neutron RBE, $R_1$, against an intermediate *reference γ-ray dose*, $D_1$=1 Gy, rather than the less tangible $RBE_{max}$.

The risk coefficient, $\alpha \cdot \lambda$, for neutrons that has been deduced in this way [12] could, in principle, be inserted into Eq.(4) to eliminate λ. However, the treatment is more coherent and transparent, if the tentatively assumed value $R_1$ of the neutron RBE against the γ-ray dose $D_1$ is introduced directly into Eq.(4). For this purpose $R_1$ needs to be expressed in terms of the parameters of Eq.(4).

Equation (4) determines the relationship between the neutron and γ-doses that have equal effect:

$$\lambda \cdot D_n = D_\gamma + \theta \cdot D_\gamma^2 \quad (5)$$

which provides the neutron *RBE* as a function of the γ-ray dose:

$$RBE = D_\gamma / D_n = \lambda / \left(1 + \theta \cdot D_\gamma\right)$$

and :

$$\lambda = R_1 \cdot (1 + \theta \cdot D_1) \quad (6)$$

Therefore, Eq.(4) takes the form:

$$\rho\left(D_\gamma, D_n\right) = \alpha \cdot \left(D_\gamma + R_1 \cdot (1 + \theta \cdot D_1) \cdot D_n + \theta \cdot D_\gamma^2\right) \quad (7)$$

The choice of $R_1$

As pointed out, the linear-quadratic dose dependence for γ-rays needs to be considered in order to gain information on the maximum curvature in the dose dependence that is still compatible with the data. However, the RERF solid cancer data exhibit – in contrast to the leukemia data – a seemingly linear dependence on dose, and this makes it difficult to appreciate the difference between using $RBE_{max}$ or $R_1$. If linearity is accepted both for neutrons and γ-rays, $RBE_{max}$ and $R_1$ are indeed equal. But it is evident that the case for or against linearity must not be made in terms of a treatment that postulates *a priori* that the γ-ray dose dependence is linear. The two parameters $RBE_{max}$ and $R_1$ must, therefore, be distinguished even if the ultimate result suggests that their values do not differ appreciably.

Reference to $R_1$, i.e. the neutron RBE at intermediate doses – instead of the more elusive limit value $RBE_{max}$ – reduces the systematic uncertainty that is inherent in the choice of a parameter to represent the relative effectiveness of neutrons in causing late effects in man. But uncertainty remains, because animal data on rodents vary considerably and need not be representative for man. A large series of experiments on male Sprague-Dawley rats with fission neutrons provides, both for non-lethal and for lethal tumors, values of $R_1$ close to 50 [14, 15]. Extensive experiments on mice where life shortening was used as a proxy for tumor induction [16, 17] have suggested lower values, but rather complex dependencies on γ-ray dose-rates. In view of the wide range of experimental results [21, 22], any assumption of a plausible range of values remains judgmental. Roughly in line with the recommendation of a joint task group of ICRP and ICRU [23] and as in the previous article on neutron risks [12], the high and low values 50 and 20 are considered for $R_1$, and $R_1$=35 is taken as a central reference value. The values $R_1$ that are assumed here may appear to be large in comparison to the ICRP radiation weighting factor $w_R$ of about 20 for fission neutrons. However, it must be noted that $w_R$ does not stand for the RBE of a pure neutron dose, but for the substantially lower RBE of the mixed neutron and γ-ray dose that is caused by an external neutron field in the human body [24]. In contrast, $R_1$ is the weighting factor that relates to the true neutron component of the dose. All resulting risk coefficients are reported for the different values of $R_1$. This permits an approximate judgment, even if values of $R_1$ outside the range 20–50 are considered.

Choosing two nearly orthogonal parameters

Both parameters α and θ in Eq.(7) are subject to considerable statistical error. The uncertainty in the initial slope of the dose relation, i.e. the error of α, is of particular interest. However, the second parameter, θ, is strongly (negatively) correlated with α. Its error specifies, therefore, essentially the same uncertainty and thus

provides no additional information. Rescaling θ to a parameter that is roughly "orthogonal" to α is, therefore, more informative. A suitable parameter[1], subject to considerably smaller error than either α or θ, is the effect level at an intermediate acute γ-ray dose, $D_1$, divided by this dose:

$$c = \rho(D_1, 0) = \alpha \cdot (1 + \theta \cdot D_1) \tag{8}$$

where $c$ is the slope through the point $D_1$ on the dose relation for γ-rays; it will here be called the *reference* (γ-*ray*) *slope*. The effect at the intermediate γ-ray dose $D_1$ is reliably determined by the epidemiological observations. The reference slope $c$ is, accordingly, a meaningful parameter; in fact, it is essentially equal to the slope of the dose dependence in a linear model.

With:

$$\theta = \frac{c/\alpha - 1}{D_1} \tag{9}$$

Equation (7) takes the form:

$$\rho\left(D_\gamma, D_n\right) = \alpha \cdot \left(D_\gamma - D_\gamma^2/D_1\right) + c \cdot \left(R_1 \cdot D_n + D_\gamma^2/D_1\right) \tag{10}$$

As explained in the preceding article, $D_1$=1 Gy is – in computations with the solid cancer data – a suitable choice for the intermediate γ-ray dose. Equation (10) reduces then (written as a value equation with unit Gy) to the form that is actually used in the computations:

$$\rho\left(D_\gamma, D_n\right) = \alpha \cdot \left(D_\gamma - D_\gamma^2\right) + c \cdot \left(R_1 \cdot D_n + D_\gamma^2\right) \tag{11}$$

## Specifics of the modeling computations

Numerical values of the maximum likelihood fit parameters for the *ERR* models were obtained using the AMFIT routine in the EPICURE software [25]. In line with the approach for the RERF solid cancer mortality report [7] and the computations for UNSCEAR [1], the background rates were not modeled in parametric form, but were stratified by gender and by 5-year intervals of both attained age and age at exposure.

The modifying factor [see Eq.(1)] has been modeled either in terms of the *attained age model* [26, 27] or in terms of the traditionally applied *age at exposure model* which postulates an *ERR* that does not decrease in time after exposure. The use of these two comparatively simple models parallels the approach in the UNSCEAR report [1] and makes it unnecessary to invoke more complicated intermediate models. The results conveniently bracket the likely true values.

The modifying functions for the two models are:

$$\mu(s, a) = \exp(-g \cdot (a - 60)) \cdot (1 \pm s) \ (+ \text{ for females}, - \text{ for males}) \tag{12}$$

$$\mu(s, e) = \exp(-g \cdot (e - 30)) \cdot (1 \pm s) \ (+ \text{ for females}, - \text{ for males}) \tag{13}$$

UNSCEAR [1] uses a power function for the attained age model instead of the exponential dependence:

$$\mu(s, a) = \left(a/60\right)^{-1.5} \cdot (1 \pm s) \tag{14}$$

The power function leads to very high *ERR* values at young ages and makes the computations rather dependent on the assumed latent period. In the absence of epidemiological evidence that favors Eq.(14) over Eq.(12), the somewhat more moderate exponential attained age modifier that has been used originally with the attained age model [26], is retained here.

The dose dependent term, $\rho(D_\gamma, D_n)$, in Eq.(4) equals the excess relative risk scaled to the reference attained age 60 in the attained age model [Eqs.(12) and (14)] or scaled to the reference age at exposure 30 in the age at exposure model [Eq.(13)]. It is also scaled to the average of the genders. The gender averaged relative risks, $\rho(D_\gamma, D_n)$, are – in agreement with the familiar notation [7, 8] – denoted by $ERR_{60}$ and $ERR_{30}$. Other reference ages have actually been employed by RERF and by UNSCEAR, but here all results are rescaled to $a$=60 and $e$=30.

## Numerical results in terms of *ERR*

### Comparison to earlier linear estimates

To verify that the present computations are – apart from the more explicit treatment of the neutrons – in line with the earlier assessments, the results from RERF [7, 8] and UNSCEAR [1] are first compared in Table 1 with the coefficients that are obtained in the present analysis through the conventional approach, i.e. with a simple linear fit in weighted colon dose ($w$=10). The terms $ERR_{60}$/Gy and $ERR_{30}$/Gy stand for the dose coefficient (parameter α in the subsequent Table 2), and refer to the attained age and age at exposure model, respectively. All values in the table are derived from the same data sets, the RERF solid cancer mortality (1950–1990) and incidence data (1958–1987) and, being derived by the same computational procedure, they are very nearly equal. The slight differences reflect the choice of a relatively low dose cut-off (2 Gy) in the present computations. A further particularity is that parametric modeling of the background rates has been used by RERF in the computation of the $ERR_{30}$ for the incidence data [8].

### Results of the explicit treatment

The results of the explicit modeling computations are given in Table 2 for the solid cancer mortality data. Analogous results for the solid tumor incidence are given in terms of diagrams in the appendix. The numerical

[1] The notation θ and λ is adopted from Pierce and Preston [18]. The choice of the familiar symbol α (rather than β) for the initial slope with regard to γ-rays is the same as in the preceding article [12], so is the notation $c$ for the reference slope $c$.

**Table 1** Comparison of dose coefficients obtained through the conventional approach, i.e. with a linear model in weighted ($w$=10) colon dose. $ERR_{60}$ refers to the attained age model, $ERR_{30}$ to the age at exposure model. The present results are obtained with a dose cut-off 2 Gy. RERF [7, 8] and UNSCEAR [1] employed a larger cut-off. All results, except the $ERR_{30}$ for solid cancer incidence were derived with stratified background rates

| Source | Solid cancer mortality | | Solid cancer incidence | |
|---|---|---|---|---|
| | $ERR_{60}$/Gy | $ERR_{30}$/Gy | $ERR_{60}$/Gy | $ERR_{30}$/Gy |
| RERF | – | 0.57 | – | 0.58 |
| UNSCEAR 2000 | 0.48 | 0.57 | 0.57 | 0.59 |
| Present analysis, conventional approach | 0.50 | 0.53 | 0.57 | 0.58 |

**Table 2** Results of the maximum likelihood fits to the solid cancer mortality data. The estimated parameters relate to acute γ-irradiation. α is the initial slope ($ERR_{60}/D_\gamma$ for the attained age model, $ERR_{30}/D_\gamma$ for the age at exposure model), $c$ is the slope to $ERR_{60}$ or $ERR_{30}$ due to 1 Gy γ-rays; it corresponds closely to the dose coefficient in a linear dose model. The 95% confidence limits are given in brackets. $c/\alpha_{min}$ (=1+$\theta_{max}$) is the largest *DDREF* consistent with the data on the 95% confidence level, $g$ and $s$ are the age and the gender modifiers [see Eqs.(12) and (13)]

Solid cancer mortality 1950–1990 ($df$=13,201)

| | α (Gy$^{-1}$) | $c$ (Gy$^{-1}$) | $c/\alpha_{min}$ | $g$ | $s$ | *deviance* |
|---|---|---|---|---|---|---|
| Attained age model | | | | | | |
| $w$=10 | 0.40 (0.11–0.69) | 0.50 (0.36–0.64) | 4.7 | 0.0254 | 0.339 | 6642.6 |
| $R_1$=20 | 0.34 (0.06–0.62) | 0.41 (0.29–0.52) | 6.4 | 0.0252 | 0.339 | 6642.0 |
| $R_1$=35 | 0.31 (0.04–0.59) | 0.36 (0.26–0.46) | 8.7 | 0.0250 | 0.340 | 6641.6 |
| $R_1$=50 | 0.29 (0.02–0.56) | 0.32 (0.23–0.41) | 14.3 | 0.0249 | 0.341 | 6641.4 |
| Age at exposure model | | | | | | |
| $w$=10 | 0.48 (0.18–0.78) | 0.53 (0.39–0.68) | 2.9 | 0.0403 | 0.335 | 6633.1 |
| $R_1$=20 | 0.42 (0.14–0.71) | 0.43 (0.31–0.55) | 3.2 | 0.0397 | 0.333 | 6632.4 |
| $R_1$=35 | 0.40 (0.11–0.68) | 0.38 (0.28–0.49) | 3.4 | 0.0392 | 0.333 | 6632.1 |
| $R_1$=50 | 0.37 (0.09–0.65) | 0.34 (0.25–0.44) | 3.7 | 0.0387 | 0.333 | 6631.9 |

values are specified here to more digits than is warranted by their statistical uncertainty; this is done to make the computational details traceable and to facilitate the comparison to the earlier analyses that are based on the same input data.

The rows labeled $w$=10 give the results obtained with the linear-quadratic dose model, but with the conventional approach in terms of weighted dose to the colon [see Eq.(2)]. These results are included to highlight the difference to the present computation with the change from colon to organ-averaged dose and the more explicit treatment of the neutrons.

The *reference slope*, $c$, corresponds closely to the γ-ray dose coefficient in a linear dose model. The estimate, α, of the initial slope of the dose dependence for the γ-rays differs to varying degrees from $c$, but the difference is never significant. Linearity can, therefore, be accepted and the parameter $c$ with its smaller uncertainty (95% confidence interval ±28%) serves then as a better estimate of the dose coefficient than the coefficient α with its larger uncertainty (average 95% confidence interval ±80%). The parameter, $c$, is also suitable for a comparison to the risk estimates of RERF [7, 8] and UNSCEAR [1] which have been based on linear dose models.

With $R_1$=35, the value $c=ERR_{60}$/Gy=0.36 (attained age model) or $c=ERR_{30}$/Gy=0.38 (age at exposure model) is obtained. The value of $c$ decreases, of course, with increasing $R_1$, i.e. with higher effect attribution to the neutrons. However, the results are not highly sensitive to the assumed value of $R_1$.

## Implications on *DDREF*

While $c$ is the main reference parameter, the parameter values α are informative because their general consistency with $c$ confirms the agreement of the data with linearity in γ-ray dose. The fairly large confidence intervals of α indicate, on the other hand, that the true value of the initial slope might deviate considerably from the best estimate.

The apparent linearity in γ-ray dose is, of course, at variance with the majority of dose-effect relations obtained for γ-rays in experimental radiobiology. These relations tend to be curvilinear, with ratios $c/\alpha$ (=1+θ) substantially larger than unity. ICRP has, in view of the conflict between the epidemiological data and the general radiobiological evidence, adopted the *dose and dose rate effectiveness factor*, *DDREF*=2. This factor was taken to be a ratio of the apparent slope to the initial slope that would still be consistent with the epidemiological data. For leukemia the choice of a *DDREF* was natural because the RERF data for leukemia are actually sugges-

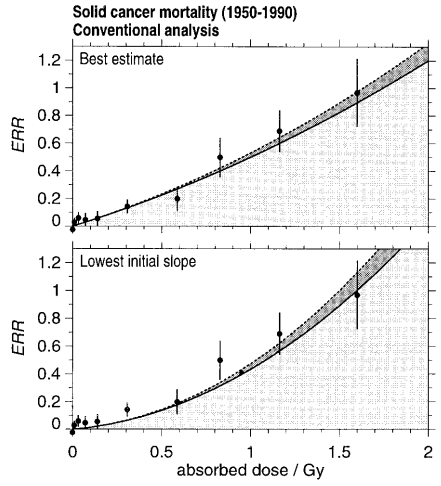


**Fig. 1** Dose dependencies for solid cancer mortality inferred from the A-bomb survivors data in terms of the *attained age model* against total absorbed dose to the colon. The data points (with standard errors) represent the $ERR_{60}$ for separate dose categories. The curves result from the *conventional analysis* in terms of a constant neutron *RBE*=10. The *dotted curves* represent the best fits to the data points. The *solid curves* represent the effect attributed to the γ-rays, the dark shaded areas represent the effect attributed to the neutrons. *Upper panel*: maximum likelihood fits. *Lower panel*: best fits with the minimum value of the initial slope, α, consistent with the data on the 95% confidence level (see Table 1)

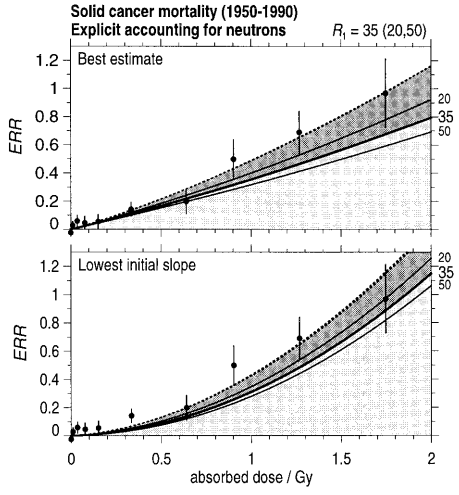


**Fig. 2** Dose dependencies for solid cancer mortality inferred from the A-bomb survivors data in terms of the *attained age model* against total organ-averaged absorbed dose. The data points (with standard errors) represent the $ERR_{60}$ for separate dose categories. The curves result from modeling computations with *explicit treatment of the neutrons*. The *dotted curves* represent the best fits to the data points. The *solid curves* represent the effect attributable to the γ-rays. In each panel, the results are given for the values $R_1$=20, 35, and 50 (from top to bottom; the dotted curves coincide for the assumed values of $R_1$). The dark shaded areas represent the effect attributable to the neutrons ($R_1$=35). *Upper panel*: maximum likelihood fits. *Lower panel*: best fits with the minimum value of the initial slope, α, consistent with the data on the 95% confidence level (see Table 1)

tive of considerable curvature. For the solid cancers any assumed *DDREF* must be measured against the lowest value $c/\alpha_{min}$ ($=1+\theta_{max}$) that is statistically still consistent with the data. This ratio is, therefore, separately tabulated in column 4 of Table 2.

The results show that substantial values of *DDREF* ($=c/\alpha_{min}$) are statistically consistent with the solid cancer mortality data. Computations with the published incidence data (1958–1987) indicate a considerably more narrow range of possible values, the maximum admissible value being $c/\alpha_{min}=1.7$ (see Appendix). Pierce and Preston had already pointed this out in their recent analysis [18] of the new incidence data (1958–1994).

## Diagrams of the dose dependencies

Graphic representations of the risk estimates and their uncertainties will be given in the next section in a form that relates also to lifetime attributable risk. Before this issue is dealt with, diagrams are given in Figs. 1 and 2 to illustrate the observed data points (with standard errors) and the inferred dependencies of the *ERR* (cancer mortality) on total absorbed dose. The figures refer to the results obtained with the attained age model, but the dose dependencies for the age at exposure model are very nearly the same. Figure 1 gives results from the conventional analysis (with colon as reference organ and $w$=10). Figure 2 depicts the results from the present treatment, i.e. modeling computations with explicit accounting for neutrons [see Eqs.(3) and (11)]. The solid curves give the effect contribution due to the γ-rays in terms of the model parameters from Table 2; the dotted curves represent the total effect. The abscissa values are the organ-averaged absorbed doses (including the neutrons). The effect contribution of the neutrons increases more than proportional to total dose, which reflects the fact that the neutron absorbed dose fraction increases with dose. The points (with standard errors) are direct fits to the data in the individual dose bins.

The upper panels of Figs. 1 and 2 give the maximum likelihood results, the lower panels give the dependencies with the lowest value of the initial slope (highest *DDREF*) on the 95% confidence level.

The effect attribution to neutrons is, of course, unrealistically low in the conventional treatment (Fig. 11), since it corresponds to a constant RBE of neutrons of only 10. In fact, in the conventional treatment the weighting factor $w$=10 [Eq.(1)] is applied to the colon, where the neutron contribution is least; this would correspond to using the weighting factor 5 with the organ-averaged dose [12].

In Fig. 2 the results from the explicit treatment are given for the intermediate value $R_1$=35 and for the high and low values 50 and 20 that are here invoked. The triplets of curves thus indicate the uncertainty in the inferred relation for γ-rays that is due to the choice of the neutron RBE, $R_1$. They do not represent the statistical uncertainty of the estimates in Table 2. This uncertainty is visualized in the comparison of the upper and lower panels.

The fit to the actual mixed radiation depends so little on the assumed value $R_1$, that the dotted curves coincide for the assumed values 20, 35, and 50 of $R_1$. The main purpose of the diagrams is to illustrate the substantial attribution to neutrons (dark shaded areas) in the explicit treatment (Fig. 2) and the fairly low initial slopes that are still consistent with the mortality data in terms of the attained age model.

## Numerical results in terms of *LAR*

Risk coefficients are usually expressed in terms of expected numbers of fatalities (or cases) per unit dose.[2] Comparing the present results with such risk coefficients thus requires a conversion of excess relative risk per Gy into lifetime attributable risk per Gy.

As in the preceding paper [12], *lifetime attributable risk*, *LAR*, will be expressed in terms of the excess solid cancer mortality integrated over the survival function of the reference population. While this quantity has earlier been termed *risk of untimely death* (*RUD*) [28], the simpler name *lifetime attributable risk* is used here. This quantity corresponds to the risk coefficients derived earlier by ICRP and – apart from some numerical differences in the derivation of the conversion coefficients – to those more recently presented by UNSCEAR for low doses (0.1 Sv).[3]

The present considerations are restricted to the "transport" of excess relative risk (*ERR*) from the study population – here the A-bomb survivors – to the reference populations. This leads, as seen in the UNSCEAR results, to risk estimates that are roughly 10% higher than in the transport of excess absolute risk (*EAR*).

The computation of *LAR* involves integrating the excess relative risk over the background cancer mortality rates and the survival function of the selected reference population. In their computations for ICRP, Land and Sinclair [10] have invoked the populations US, UK, Japan, China and Puerto Rico and have computed the conversion factor from *ERR* to *LAR* for each of these five populations. They have then used the average of these factors to derive the nominal risk coefficient. While this procedure is to some degree arbitrary, it defines a usable standard that permits exact comparison. For this reason the same approach and the same population data as used for ICRP [9, 10] are employed here. The concepts and computations for deriving the factors for the conversion of *ERR* to *LAR* are described separately [29]. It is here sufficient to list the numerical results (for an assumed latency period of 5 years, and the modifying factors given in Table 1).

[2] Reference is made to Gy in the present treatment. This is done to avoid misinterpretations that can arise when computations are performed with different *RBE* values which must not be confused with the *quality* or *radiation weighting factors*.

[3] UNSCEAR uses a somewhat more complicated quantity, *REID*, which equals *LAR* at low doses. Since there is no need for summary risk coefficients relative to high doses, it is sufficient to consider the simpler quantity, *LAR* (for details see [29]).

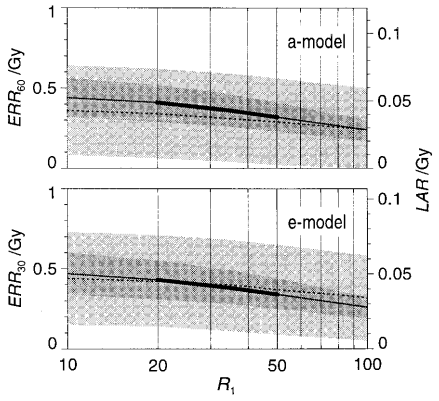


**Fig. 3** The solid lines and the dark shaded bands represent – for the two projection models – the parameter *c*, i.e. the *ERR* for solid cancer mortality due to an acute γ-ray dose of 1 Gy and its 95% confidence range. The *broken lines* and the *light shaded bands* give the estimate of the initial slope, α, and its 95% confidence range in a linear-quadratic dose dependence for the γ-rays. The results are given in dependence on the assumed neutron RBE, $R_1$, vs. an acute γ-ray dose 1 Gy (see Table 2). The right ordinate gives the same quantities expressed in terms of the lifetime attributable risk for solid cancer mortality for a population of working ages. The confidence bands express only the statistical uncertainty in the *ERR*, not the uncertainty of the conversion coefficient *LAR/ERR*

Averaged over all ages one obtains:

$$\begin{aligned} LAR/ERR_{60} &= 0.116 \quad \text{(attained age model)} \\ LAR/ERR_{30} &= 0.178 \quad \text{(age at exposure model)} \end{aligned} \tag{15}$$

If the power function [Eq.(14) instead of Eq.(12)] is used in the age attained model a somewhat larger conversion factor is obtained.

For a gender averaged working population of age range 25–65 (as specified in [9]) the conversion factors are similar for the two different projection models:

$$\begin{aligned} LAR/ERR_{60} &= 0.124 \quad \text{(attained age model)} \\ LAR/ERR_{30} &= 0.108 \quad \text{(age at exposure model)} \end{aligned} \tag{16}$$

Figure 3 depicts, with reference to the left ordinate, the results from Table 2, i.e. the risk estimates in terms of *ERR* depending on the assumed value $R_1$ of the neutron RBE. The solid lines and the dark shaded bands give the reference slope, *c*, i.e. the slope through the *ERR* due to 1 Gy γ-rays, together with its 95% confidence ranges. This quantity, essentially the γ-ray slope in a linear dose dependence, is – as stated in the preceding section – fairly narrowly defined. It is given as a bold line in the range 20–50 of plausible values $R_1$. The results are not substantially different for the two projection models, the attained age model and the age at exposure model.

The broken lines and the light shaded bands give the estimates of the initial slope and their 95% confidence ranges. The essential point here is the broad range of initial slopes in the linear-quadratic dose dependence that are statistically consistent with the data. In this context it must be noted that the confidence ranges represent the uncertainty of the excess relative risk, *ERR*, but not the uncertainty of the conversion factors from Eq.(16).

The right ordinate gives the risk coefficient in terms of the lifetime attributable risk, *LAR*, for solid cancer mortality for a working population. For a population of all ages the values are higher by the factor 1.65 with the age at exposure model, and slightly smaller by the factor 0.94 with the attained age model.

### Comparison to ICRP

The current ICRP solid cancer fatality coefficient is 0.045/Gy for a population of all ages, and 0.036/Gy for a working population [9]. These values were derived in terms of the age at exposure model. If the factor *DDREF*=2 is omitted, the values are 0.09/Gy and 0.072/Gy. The present computations provide – with the same conventional approach ($w$=10 and reference to colon dose), but with the 1950–1990 data (instead of the 1950–1987 data) – the coefficients 0.094/Gy and 0.057/Gy.

With the explicit treatment of neutrons the estimates are notably lower. The central estimates ($R_1$=35) in terms of the present explicit computations are 0.068/Gy (all ages) and 0.041/Gy (working ages) with the age at exposure model. For the attained age model, the result is 0.045/Gy for occupational exposures. For a population of all ages, the attained age model provides the value 0.042/Gy. However, the age at exposure model fits the data somewhat better. Thus the true value for a population of all ages may be closer to 0.068/Gy than to 0.042/Gy.

### Comparison to UNSCEAR

UNSCEAR [1] quotes separate risk estimates for the five different reference populations. As averages over these populations and for all ages at exposure one obtains *LAR*=0.13/Gy for the age at exposure model, and 0.082/Gy for the attained age model. These values are twice as large as the central estimates 0.068/Gy and 0.042/Gy that are obtained here with the same solid cancer mortality data.

The difference is not entirely a matter of the more explicit treatment of the neutrons. UNSCEAR translates the *ERR* values for total solid cancer mortality (see [1], Annex I, Table 2 : $ERR_{60}$/Gy=0.48 and $ERR_{30}$/Gy=0.57) into the risk coefficients *LAR*/Gy=0.082 (attained age model) and *LAR*/Gy=0.13 (age at exposure model). This corresponds to the conversion coefficients $LAR/ERR_{60}$=0.171 and $LAR/ERR_{30}$=0.228. These values are larger by factors of 1.5 and 1.3 than the conversion factors in Eq.(15). One reason for the difference is that UNSCEAR has utilized somewhat more recent population data for the US, the UK, and Japan than ICRP and that they have employed actual age distributions of the populations, rather than the equilibrium distributions that correspond to the actuarial survival functions. This has increased the conversion factors somewhat (see [29]). A further part of the difference results from the fact that the UNSCEAR Committee chose to derive the overall risk estimate for solid cancers not through a joint *ERR* (for each sex). Instead it determined it by deriving individual *ERR*s for eight cancer categories and by summing the estimated contributions. While the effect is not large, it is difficult to quantify the uncertainty that is associated with this less direct procedure.

### *LFR* as an alternative expression of attributable risk

The lifetime attributable risk, *LAR*, specifies the probability of a fatal cancer due to the radiation exposure or the expected number of fatalities in a reference population. Such numbers can be misleading, if they are given without a reference scale. A relative parameter can be more meaningful, and a suitable quantity is the lifetime attributable risk, *LAR*, divided by the spontaneous lifetime cancer mortality risk, *B*, in the reference population, i.e. the fraction of deaths due to cancer. The modified quantity has tentatively been termed *lifetime fractional risk*, *LFR* [29], which is the fractional increase over the spontaneous lifetime cancer mortality. Besides being more indicative of the actual magnitude of the radiation risk, it has the attractive feature of depending little on the particularities of the reference population. In contrast to *LAR* (and the familiar risk coefficient), *LFR* is not larger for populations with high life expectancy, but is fairly equal for different reference populations [29].

The average of the ratio *LFR*/*LAR* for the five ICRP reference populations is 5.5, almost equally for the two projection models and both for a population of all ages and a working population [29]. This makes it a simple matter to translate *lifetime attributable risk* into *lifetime fractional risk*. Thus, for a working population, one can either specify the lifetime attributable solid cancer fatality as 0.043/Gy, or the lifetime fractional risk as 0.23/Gy.

## Conclusions

Risk estimates for solid cancer mortality and incidence have here been obtained in terms of a treatment that includes an explicit accounting of the neutron effect contribution. The resulting estimates are lower by about a factor 1.4 than the values obtained in the conventional analysis that refers to the colon doses and utilizes a constant weighting factor $w$=10 for the neutrons.

The treatment is similar to the approach Pierce and Preston have taken in their recent analysis of the new incidence data [18]. They postulate – as was done here – a linear (neutrons), linear-quadratic ($\gamma$-rays) dose dependence, and they consider a low dose limit, $RBE_{max}=\lambda=40$, of the neutron RBE. The neutron RBE against the reference $\gamma$-ray dose $D_1$ equals $R_1=\lambda/(1+\theta\cdot D_1)$, where $\theta$ is the ratio of the quadratic to the linear dose coefficient for $\gamma$-rays (inverse of the *cross-over dose*). For dose dependencies with little or no curvature it would appear that the value 40 invoked by Pierce and Preston is

roughly in line with the range 20–50 for $R_1$ in the present computations. However, it is a major difference that the value λ=40 in the analysis of Pierce and Preston refers to the colon dose. Since the neutron to γ-ray absorbed dose ratio is larger by about a factor 2 for the organ-averaged dose than for the colon dose, the assumption $RBE_{max}$= λ=40 by Pierce and Preston is, in fact, equivalent to $RBE_{max}$=λ=20 with reference to the organ-averaged doses.

Averaged over the five populations that were invoked by ICRP, UNSCEAR derives the nominal risk coefficients *LAR*=0.13/Gy (age at exposure model) and *LAR*=0.082/Gy (attained age model) for solid cancer mortality. This exceeds the results *LAR*=0.068/Gy and 0.042/Gy from the present analysis (with $R_1$=35) by a factor of 2. The change from the conventional approach to the more explicit treatment of the neutrons accounts for about half of the difference. The remaining difference results partly from the fact that the UNSCEAR has invoked – for the transport of the *ERR* into *LAR* – the same reference populations as Land and Sinclair in their computations for ICRP [10], but has employed somewhat different population data and has used actual age distributions instead of the equilibrium distributions. A further difference is that UNSCEAR has not simply transported the overall *ERR* for all solid tumors to the reference populations, but has added up individually estimated contributions from different tumor sites to derive the overall solid cancer mortality risk.

The choice of the correct projection model in age is still open, and a definitive projection model will have to await the completion of the follow-up of the A-bomb survivors. The age at exposure model leads with the present solid cancer mortality data (1950–1990) to risk estimates for a population of all ages that are larger by a factor of about 1.6 than the estimates from the attained age model. This fairly large difference reflects a markedly elevated *ERR* in the youngest age at exposure cohorts. Whether these high values are real, has major implications with regard to the risk due to radiation exposure of children and juveniles.

The evidence for the elevated risk at young ages of exposure rests, at present, on a relatively small number of excess cancer cases (or cancer deaths) in these age cohorts. In this context it is of interest that the stratified treatment of the background of cancer mortality implies a somewhat peculiar secular trend of decreasing rates below age 60 and increasing rates above this age. With a parametric modeling of the background rates which does not include this complexity, the age at exposure dependence of the *ERR* is less marked. A similar reduction of the difference between the models results, if absolute risk – rather than relative risk – is transported in the computation of the *LAR*. Definitive conclusions on the dependence of *LAR* on age at exposure will require the continued follow-up of the A-bomb survivors. The attained age and the age at exposure model can in the meantime – in line with the approach chosen by UNSCEAR – be useful references that bracket the likely true value of the solid cancer risk coefficient.

The dose limits to the population are so low that a comparison to natural background radiation is more meaningful than a comparison to nominal risk numbers. In this sense the nominal risk coefficients are primarily of interest with regard to occupational exposures. For a gender averaged working population (age 25–65) the two projection models provide almost the same *LAR*, i.e. the choice of the projection model has ceased to be critical. With an assumed neutron RBE $R_1$=35, the solid cancer fatality risk coefficient 0.043/Gy is obtained. With a lower assumed value $R_1$=20 the coefficient is only moderately increased to 0.048/Gy.

Fairly large values of *DDREF* are – as shown in Table 2 and Fig. 3 – consistent with the data for the solid cancer mortality. Considerably smaller risk coefficients than the central estimates can, therefore, not be ruled out. The incidence data define – as shown in Appendix, Fig. 4 – a more narrow range of the initial slope of the dose dependence for γ-rays. The maximum likelihood estimates of the *ERR* are moderately – although not with statistical significance – larger than the values for solid cancer mortality. The major difference is that the incidence data appear to be inconsistent with a *DDREF* larger than about 1.7.

The result of the present analysis is remarkable insofar as the derived risk coefficient for occupational exposure corresponds closely to the current ICRP nominal risk coefficient, although it does not invoke the ICRP reduction factor *DDREF*=2. The risk coefficient could, therefore, remain largely unchanged if the *DDREF* were abandoned.

The *DDREF* remains a somewhat controversial issue. Radiobiological studies suggest a *DDREF* both for x-rays and γ-rays. ICRP has, therefore, adopted *DDREF*=2 and has applied it to the risk estimates derived from the A-bomb data. On the other hand, there is evidence from radiobiological studies [30] that the *RBE* of x-rays compared to γ-rays is about 2 at low doses. Since the nominal risk coefficient is intended to be applicable not only to γ-rays, but also to x-rays, the two possible modifying factors cancel out. This would tend to suggest that the *DDREF* ought to be abandoned. Radioepidemiology, likewise, fails to provide strong support for a *DDREF*. There is no evidence for a *DDREF* in the A-bomb data and no consistent evidence from other cohorts. At the same time, there is no indication of higher risk coefficients for x-rays than γ-rays in the epidemiological data. In this sense there appears to be little justification, both on the grounds of biology and epidemiology, to adopt a *DDREF*.

However, as stated at the outset, the present study is not aimed at deriving a new nominal risk coefficient. It focuses, instead, on methodological aspects that can be taken into account in future analyses based on a more recent follow-up of the A-bomb survivor data and an updated dosimetry.

A preceding paper [12] deduced the risk coefficient for neutrons in terms of a Poisson regression which required – in addition to an assumed $R_1$ – only the $ERR_{obs}$

at a dose of 1 Gy from the A-bomb radiation. An attractive feature of this approach is – apart from its simplicity – the fact that it is insensitive to uncertainties of the neutron dosimetry that still exist at lower doses. The present, more detailed modeling provides, of course, also a risk estimate for neutrons, $\alpha_n = c \cdot R_1$, and it is of interest to examine the consistency of the two results. The preceding paper derived (with $R_1$=35) the risk coefficients for neutrons *ERR*/Gy=12.8. The present, more explicit computations provide – in terms of the values *c* in Table 2 – the values *ERR*/Gy=13.0 as an average of the two different projection models. The degree of numerical equality may be accidental, but the comparison confirms the consistency of the two similar approaches.

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## Appendix

Results obtained from the solid cancer incidence data

Figure 4 gives the results for the solid cancer incidence data (1958–1987) in analogy to those for the solid cancer mortality data (Fig. 3). Only the results for the age at exposure model are given, because the two projection models (in terms of $ERR_{30}$ and $ERR_{60}$) give almost precisely the same results. As with the mortality data, the incidence data fit the *e*-model better than the *a*-model. The maximum likelihood estimates of the initial slope $\alpha$ is somewhat larger – although not significantly so – than the maximum likelihood value of *c*. This implies – in agreement with an analysis of the more recent incidence data [18] – that the incidence data are inconsistent with a *DDREF* in excess of about 1.7. Since there is no standard for the incidence rates, the diagram does not give a right ordinate with lifetime attributable incidence.

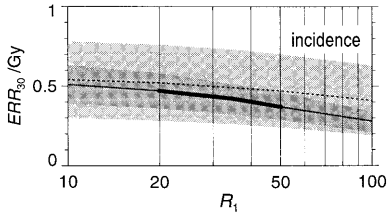


**Fig. 4** The *solid line* and the *dark shaded band* represent – for the age at exposure model – the parameter *c*, i.e. the $ERR_{30}$ for solid cancer incidence due to an acute $\gamma$-ray dose of 1 Gy and its 95% confidence range. The *broken line* and the *light shaded band* gives the estimate of the initial slope, $\alpha$, and its 95% confidence range. The diagram is analogous to the diagrams in Fig. 3

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