RADIATION EFFECTIVENESS FACTORS (REFs) FOR USE IN CALCULATING PROBABILITY OF CAUSATION OF RADIOGENIC CANCERS

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INTRODUCTION

Workers and members of the public can be exposed to various types of ionizing radiation (e.g., photons, electrons, and alpha particles) that may differ in their biological effectiveness. That is, for a given absorbed dose in tissue, the probability of a stochastic response (e.g., cancer) may depend on the radiation type, and sometimes its energy, as well as the absorbed dose. Differences in biological effectiveness of different radiation types must be taken into account in estimating cancer risks and the probability of causation of radiogenic cancers in humans.

This report presents so-called radiation effectiveness factors (REFs) which are intended to represent the biological effectiveness of different types of ionizing radiation for the purpose of calculating the probability of causation of specific cancers in humans. REFs are expressed as probability distributions, taking into account uncertainties in relevant radiobiological data and other judgments involved in evaluating available information. The different types of ionizing radiation considered in this report include photons (gamma rays and *X* rays),[2] electrons, alpha particles, and neutrons. Except in cases of exposure of the lung to alpha particles emitted by short-lived decay products of radon in air, probability distributions of REFs are intended to be applied in calculating the probability of causation of radiogenic cancers in any organ or tissue and for any exposure situation.[3] The REFs developed in this report are incorporated in the Interactive RadioEpidemiological Program (IREP).[4]

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[2]Gamma rays are the electromagnetic radiations emitted in de-excitation of atomic nuclei, whereas *X* rays are the electromagnetic radiations emitted in de-excitation of atomic electrons, often referred to as characteristic *X* rays, or produced in deceleration of charged particles (e.g., electrons) in passing through matter, often referred to as continuous *X* rays or bremsstrahlung.

[3]The probability of causation of lung cancer due to inhalation of radon and its decay products in air is calculated based on an estimate of the risk per unit exposure to the short-lived alpha-emitting decay products in Working Level Months (WLM), and an REF for alpha particles that would be applied to estimates of absorbed dose in the lung is not used.

[4]Methods used in IREP to calculate the probability of causation of radiogenic cancers may be found on the Internet at http://216.82.51.38/irep_niosh and in Appendix F of Land et al. (2002).

The probability distributions of REFs developed in this report are based in large part on data on the relative biological effectiveness (RBE) of different radiation types obtained from relevant radiobiological studies. The RBE of radiation *i* compared with a reference radiation, *r*, is defined as the absorbed dose of the reference radiation (D_r) required to produce a specific level of response relative to the absorbed dose of the radiation of concern (D_i) required to produce an equal response:

$$\mathrm{RBE}_i = \frac{D_r}{D_i}, \qquad (1)$$

with all physical and biological variables, except differences in radiation type, being held as constant as possible. The definition of RBE as a ratio of doses that produce an equal response does not depend on the dose-response relationships for the two radiation types being the same, or that either dose-response relationship be linear. Values of RBE are specific to each study, and they generally depend on the biological system and specific response under study, the magnitude of the absorbed doses, the dose rate, and the dose per fraction if the dose is fractionated.[5]

In most radiobiological studies to estimate RBEs, the reference radiation is either orthovoltage (deeply penetrating) *X* rays, usually 180-250 kVp,[6] or higher-energy gamma rays produced in decay of ^{60}Co (photon energies of 1.2 and 1.3 MeV) or, less often, ^{137}Cs (0.66 MeV). Knowledge of the reference radiation in any study is important because, as discussed in this report, the biological effectiveness of *X* rays apparently is greater than that of higher-energy gamma rays. In this report, the reference radiation is taken to be high-energy gamma rays, specifically gamma rays emitted in ^{60}Co decay, at high doses and high dose rates. This choice is appropriate for the purpose of calculating the probability of causation of cancers because estimates of cancer risks in humans are based primarily on data obtained from studies of the Japanese atomic-bomb survivors who received high acute doses of high-energy gamma rays.[7]

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[5]It is because the term "RBE" strictly applies only to results of specific radiobiological studies under controlled conditions that the new term "radiation effectiveness factor" (REF) is used in this report. REFs for induction of cancers in humans are assumed values based primarily on evaluations of RBEs obtained from studies of a variety of stochastic responses in other biological systems, augmented in a few cases by information obtained from epidemiological studies of human populations.

[6]The term "kVp" denotes the maximum potential difference in kilovolts (kV) across an *X*-ray tube during an exposure; this potential difference determines the maximum electron energy in keV. The average energy of the continuous spectrum of bremsstrahlung produced when the electrons are stopped in a target is a fraction of the peak tube potential in kVp.

[7]In IREP, the only cancer risks that are not estimated based on data in the Japanese atomic-bomb survivors, in addition to risks of lung cancer from inhalation of radon and its short-lived decay products, are risks of thyroid cancer resulting from exposure in childhood (Land et al., 2002). These risks are estimated based primarily on studies of children exposed to *X* rays.

The probability distributions of REFs for induction of cancers in humans presented in this report are based primarily on published reviews and evaluations of radiobiological studies. For the most part, we relied on reviews by such expert advisory groups as the International Commission on Radiological Protection (ICRP), the International Commission on Radiation Units and Measurements (ICRU), the National Council on Radiation Protection and Measurements (NCRP), the U.K.'s National Radiological Protection Board (NRPB), and the Committee on Interagency Radiation Research and Policy Coordination (CIRRPC), as well as reviews by the U.S. Environmental Protection Agency (EPA) and individuals who are recognized experts. We used other information from the primary literature only to a limited extent.

It cannot be overemphasized that the development of probability distributions of REFs relies to a significant extent on subjective scientific judgment. The most important judgment is an assumption that RBEs obtained from studies of a number of stochastic responses in a variety of biological systems are applicable to induction of cancers in humans. This assumption is necessitated by the lack of data on RBEs for cancer induction in humans. Scientific judgment also is applied by experts and expert groups in their reviews and evaluations of published studies, and in the conclusions they draw from these reviews. Finally, we have applied our own scientific judgments in developing probability distributions of REFs, and we recognize that knowledgeable individuals could reach different conclusions based on the same body of information.

Given the importance of subjective scientific judgment, it also should be emphasized that the probability distributions of REFs developed in this report are nothing more than a representation of the current state of knowledge of the effectiveness of different radiation types in inducing cancers in humans; they are not intended to represent uncertainty in a strict statistical sense. That is, the assumed probability distributions of REFs are not intended to represent a frequency distribution of actual outcomes that would be obtained if repeated experiments to estimate the biological effectiveness of different radiation types in humans were performed.

In developing probability distributions of REFs for use in calculating probability of causation of radiogenic cancers, an important consideration is the extent to which these distributions should be consistent with recommendations developed by national and international advisory groups for purposes of radiation protection. In radiation protection, the quantities that are analogous to an REF are the effective quality factor, $\overline{Q}$ (ICRU, 1986), and the radiation weighting factor, w_R (ICRP, 1991; NCRP, 1993).[8]

Effective quality factors and radiation weighting factors used in radiation protection are prescribed point values that are intended to represent relevant data on RBE. For the radiation

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[8]Effective quality factors are intended to be applied to radiations at the locations in tissue where an absorbed dose is delivered, and are used to calculate dose equivalent at a point (ICRU, 1986), whereas radiation weighting factors are intended to be applied to radiations incident on the body or emitted by internally deposited radionuclides, and are used to calculate equivalent dose in an organ or tissue from the average absorbed dose in that organ or tissue (ICRP, 1991).

types considered in this report, the values of $\overline{Q}$ recommended by the ICRU (1986), which were developed by a Joint Task Group of the ICRP and the ICRU, and the values of w_R currently recommended by the ICRP (1991) and the NCRP (1993) are given in Table 1. Although there is general agreement between the two sets of recommendations, there are some differences, especially in the recommendations for photons of energy less than 30 keV and low-energy beta particles emitted in decay of tritium (^{3}H). There also are differences in the recommendations for alpha particles and neutrons.

Although consistency between the REFs developed in this report and the effective quality factors and radiation weighting factors recommended by national and international authorities may be desirable, there are two important issues to be considered. First, point values of radiation protection quantities do not reveal the state of knowledge (uncertainty) in the values, including uncertainties in RBEs obtained from relevant radiobiological studies and uncertainties in other judgments used to develop the point values. A full accounting of uncertainties in all parameters is essential when estimating probability of causation for the purpose of evaluating claims by individuals that their cancer was caused by radiation exposure.

Second, for some radiations, it is evident that the recommended point values of radiation protection quantities given in Table 1 are not consistent with the preponderance of relevant radiobiological information. For example, based on a review of available data, the ICRU (1986) concluded that there is clear evidence that the biological effectiveness of orthovoltage *X* rays is approximately twice that of high-energy ^{60}Co gamma rays. This conclusion is consistent with a calculation of the energy dependence of the effective quality factor for photons shown in Fig. 1. Nonetheless, neither the ICRU nor the ICRP and the NCRP have incorporated this difference in their current recommendations. Similarly, the current ICRP and NCRP recommendations do not take into account the clear evidence from many studies that beta particles emitted in decay of ^{3}H are biologically more effective than high-energy gamma rays.[9]

It is important to recognize that the needs of radiation risk assessment and calculations of probability of causation in cases where actual exposures of specific individuals are of concern differ significantly from the needs of radiation protection. The primary concern in radiation protection is control of exposures based on evaluations of compliance with applicable limits on radiation dose and other radiation protection requirements, and the use of standard assumptions for this purpose is appropriate. However, as noted above, estimates of probability of causation must be based on the state of knowledge of actual doses and risks to exposed individuals. Thus, we have not assumed *a priori* that effective quality factors or radiation weighting factors developed for use in radiation protection provide "best" estimates of REFs for the purpose of calculating probability of causation. Rather, we have developed probability distributions of REFs based primarily on data obtained from relevant radiobiological studies.

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[9]In earlier recommendations (ICRP, 1960), absorbed dose from ^{3}H beta particles was modified by a factor $N = 1.7$ in calculating dose equivalent to account for an increased biological effectiveness of these radiations, but such a modifying factor is not included in current ICRP recommendations.

Table 1. Values of effective quality factor, $\overline{Q}$, and radiation weighting factor, w_R, for selected radiation types currently recommended for use in radiation protection[a]

Radiation type	Effective quality factor[b] ($\overline{Q}$)	Radiation weighting factor[c] (w_R)
Photons		
All energies		1
> 30 keV[d]	1	
Electrons		
All energies[e]		1
> 30 keV	1	
Tritium beta particles	2	
Neutrons		
Unknown energy[f]	25	
< 10 keV		5
10-100 keV		10
100 keV-2 MeV		20
2-20 MeV		10
> 20 MeV		5
Alpha particles	25	20

[a]Distinction between effective quality factor and radiation weighting factor is described in footnote 8 of main text. Recommended effective quality factors and radiation weighting factors for other radiation types, including protons and ions heavier than alpha particles, are not listed.

[b]Values recommended by ICRU (1986) based on calculation of quality factor vs. lineal energy in a 1-μm diameter sphere of tissue-equivalent material.

[c]Values recommended by ICRP (1991) and NCRP (1993).

[d]At photon energies less than 30 keV, calculated effective quality factor increases with decreasing energy (see Fig. 1).

[e]Auger electrons emitted in decay of radionuclides incorporated into DNA are excluded; see paragraphs A13 and B67 of ICRP (1991).

[f]When neutron energy at location of interest in tissue is known, energy dependence of effective quality factor shown in Fig. 2 can be used.

The next section presents the equations used in IREP (Land et al., 2002) to calculate the risk of a specific cancer resulting from a given absorbed dose of a particular radiation type. These risk estimates provide the basis for calculations of probability of causation. The equations illustrate how REFs are used in calculating risk, and they indicate the particular kinds of REFs that are developed for each radiation type. The following sections then present the probability distributions of REFs for neutrons, alpha particles, photons, and electrons.

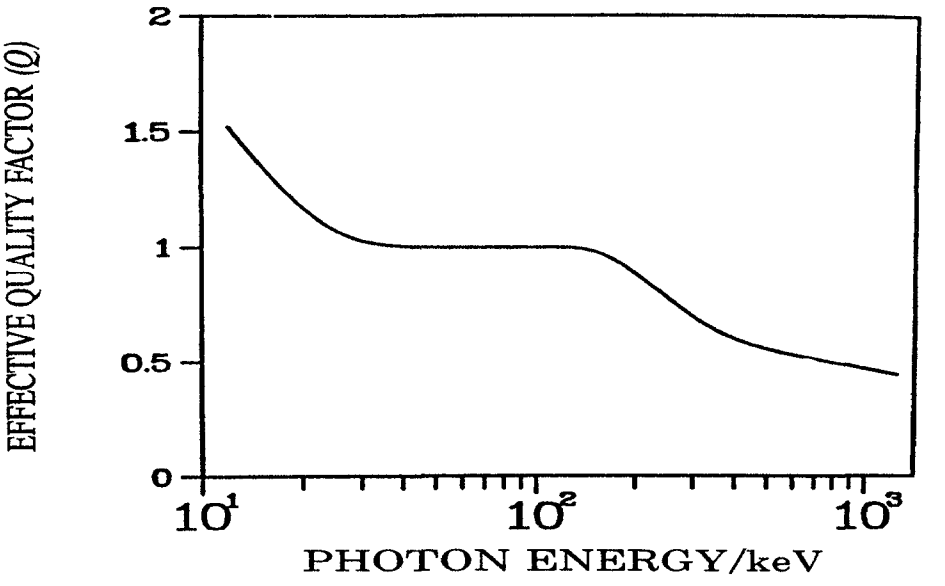

Fig. 1. Calculated effective quality factor, $\overline{Q}$, vs. photon energy under conditions of charged-particle equilibrium given in Fig. 3 of ICRU (1986). Values are normalized to unity at energies of orthovoltage *X* rays often used in radiobiological studies; energies of gamma rays emitted in decay of ^{60}Co are at right end of curve.

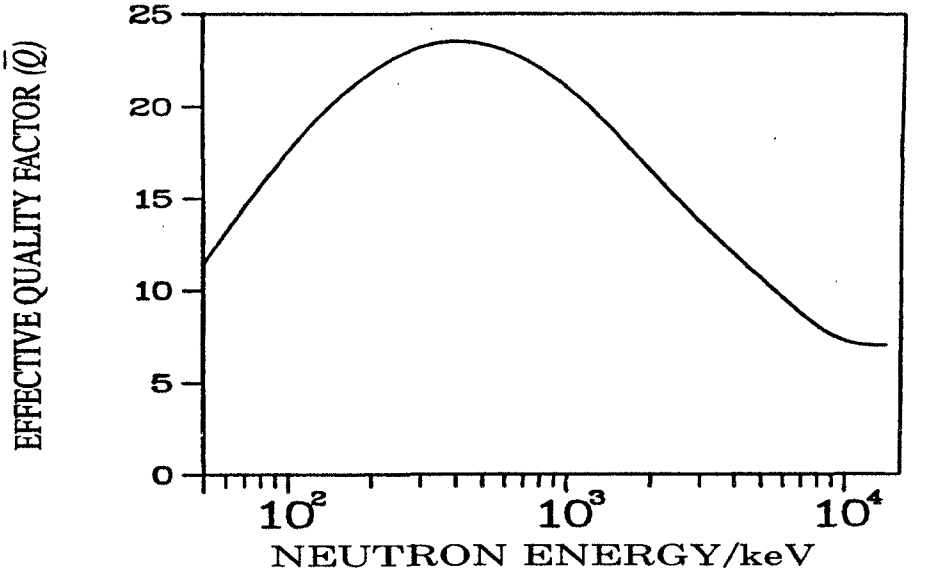

Fig. 2. Calculated effective quality factor, $\overline{Q}$, vs. neutron energy under conditions of charged-particle equilibrium given in Fig. 4 of ICRU (1986).

CALCULATION OF CANCER RISKS

Different approaches are used in IREP to calculate risks of solid tumors and leukemias, based on assumptions that the dose-response relationships in the Japanese atomic-bomb survivors who received high acute doses of high-energy gamma rays are linear for solid tumors but linear-quadratic for leukemias (Land et al., 2002), and that these relationships apply at lower doses. Two additional assumptions are made. First, for any cancer type, the dose-response relationships for neutrons and alpha particles are linear at any dose and dose rate. Second, for a particular cancer type and conditions of exposure, the dose-response relationships for photons and electrons have the same form (i.e., linear or linear-quadratic).

Based on these assumptions, cancer risks in exposed individuals are calculated using one of the following equations:

Solid tumors –

$$\Re = \mathrm{REF_L} \times \frac{R_{\gamma,\mathrm{H}}}{\mathrm{DDREF}_\gamma} \times D \tag{2}$$

$$\Re = \mathrm{REF_H} \times R_{\gamma,\mathrm{H}} \times D \tag{3}$$

Leukemias –

$$\Re = a(\mathrm{REF_L} \times D) + b(\mathrm{REF_L} \times D)^2 \tag{4}$$

$$\Re = a \times \mathrm{REF_L} \times D \tag{5}$$

In these equations –

- $\Re$ is the risk of a particular cancer (i.e., the excess relative risk, ERR) due to exposure to a particular radiation type;
- $R_{\gamma,\mathrm{H}}$ is the risk coefficient (ERR per Gy) for a particular solid tumor at high acute doses of high-energy gamma (γ) rays, which have a defined biological effectiveness of 1.0;
- the subscript L or H in the radiation effectiveness factor indicates that the REF is derived based on estimates of RBE at low doses and low dose rates or at high doses and high dose rates of the reference high-energy gamma rays, respectively;
- DDREF_γ is the dose and dose-rate effectiveness factor, which takes into account that, for solid tumors, the ERR per Gy at low doses and low dose rates of photons (and electrons) may be less than the values of $R_{\gamma,\mathrm{H}}$ at high acute doses obtained from studies of exposed populations;

- a and b are the coefficients of the linear and quadratic terms, respectively, in the assumed linear-quadratic dose-response relationship for leukemias under conditions of acute exposure to high-energy gamma rays; and
- D is the absorbed dose of the radiation type of concern.

The equation selected depends on the radiation type and cancer of concern. For solid tumors, eq. (2) is used in cases of exposure to photons, electrons, and alpha particles, and eq. (3) is used in cases of exposure to neutrons; the different approach to estimating risk from exposure to neutrons is discussed in the next section. For leukemias, eq. (4) is used in cases of acute exposure to photons and electrons, and eq. (5) is used in cases of chronic exposure[10] to photons and electrons and any exposures to alpha particles and neutrons; for this type of cancer, the assumed dose-response relationships for photons and electrons are different under conditions of acute and chronic exposure (linear-quadratic for acute exposure, but linear for chronic exposure).

The dose and dose-rate effectiveness factor (DDREF) is applied to radiations with a low linear energy transfer (LET) in tissue and is based on observations that dose-response relationships at low doses and low dose rates of photons often are different than at high doses and dose rates, with the response per unit dose usually lower at low doses and dose rates (ICRP, 1991; NCRP, 1993).[11] A DDREF is used to estimate risk for solid tumors only, and only when the REF for the radiation type of concern is derived based on estimates of RBE at low doses and low dose rates of the reference radiation. When the dose-response relationship for high-energy gamma rays is assumed to be linear, DDREF renormalizes the risk coefficient at high acute doses, $R_{\gamma,H}$, as obtained mainly from studies of the Japanese atomic-bomb survivors, to give a risk coefficient at low doses and dose rates that is compatible with an REF at low doses and dose rates, REF_L. A DDREF is not used to estimate risk of leukemias. However, a similar effect is obtained by assuming that the dose-response relationship under conditions of acute exposure to low-LET radiations is linear-quadratic, and that the dose-response relationship under conditions of chronic exposure is linear and is defined by the linear term in the dose-response relationship for acute exposure.

A DDREF is not used in cases of exposure to high-LET alpha particles and neutrons. However, a factor representing an inverse dose-rate effect, which is not shown in eqs. (2), (3), and (5), is applied to all exposures to alpha particles emitted in radioactive decay and to chronic

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[10]An exposure is considered to be chronic if the absorbed dose rate, averaged over a period of a few hours, is less than 6 mGy/h.

[11]For purposes of radiation protection, the ICRP (1991) and the NCRP (1993) currently recommend a $DDREF_\gamma$ of 2; i.e., estimated cancer risks per unit dose in the atomic-bomb survivors are reduced by a factor of 2 in estimating risks from exposure to gamma rays and other low-LET radiations at lower doses and dose rates. In IREP, $DDREF_\gamma$ is treated as an uncertain parameter at doses and dose rates less than those experienced in the atomic-bomb survivors (Land et al., 2002).

exposures to neutrons. This factor, which is a multiplier on the right-hand side of these equations, is discussed in the sections that present the REFs for these radiation types.

Given an estimate of the excess relative risk, ERR, for a particular cancer type, the probability of causation (PC) is estimated as PC = ERR/(ERR + 1) (Land et al., 2002).

NEUTRONS

Approaches to Estimating RBEs

RBEs for neutrons have been estimated in many radiobiological studies involving different organisms, stochastic endpoints (responses), and doses and dose rates. Most studies used fission neutrons or other neutrons of comparable energies; relatively few studies used neutrons of lower or higher energies. Extensive reviews and evaluations of these data have been presented by the ICRU (1986), the NCRP (1990), and the NRPB (Edwards, 1997).

In most studies, the doses and dose rates of neutrons and the reference radiation were substantially above levels that are encountered in routine exposures of workers and the public. Furthermore, as illustrated in Fig. 3, RBEs for neutrons generally increase with decreasing dose. Therefore, an important focus of radiobiological studies and the primary concern of reviews by expert groups has been to develop estimates of RBE that are appropriate at low doses and dose rates. These RBEs are obtained by extrapolation of data on dose-response for neutrons and the reference radiation at higher doses and dose rates. An RBE at low doses and dose rates obtained by this extrapolation usually is denoted by RBE_M.[12] Summaries of estimates of RBE_M for fission neutrons developed by the ICRU (1986) and the NCRP (1990) are given in Table 2.[13]

From an evaluation of estimates of RBE_M obtained from studies that are deemed relevant to estimating cancer risks in humans, a representative probability distribution of REF at low doses and low dose rates, which we denote by REF_L, could be developed. This distribution could be used to estimate cancer risks in accordance with eq. (2) for solid tumors or eq. (5) for leukemias. As indicated by the summary in Table 2, estimates of RBE_M for fission neutrons obtained from different radiobiological studies vary widely. Thus, a probability distribution of REF_L that would represent these data would span a wide range of values.

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[12]The subscript M denotes that an RBE at low doses and dose rates of the reference radiation is a maximum value (see Fig. 3).

[13]In some cases, such as studies of tumor induction in mice summarized in Table 6.3 of NCRP (1990), particular values of RBE_M lie outside the range given in Table 2. Furthermore, the ranges in Table 2 generally are based on central estimates of RBE_M, and values well outside these ranges cannot be ruled out when uncertainties in the data are taken into account.

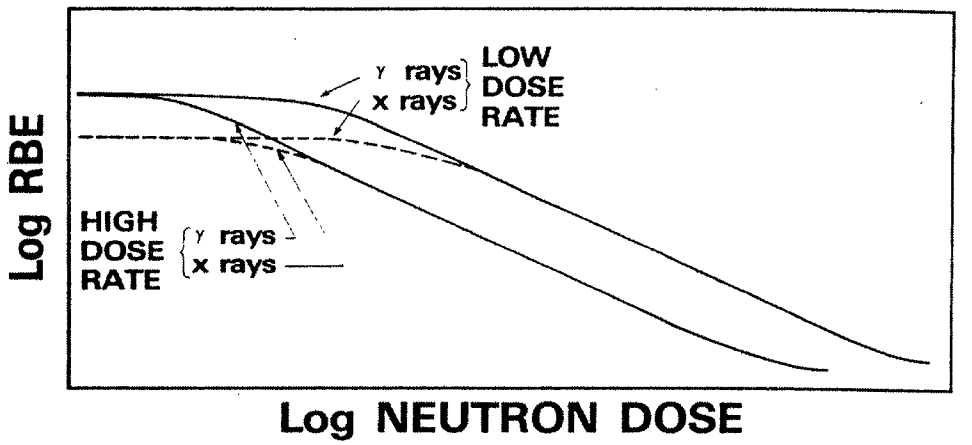

Fig. 3. Schematic representation of increase in RBE for fission neutrons with decreasing dose given in Fig. C-2 of ICRU (1986). Maximum values at low doses are values of RBE_M.

Table 2. Summary of estimates of RBE_M for fission neutrons relative to high-energy gamma rays given by expert groups[a]

Biological response	ICRU (1986)	NCRP (1990)
Tumor induction	~3 - ~200	16-59
Life shortening	15-45	10-46
Transformation	35-70	3-80[b]
Cytogenetic studies[c]	40-50	34-53
Genetic endpoints[d]	10-45	5-70[e]

[a]Estimates of RBE_M apply at low doses and low dose rates, and are obtained by extrapolation of data on dose-response for neutrons and the reference radiation at higher doses and dose rates; estimates of RBE_M generally are greater than the corresponding estimates of RBE at higher doses and dose rates (see Fig. 3). Only estimates of RBE_M for stochastic endpoints obtained from studies in mammalian systems are listed.

[b]Value of 80 was derived from one set of experiments only.

[c]Studies in human lymphocytes in culture.

[d]Studies in mammalian systems only; range of values for genetic endpoints in plant systems estimated by NCRP (1990) is 2-100.

[e]Value of 70 derived from data on specific locus mutations in mice is not necessarily an RBE_M.

In most radiobiological studies, the dose-response relationship for neutrons is linear at absorbed doses of a few Gy or less, whereas the dose-response relationship for the low-LET reference radiation is linear-quadratic in form (ICRU, 1986; NCRP, 1990); see Fig. 4. The variability in estimates of RBE_M for neutrons obtained from different studies is due in part to pronounced differences in the linear-quadratic dose-response relationships for the reference radiation, which result in a wide range of DDREFs for these radiations when calculated as indicated in Fig. 5 (CIRRPC, 1995; Edwards, 1997; Edwards, 1999). That is, RBE_M is sensitive to variations in biological effectiveness at low doses of the reference radiation, with higher values of RBE_M associated with high DDREFs and lower values with low DDREFs. Since the DDREFs for the reference radiation embodied in values of RBE_M for neutrons generally are not the same as a $DDREF_\gamma$ that might be used to adjust observed cancer risks in humans at high acute doses of high-energy gamma rays to obtain estimates of risk at low doses and low dose rates (see footnote 11), a probability distribution of REF_L that is based on the variability in estimates of RBE_M may not provide the best representation of the biological effectiveness of low doses of neutrons in humans relative to low doses and dose rates of gamma rays.

Difficulties with developing a representative probability distribution of REF_L based on highly variable estimates of RBE_M obtained from different studies can be addressed by using an alternative approach recommended by CIRRPC (1995) and discussed by Edwards (1997; 1999). This approach is based on the view that the assumed REFs for neutrons should be consistent with the data used to estimate cancer risks from exposure to photons. That is, the appropriate REFs are values based on RBEs at high doses and high dose rates of reference high-energy gamma rays, because this was the condition of exposure of the Japanese atomic-bomb survivors from which most estimates of cancer risks in humans have been derived; we denote these REFs by REF_H. Then, if DDREF for neutrons is assumed to be unity, based on the observation that the dose-response relationship usually is linear at absorbed doses of a few Gy or less and the usual presumption of linearity at low doses for all high-LET radiations, a probability distribution of REF_H that represents RBEs at high doses and high dose rates of reference high-energy gamma rays could be used to estimate cancer risk at any dose and dose rate of neutrons in accordance with eq. (3), for example. Thus, estimates of cancer risk from exposure to neutrons can be based directly on estimated RBEs at high doses and high dose rates, rather than extrapolated values at low doses and dose rates, and without the need to apply an uncertain DDREF to the risk coefficient at high acute doses of the reference radiation.

When the alternative approach described above is used to estimate cancer risk, there still is considerable variability in RBEs for neutrons at high doses and high dose rates of the reference high-energy gamma rays, RBE_H. This variability is due to several factors including the variety of biological systems and stochastic endpoints studied, as well as the dependence of RBE on dose when the dose-response relationship for the reference radiation is non-linear (see Figs. 3 and 4). However, the variability in RBE_H is considerably less than the variability in RBE_M, due mainly to the reduced influence at high doses of differences in the DDREFs for the reference radiation in the various studies. Therefore, the uncertainty in a representative value of REF_H to be used in estimating cancer risks in humans should be less than the uncertainty in REF_L.

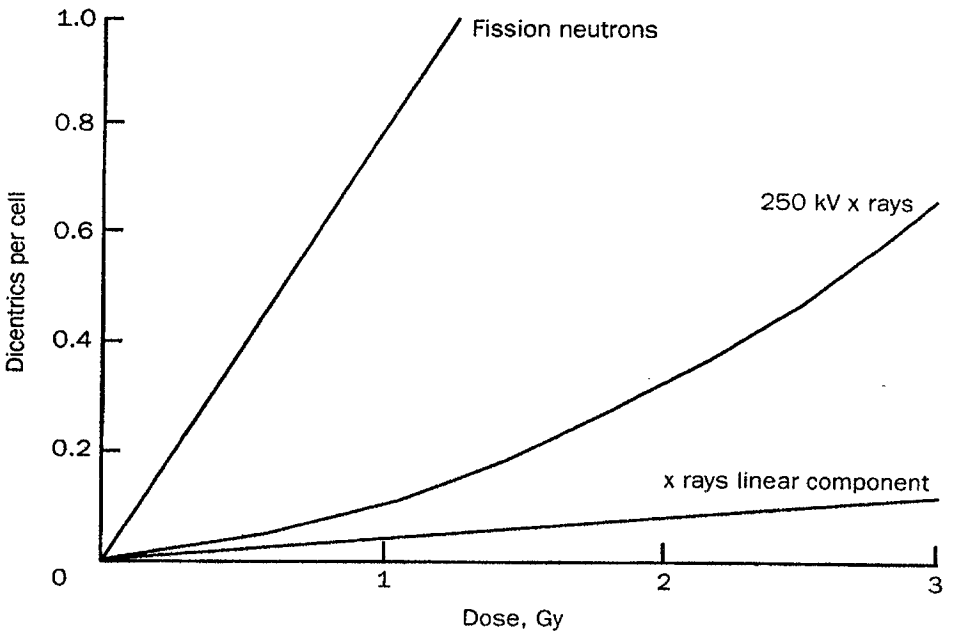

Fig. 4. Representation of linear and linear-quadratic dose-response relationships for fission neutrons and *X* rays, respectively, given in Fig. 1 of Edwards (1997). Separation of two curves at different levels of response illustrates dependence of RBE on dose (see Fig. 3); RBE at low doses, RBE_M, is determined by separation of neutron curve and linear component of *X*-ray curve.

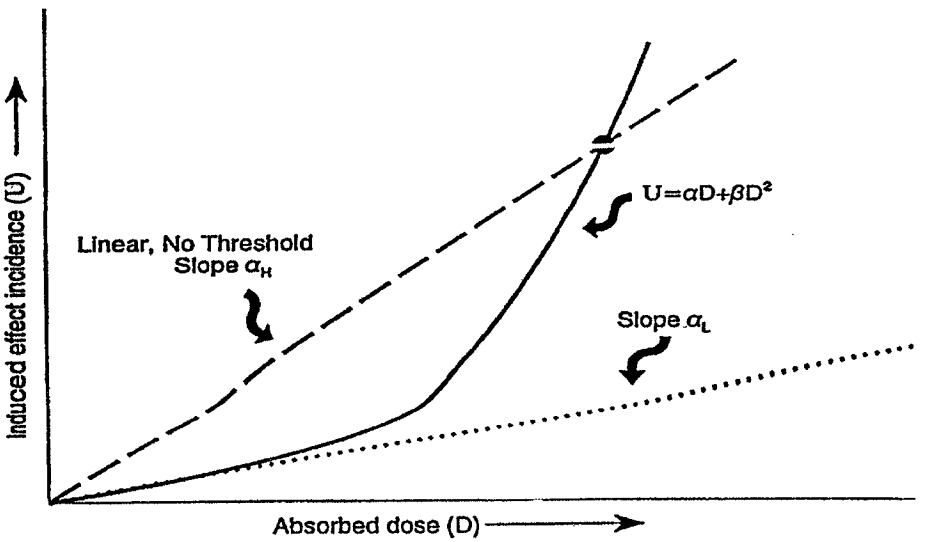

Fig. 5. Representation of linear-quadratic dose-response relationship for low-LET radiations given in Fig. 2 of CIRRPC (1995). Dose and dose-rate effectiveness factor (DDREF) is ratio of linear extrapolation at high doses, α_H, to slope of dose-response curve at low doses, α_L; DDREF thus is a function of dose given by $1 + (\beta/\alpha)D$.

It is important to emphasize that estimates of cancer risks at low doses and low dose rates of neutrons obtained using the alternative approach represented by eq. (3) would be the same as risks estimated using the conventional approach represented by eq. (2) if the DDREFs for the reference radiation embodied in the estimates of RBE_M were the same as the value of $DDREF_\gamma$ that is used to adjust observed risks at high acute doses of high-energy gamma rays in humans to obtain estimates of risk at low doses and dose rates. The advantage of the approach represented by eq. (3) is that it is directly compatible with the data in the Japanese atomic-bomb survivors who were exposed at high acute doses. Again, these are the data from which most estimates of cancer risks in humans are obtained.

In principle, the alternative approach of estimating cancer risks from exposure to neutrons based on probability distributions of REF_H obtained from RBEs at high doses and high dose rates of reference high-energy gamma rays could be used for any cancer type. However, as indicated in the previous section, the alternative approach is used only to estimate risks of solid tumors. The approach is particularly suitable in such cases because the dose-response relationships for gamma rays are assumed to be linear and risk coefficients at high acute doses of gamma rays thus are defined. The conventional approach of estimating cancer risks from exposure to neutrons based on probability distributions of REF_L obtained from RBEs at low doses and low dose rates of the reference radiation is used for leukemias, essentially because the dose-response relationship for acute exposure to gamma rays is assumed to be linear-quadratic. Consequently, if the alternative approach were used for leukemias, estimated risks from exposure to neutrons would have an additional uncertainty arising from the dependence of the risk on the choice of a reference "high" acute dose of gamma rays in the Japanese atomic-bomb survivors.

Data on RBE Used in Analysis

In this analysis, probability distributions of REFs for fission neutrons are developed based on data on RBE obtained from studies of life-shortening and induction of specific cancers in mice. Since life-shortening in mice was due mainly to induction of cancers, the different endpoints are closely related. Furthermore, compared with studies of other endpoints in various biological systems, RBEs obtained from studies of life-shortening and cancer induction in mice should be the most relevant to estimating REFs for induction of cancers in humans.

Available data on RBE for life-shortening and induction of specific cancers in mice have been reviewed and analyzed by Edwards (1999); see also a report of the NRPB (Edwards, 1997). Estimates of RBE at high acute doses of the reference high-energy gamma rays, RBE_H, and extrapolated values at low doses and low dose rates of the reference radiation, RBE_M, obtained by Edwards are given in Tables 3-5.[14]

[14]Estimates of RBE_H given by Edwards (1997) incorporate an assumed DDREF of 2 for the reference radiations and, thus, are a factor of 2 higher than the values given in the later paper (Edwards, 1999). The values in Edwards (1999) are the appropriate ones for use in this analysis.

Table 3. Estimates of RBE_H and RBE_M of fission neutrons for life-shortening in various strains of mice derived from analysis of selected studies by Edwards (1999)[a]

	RBE_H			RBE_M		
Mouse strain/Reference	LL[b]	Mean	UL[b]	LL[b]	Mean	UL[b]
RF/Un, Upton et al. (1967)[c]	2.5	3.5	4.5	2	3.5	4.5
Female				5	15	55
RFM, Storer et al. (1979)	2.1	2.4	2.7	6.7	7.5	8.3
Female						
BALB/c, Storer and Ullrich (1983)	3.5	4.5	5.5	12	15	18
Female						
B6CF1, Carnes et al. (1989)						
Male	7	8	9	35	50	65
Female	8.5	9.5	10.5	34	45	56

[a]See Table 3 of Edwards (1999). RBE_H is RBE at high doses and high dose rates of reference high-energy gamma rays, and RBE_M is RBE at low doses and low dose rates obtained by extrapolation of data on dose-response for neutrons and the reference radiation. Life-shortening in these studies was due mainly to induction of cancers. When two sets of values are given, they represent alternative interpretations that are consistent with the data.

[b]LL and UL are lower and upper 68% confidence limits on the mean, respectively, corresponding to one standard error.

[c]Results from study using *X* rays as reference radiation are omitted.

The data in Tables 3-5 illustrate two points noted previously. First, RBEs at high doses and high dose rates, RBE_H, usually are less than the extrapolated values at low doses and dose rates, RBE_M, due primarily to the influence of DDREF of the reference radiation on RBE_M. Second, the variability in RBE_H is less than the variability in RBE_M, due primarily to the reduced influence at high doses and dose rates of differences in DDREFs of the reference radiations. For example, in the studies summarized in Tables 3 and 4, DDREF estimated as the ratio of the mean value of RBE_M to the mean value of RBE_H varies from 1 to nearly 20.

The available data for fission neutrons also indicate that RBEs for leukemias and related diseases tend to be less than RBEs for solid tumors (NCRP, 1990; Edwards, 1997; Edwards, 1999). This difference is indicated, for example, by the RBEs for specific cancers in RF/Un and RFM mice given in Table 4. Given this difference, we have developed separate probability distributions for solid tumors and leukemias based on RBEs for the two types of cancers.

Table 4. Estimates of RBE_H and RBE_M of fission neutrons for induction of specific cancers in various strains of mice derived from analysis of selected studies by Edwards (1999)[a]

Mouse strain	Cancer	RBE_H			RBE_M		
		LL[b]	Mean	UL[b]	LL[b]	Mean	UL[b]
RF/Un	Myeloid leukemia	1.7	2.8	4.7	9	19	38
	Lymphoma	2.2	2.9	3.7	2.7	4.7	5.6
RFM							
Male	Myeloid leukemia	2.2	2.8	3.8	—	—	—
Female	Thymic leukemia	3.3	4.1	5.1	12	29	64
	Harderian gland tumor	7	9	11	22	33	47
	Pituitary tumor	5	7	10	17	120	∞
BALB/c							
Female	Lung adenocarcinoma	5.5	7.5	10	12	20	30
	Mammary tumor	2.5 6	3.5 11	5 20	18	27	41
CBA/H	Myeloid leukemia	4	7	10	14	21	36
SAS/4							
Male	Lung adenocarcinoma	3	5	9	—	—	—
Female	Lung adenocarcinoma	5	8	14	—	—	—

[a]See Table 4 of Edwards (1999). RBE_H is RBE at high doses and high dose rates of reference high-energy gamma rays, and RBE_M is RBE at low doses and low dose rates obtained by extrapolation of data on dose-response for neutrons and the reference radiation. When two sets of values are given, they represent alternative interpretations that are consistent with the data. Analysis was based on data given in Upton et al. (1970), Ullrich et al. (1976; 1977; 1979), Ullrich (1980; 1984), Ullrich and Preston (1987), Mole and Davids (1982), Mole et al. (1983), and Coggle (1988).

[b]LL and UL are lower and upper 68% confidence limits on the mean, respectively, corresponding to one standard error.