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.

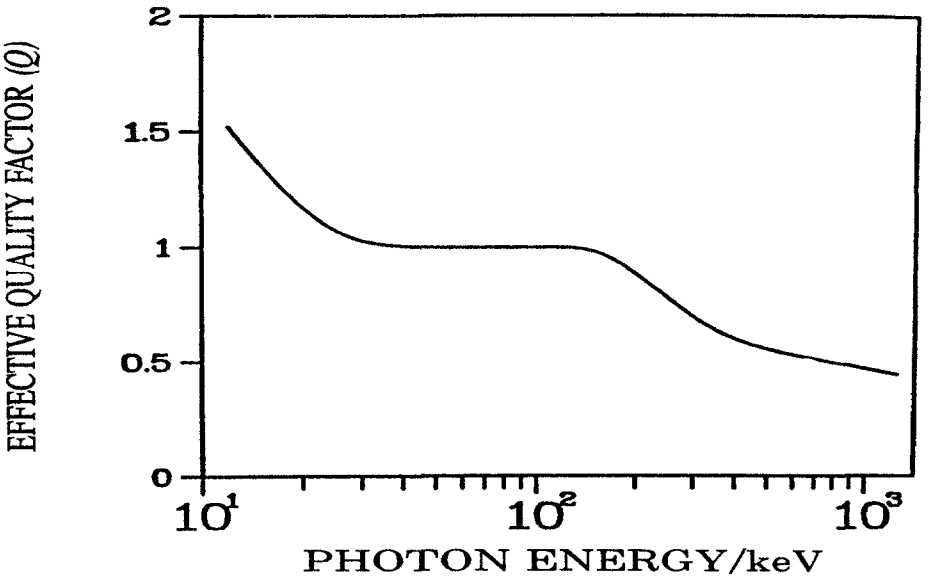

Fig. 1. Calculated effective quality factor, $\overline{Q}$, vs. photon energy under conditions of charged-particle equilibrium given in Fig. 3 of ICRU (1986). Values are normalized to unity at energies of orthovoltage *X* rays often used in radiobiological studies; energies of gamma rays emitted in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

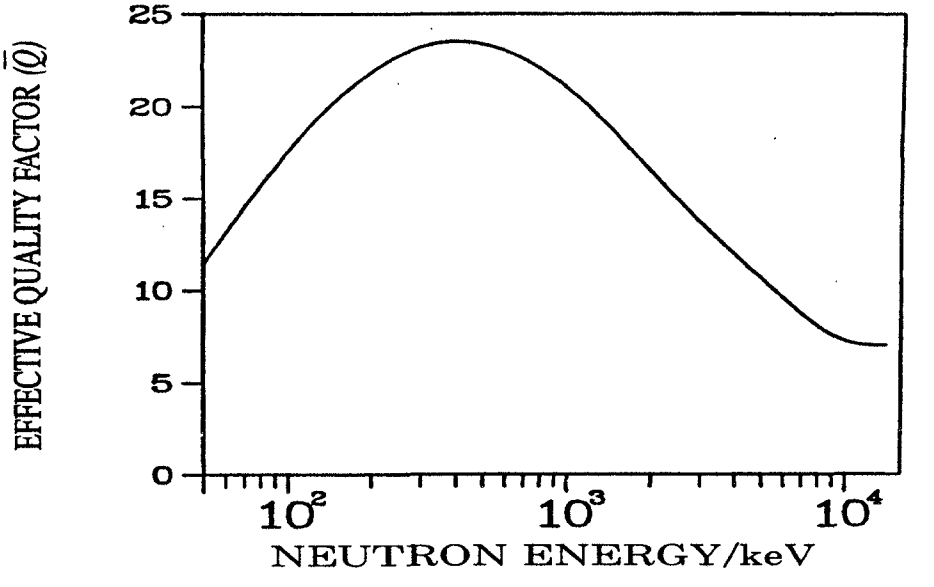

Fig. 2. Calculated effective quality factor, $\overline{Q}$, vs. neutron energy under conditions of charged-particle equilibrium given in Fig. 4 of ICRU (1986).

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.

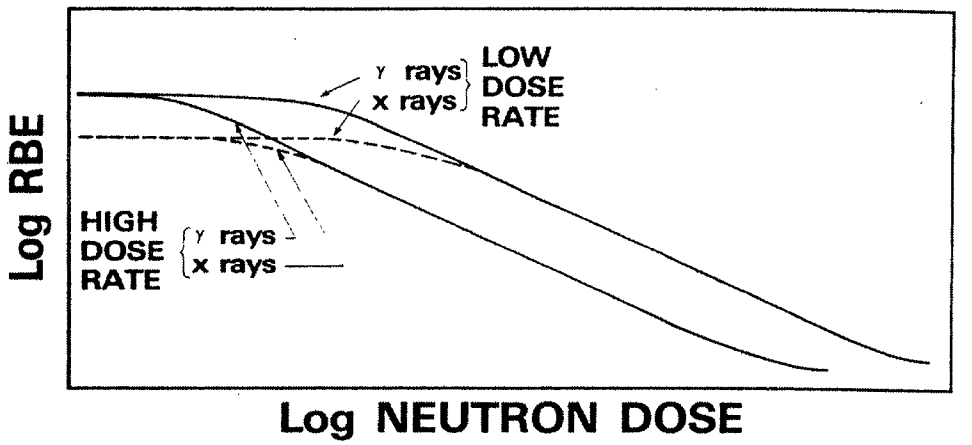

Fig. 3. Schematic representation of increase in RBE for fission neutrons with decreasing dose given in Fig. C-2 of ICRU (1986). Maximum values at low doses are values of RBE_M.

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.

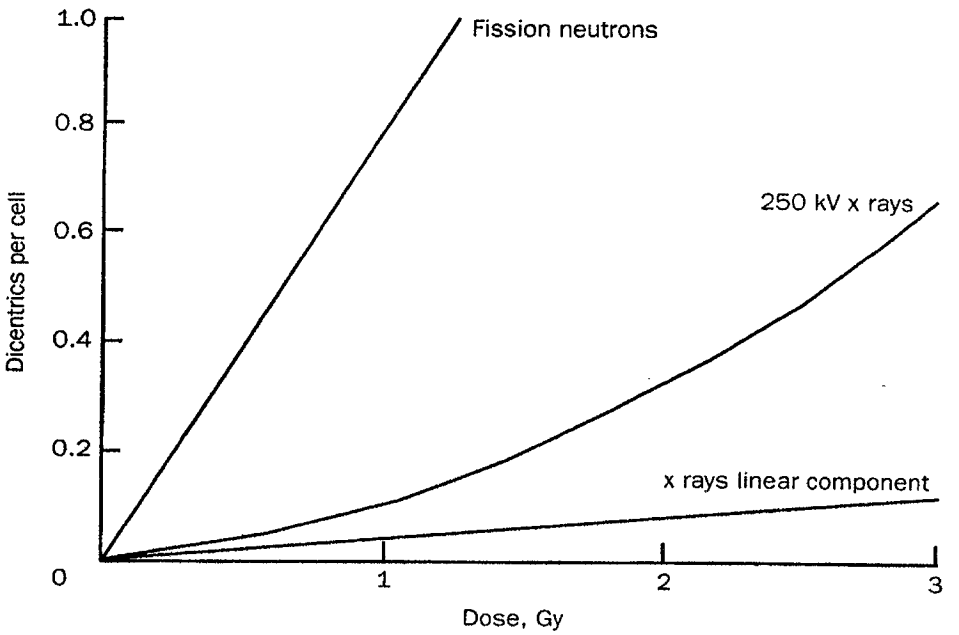

Fig. 4. Representation of linear and linear-quadratic dose-response relationships for fission neutrons and *X* rays, respectively, given in Fig. 1 of Edwards (1997). Separation of two curves at different levels of response illustrates dependence of RBE on dose (see Fig. 3); RBE at low doses, RBE_M, is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

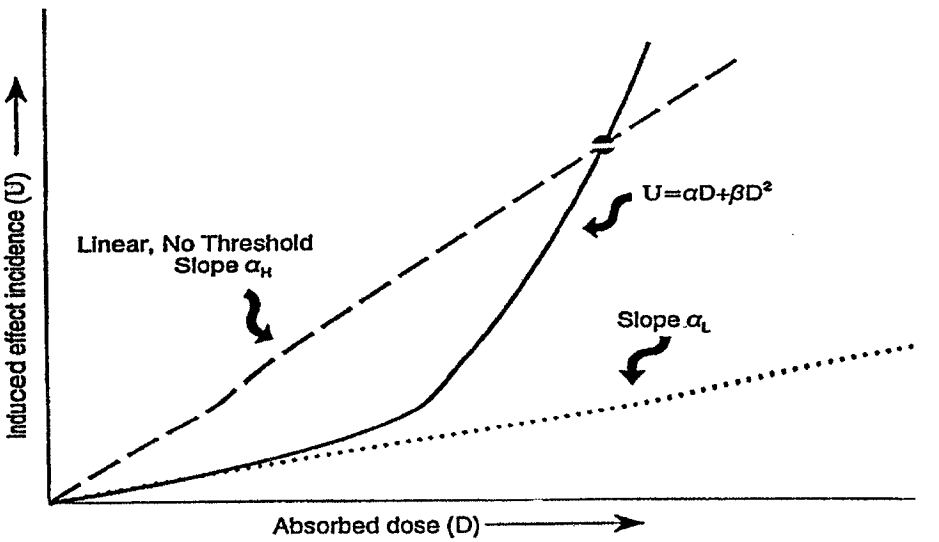

Fig. 5. Representation of linear-quadratic dose-response relationship for low-LET radiations given in Fig. 2 of CIRRPC (1995). Dose and dose-rate effectiveness factor (DDREF) is ratio of linear extrapolation at high doses, α_H, to slope of dose-response curve at low doses, α_L; DDREF thus is a function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

Table 5. Estimates of RBE_H and RBE_M of fission neutrons for tumor induction in B6CF1 mice derived from analysis of selected study by Edwards (1999)[a]

Tumor	Times of death (days after irradiation)	Sex	RBE_H[b]	RBE_M[b]
Lymphocytic	600-799	Male		6.6 ± 1.8
			2.0 ± 0.3	20 ± 5
			5.7 ± 0.9	12 ± 4
				36 ± 13
		Female	5.4 ± 0.6	8.4 ± 0.7
			11.4 ± 0.6	17.8 ± 1.5
	800-999	Male	2.5 ± 0.5	9.7 ± 1.5
			6.5 ± 1.1	25.2 ± 3.2
		Female	8.5 ± 3.0	8.5 ± 1.8
			17 ± 5	15.8 ± 2.6
Vascular tissue	600-799	Male	4.7 ± 0.6	13.9 ± 2.6
		Female	3.7 ± 1.0	7.2 ± 3.2
	800-999	Male	4.8 ± 1.0	13.7 ± 1.6
		Female	6.4 ± 1.4	8.9 ± 2.0
All epithelial tissue or ovary	600-799	Male	5.5 ± 1.0	23 ± 5
			11.0 ± 1.5	45 ± 7
		Female	10.5 ± 1.5	23 ± 4
	800-999	Male	6.2 ± 1.3	14.4 ± 2.9
			13.4 ± 2.2	31 ± 5
		Female	9.7 ± 1.9	19 ± 6

[a]See Table 5 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. Analysis was based on data given in Grahn et al. (1992). When two sets of values are given, they represent alternative interpretations that are consistent with the data.

[b]Uncertainties are one standard error.

REF for Fission Neutrons and Solid Tumors

Risks of solid tumors from exposure to neutrons are estimated using eq. (3). The probability distribution of REF_H at high doses and high dose rates of reference high-energy gamma rays is developed based on estimates of RBE_H for solid tumors given in Tables 3-5. The relevant data are those for BALB/c and B6CF1 mice in Table 3, since life-shortening in these mice was due primarily to solid tumors, the various tumors and adenocarcinomas in Table 4, and the non-lymphocytic tumors in Table 5. Based on these data, we assume a lognormal probability distribution of REF_H for fission neutrons and solid tumors having a 95% confidence interval between 2.0 and 30. This distribution, which is shown in Fig. 6, has a geometric mean (median or 50th percentile) and geometric standard deviation of 7.7 and 2.0, respectively. A lognormal distribution was selected based mainly on the variability in estimates of RBE_H and the difficulty in judging a credible upper bound of possible values. Lognormal probability distributions are assumed for several other REFs developed in this report.

Data obtained from studies of tumor induction in other animals are consistent with the probability distribution of REF_H for fission neutrons and solid tumors described above. For example, Wolf et al. (2000) deduced an RBE of about 20-25 for lethal tumors in Sprague-Dawley rats at an acute dose of fission neutrons of 0.1 Gy. In a study in which monkeys were given average doses of 6.7 Gy of *X* rays and 3.4 Gy of fission neutrons, Broerse et al. (1991) derived an RBE for tumor induction of about 4-5. When this RBE is adjusted to account for the difference of about a factor of 2 in the biological effectiveness of *X* rays and gamma rays, as discussed in a later section, an RBE relative to gamma rays of about 8-10 is obtained. Other studies of tumor induction in animals are discussed by the NCRP (1990).

The assumed probability distribution of REF_H for fission neutrons and solid tumors applies to a continuous spectrum of energies that normally ranges from 0.1 to 15 MeV. This spectrum has a most probable energy of 0.8 MeV and an average energy of 2.0 MeV (Shleien et al., 1998). As described later in this section, probability distributions of REFs based on RBEs for fission neutrons are assumed to apply at energies of 0.1-2 MeV.

REF for Fission Neutrons and Leukemias

Risks of leukemias and related diseases, including lymphomas and lymphocytic cancers, from exposure to neutrons are estimated using eq. (2). The probability distribution of REF_L at low doses and low dose rates of reference high-energy gamma rays is developed based on estimates of RBE_M for leukemias given in Tables 3-5. The relevant data are those for RF/Un and RFM mice in Table 3, since life-shortening in these mice was due primarily to leukemias, lymphoma and the various leukemias in Table 4, and lymphocytic tumors in Table 5. Based on these data, we assume a lognormal probability distribution of REF_L for fission neutrons and leukemias having a 95% confidence interval between 2.0 and 60. This distribution has a geometric mean and geometric standard deviation of 11 and 2.4, respectively; it resembles the distribution shown in Fig. 6, except it is more highly skewed toward lower values.

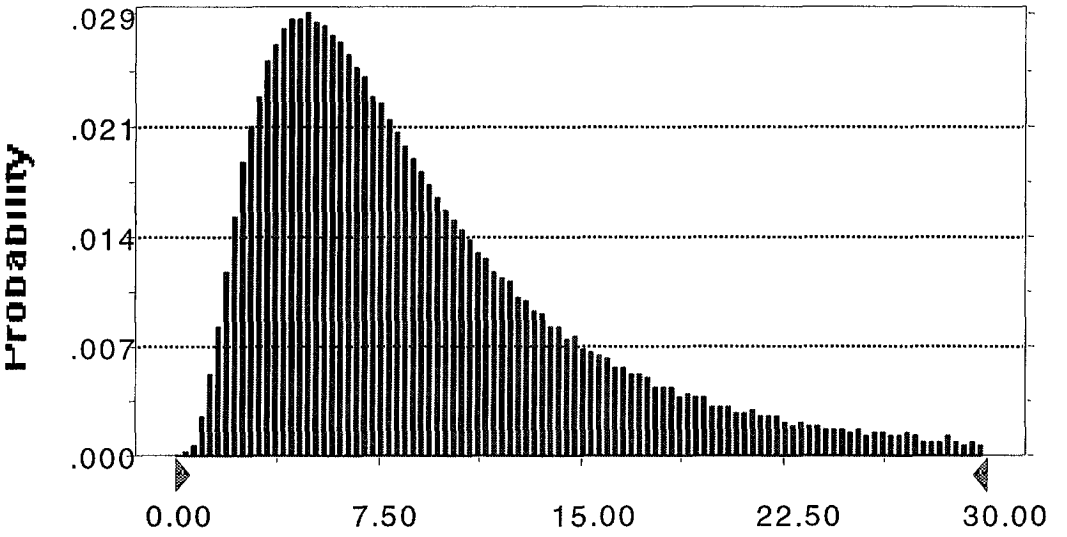

Fig. 6. Assumed lognormal probability distribution of radiation effectiveness factor at high doses and high dose rates of reference high-energy gamma rays, REF_H, for induction of solid tumors by fission neutrons having a 95% confidence interval between 2.0 and 30. Median (50th percentile) of distribution is at 7.7, and 2.5% of values lie beyond 30.

Comparison of REFs for Fission Neutrons with Radiation Protection Quantities

The probability distributions of REFs for fission neutrons described above can be compared with the effective quality factor, $\overline{Q}$, for neutrons of unknown energy recommended by the ICRU (1986) and the radiation weighting factor, w_R, for neutrons of energy 0.1-2 MeV recommended by the ICRP (1991) and the NCRP (1993); see Table 1. The point values of $\overline{Q}$ and w_R are based on estimates of RBE_M and, thus, are directly comparable to the probability distribution of REF_L for leukemias. If we use a $DDREF_\gamma$ of 2 as normally assumed in radiation protection (ICRP, 1991; NCRP, 1993), the probability distribution of REF_H for solid tumors corresponds to a distribution of REF_L having a 95% confidence interval between 4.0 and 60.[15] Therefore, the assumed probability distributions of REFs for fission neutrons encompass the point values of the recommended radiation protection quantities.[16]

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[15]This confidence interval does not represent the range of estimates of RBE_M for fission neutrons obtained from analyses of radiobiological studies, because DDREF for the reference radiation often differed greatly from the value of 2 assumed here. As illustrated in Tables 3-5, upper confidence limits of RBE_M considerably greater than 60 are obtained in some studies (see also Table 2).

[16]The point values $w_R = 20$ and $\overline{Q} = 25$ in Table 1 are at about the 70th and 80th percentiles, respectively, of the inferred probability distribution of REF_L for solid tumors, and are at about the 75th and 85th percentiles of the probability distribution of REF_L for leukemias, respectively.

REFs at Other Neutron Energies

Estimation of cancer risks in humans from exposure to neutrons is complicated by the apparent dependence of RBEs on neutron energy. This energy dependence is represented by the radiation weighting factors currently recommended by the ICRP (1991) and the NCRP (1993) for use in radiation protection (see Table 1 and Fig. 7). In comparison, quality factors at different neutron energies currently used by the U.S. Nuclear Regulatory Commission (NRC, 1991) and the U.S. Department of Energy (DOE, 1993) are given in Table 6. These quality factors were developed by the NCRP (1971) based on calculated depth-dose distributions in a cylindrical phantom or tissue slab at incident neutron energies of 0.025 eV to 400 MeV. The recommended radiation weighting factors and the quality factors used by regulatory authorities in the U.S. indicate that the probability distributions of REFs for fission neutrons described above apply at energies where the biological effectiveness is the highest.

The reductions in the radiation weighting factor by a factor of 2 or 4 at neutron energies outside the range of 0.1-2 MeV recommended by the ICRP (1991) and the NCRP (1993) are based mainly on limited data on the energy dependence of RBE_M obtained from studies in animals and cell cultures, which are reviewed by the NCRP (1990) and the NRPB (Edwards, 1997), and calculations of the energy dependence of the neutron quality factor, such as those shown in Fig. 2 (ICRU, 1986) and given in Table 6 (NCRP, 1971). The variation of RBE_M with neutron energy is illustrated by the data shown in Figs. 8 and 9 (Edwards, 1997; 1999).

The ICRP (1991) also suggested that its recommended step function for the radiation weighting factor given in Table 1 can be represented by a smooth function of the form

$$w_R = 5 + 17\exp[-(\ln(2E))^2/6] \ , \qquad (6)$$

where E is the neutron energy in MeV. This relationship is not intended to imply any biological significance, but it does provide a convenient calculational tool when incident neutron energies are well known. The smooth function in eq. (6) is shown with the recommended step function for the radiation weighting factor in Fig. 7.

As indicated by the data shown in Figs. 8 and 9, experimental information on the energy dependence of RBEs for neutrons is sparse. There are a few studies at energies of 10-100 keV or 2-20 MeV. However, reviews by the NRPB (Edwards, 1997) and the NCRP (1990) did not provide any data on RBEs at energies less than 10 keV or greater than 20 MeV. Thus, based on available data, there is considerable uncertainty in REFs that would represent the biological effectiveness of neutrons in these energy ranges relative to fission neutrons.

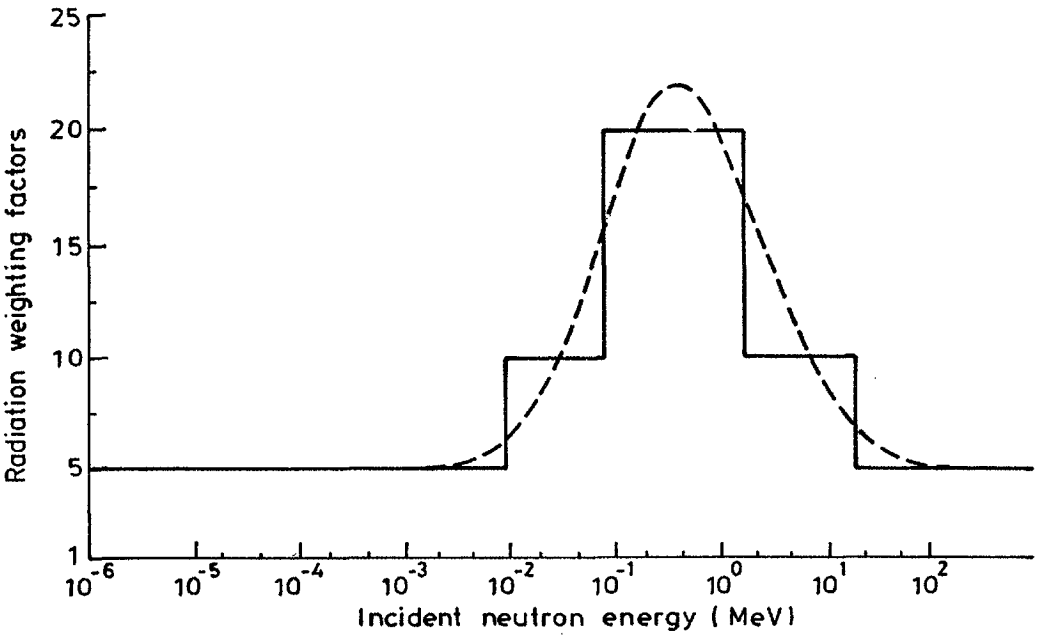

Fig. 7. Radiation weighting factor, w_R, vs. neutron energy given in Fig. A.1 of ICRP (1991). Dashed curve is approximation given by eq. (6).

Table 6. Quality factors for neutrons currently used by U.S. Nuclear Regulatory Commission and U.S. Department of Energy[a]

Neutron energy (MeV)	Mean quality factor	Neutron energy (MeV)	Mean quality quality
≤0.001	2	10	6.5
0.01	2.5	14	7.5
0.1	7.5	20	8
0.5	11	40	7
1	11	60	5.5
2.5	9	100	4
5	8	≥200	3.5
7	7		

[a]Values given in NRC (1991) and DOE (1993) are based on calculations and recommendations by the NCRP (1971).

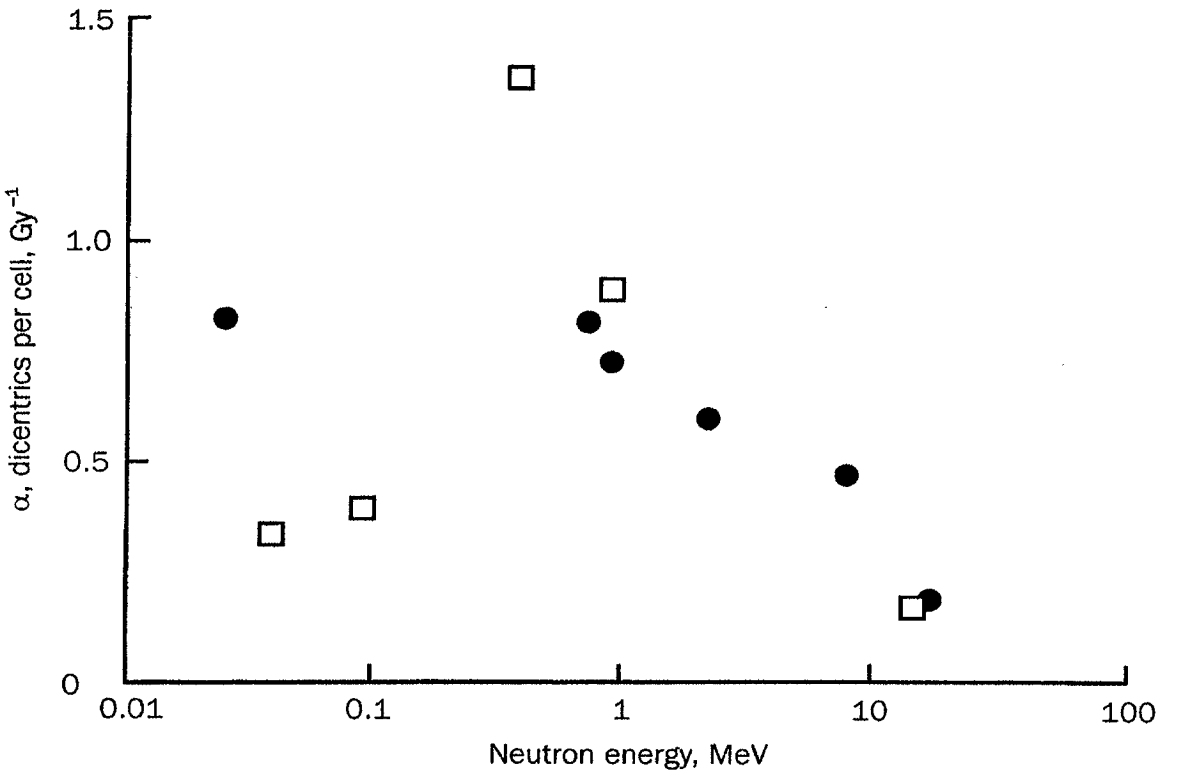

Fig. 8. Variation of RBE_M with neutron energy for induction of dicentric chromosomes in human lymphocytes given in Fig. 6 of Edwards (1997; 1999). Solid circles are data of Edwards et al. (1985; 1990), and open squares are data of Sevan'kaev et al. (1979).

Given the paucity of data on the energy dependence of RBEs for neutrons, we develop subjective probability distributions of REFs for solid tumors and leukemias at energies other than 0.1-2 MeV based on the probability distributions for fission neutrons developed previously and an assumption that the ICRP's step function representation of the radiation weighting factor shown in Fig. 7 provides a general indication of the energy dependence of REFs. We then assume that the probability distributions of REFs for neutrons at energies other than 0.1-2 MeV should have the following three properties:

[1] The lower bound of each distribution should be at 1.0, based on an assumption that neutrons of any energy should not be less effective than high-energy gamma rays in inducing cancers in humans.

[2] The median (50^{th} percentile) of each distribution should be less than the geometric mean of the appropriate lognormal probability distribution for fission neutrons by a factor of about 2 or 4, based on the ICRP's step function representation of the radiation weighting factor (see Table 1 and Fig. 7).

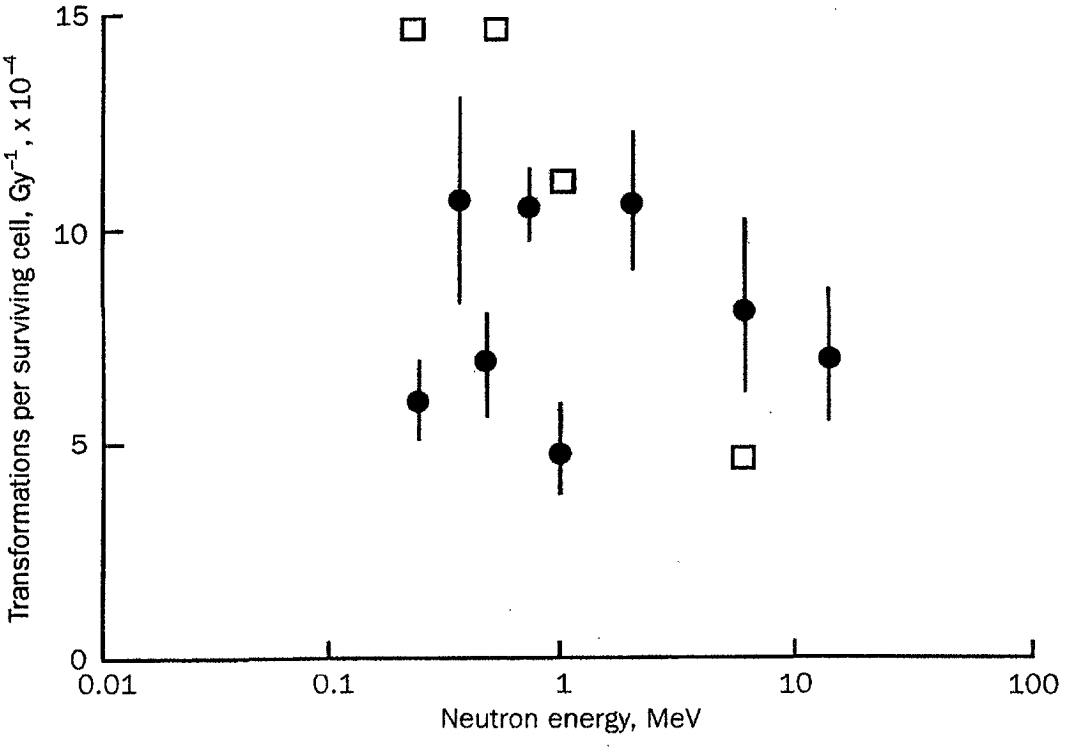

Fig. 9. Variation of RBE_M with neutron energy for transformation of C3H10T½ mouse cells given in Fig. 7 of Edwards (1997). Solid circles are data of Miller et al. (1989), and open squares are data of Coppola (1993); error bars represent one standard error.

[3] The upper 97.5% confidence limit of each distribution should be less than the upper confidence limit of the appropriate distribution for fission neutrons, but by less than a factor of 2 or 4 to take into account that there is substantial uncertainty in the reductions in REFs compared with fission neutrons. Thus, the upper confidence limit relative to the median should increase compared with the ratio of these quantities in the lognormal probability distributions for fission neutrons.

In general, probability distributions of REFs that have these properties must be highly skewed toward values at the low end of an assumed range of values. Only a highly skewed distribution has a fixed lower bound and a decreased median and upper confidence limit but an increased upper confidence limit relative to the median compared with an assumed lognormal distribution for fission neutrons.

There are many probability distributions that can be constructed to represent REFs based on the three properties described above. In the interest of simplicity, we represent the REFs in all

cases by piece-wise uniform (step-function) probability distributions. We assume that each probability distribution has three steps (intervals), and we assign probabilities (weights) of 30% to the first interval, 50% to the second interval, and 20% to the third interval in all cases. The width of each interval in the piece-wise uniform distribution then is adjusted to obtain a distribution in which the median and upper 97.5% confidence limit approximate the desired values. Again, the median is assumed to be about a factor of 2 or 4 less than the median of the appropriate lognormal distribution for fission neutrons, and the reduction in the upper confidence limit is assumed to be less than a factor of 2 or 4. We assume that the upper confidence limit should be reduced by a factor of about 1.7-1.8 when the median is reduced by a factor of 2, and that the reduction should be a factor of $(1.7\text{-}1.8)^2$, or about 3, when the median is reduced by a factor of 4. We believe that reducing the upper confidence limit by a substantially lower factor (e.g., a factor of 1.5 when the median is reduced by a factor of 2) would give too much weight to the uncertainty in the reduction of the median compared with the uncertainty in the appropriate REF for fission neutrons.

The assumed piecewise-uniform probability distributions of REFs for neutrons of energy other than 0.1-2 MeV that have the properties described above are summarized as follows:

E = 10-100 keV or 2-20 MeV (factor of 2 reduction in median) –

Solid tumors (REF_H) –

30% weight to interval from 1.0 to 3.0;
50% weight to interval from 3.0 to 5.0;
20% weight to interval from 5.0 to 20;
Median of 3.8 and upper 97.5% confidence limit of 18.

Leukemias (REF_L) –

30% weight to interval from 1.0 to 4.0;
50% weight to interval from 4.0 to 8.0;
20% weight to interval from 8.0 to 40;
Median of 5.6 and upper 97.5% confidence limit of 36.

E < 10 keV or > 20 MeV (factor of 4 reduction in median) –

Solid tumors (REF_H) –

30% weight to interval from 1.0 to 1.6;
50% weight to interval from 1.6 to 2.4;
20% weight to interval from 2.4 to 12;
Median of 1.9 and upper 97.5% confidence limit of 11.

Leukemias (REF_L) –

30% weight to uniform distribution from 1.0 to 2.3;
50% weight to uniform distribution from 2.3 to 3.5;
20% weight to uniform distribution from 3.5 to 25;
Median of 2.8 and upper 97.5% confidence limit of 22.

The assumed probability distribution of REF_L for leukemias at neutron energies of 10-100 keV or 2-20 MeV is shown in Fig. 10. The distributions in the other cases are similar, the differences being in the assumed widths of each interval in a piece-wise uniform distribution.

The probability distributions of REFs for neutrons of energy other than 0.1-2 MeV described above illustrate the important point discussed in the Introduction that the assumed distributions represent states of knowledge about the biological effectiveness of different radiation types. These distributions are defined by the assumed properties of the lower bound, median, and upper confidence limit and the assumption of a particular form of the distribution (piece-wise uniform), but many other plausible distributions that are consistent with the limited data on RBEs could be developed. The assumed piece-wise uniform distributions clearly do not represent frequency distributions of RBEs that would be obtained if repeated radiobiological experiments were performed, nor are they intended to.

In the piece-wise uniform probability distributions described above, some weight is given to the possibility that the REF for a particular cancer type at energies of 10-100 keV or 2-20 MeV is higher than the corresponding REF for fission neutrons (energies of 0.1-2 MeV), and similarly for the REF for a particular cancer type at energies less than 10 keV or greater than 20 MeV compared with the corresponding REF at 10-100 keV or 2-20 MeV. This possibility is supported by the data shown in Figs. 8 and 9, and by the results of a recent study which indicated that the biological effectiveness of 70-keV and 350-keV neutrons was not significantly different (Miller et al., 2000).

In comparing the assumed probability distributions of REFs for solid tumors and leukemias that apply at particular neutron energies, it is important to bear in mind that the REFs for solid tumors apply at high doses and high dose rates of the reference high-energy gamma rays, whereas the REFs for leukemias apply at low doses and dose rates. Consequently, the probability distribution of REF_L for leukemias at a given energy has higher values than the corresponding distribution of REF_H for solid tumors even though, as noted previously, RBEs for leukemias induced by fission neutrons tend to be lower than RBEs for solid tumors. To provide a better comparison, the assumed distributions of REF_H for solid tumors could be increased by a factor of about 2 to yield equivalent distributions of REF_L, based on the DDREF for the reference radiation generally used in radiation protection (ICRP, 1991; NCRP, 1993).

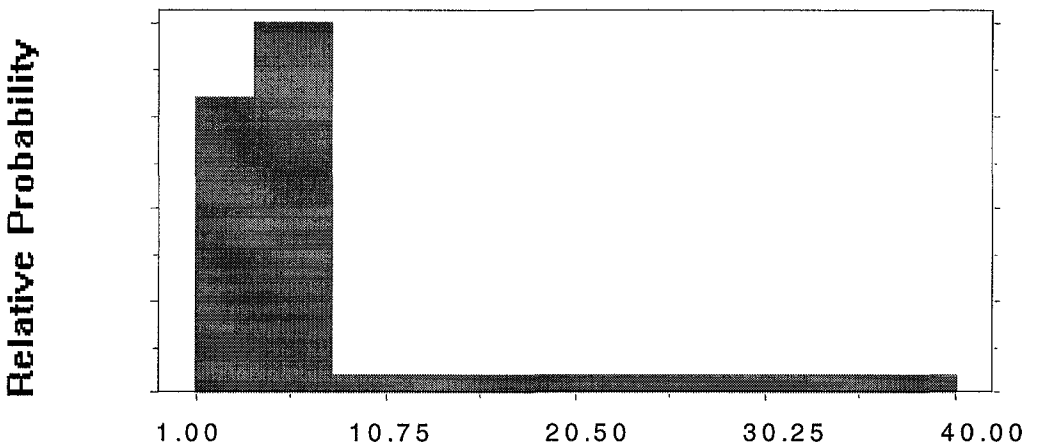

Fig. 10. Assumed piece-wise uniform probability distribution of radiation effectiveness factor at low doses and low dose rates of reference high-energy gamma rays, REF_L, for induction of leukemias by neutrons of energy 10-100 keV or 2-20 MeV. Other probability distributions of REFs for solid tumors and leukemias at neutron energies other than 0.1-2 MeV are similar.

Correction for Inverse Dose-Rate Effect

An additional consideration in estimating cancer risks from exposure to neutrons is the possibility that the biological effectiveness of neutrons and other high-LET radiations increases as the dose rate decreases. This phenomenon is referred to as the inverse dose-rate effect. Some studies of life-shortening and tumor induction in small mammals at relatively high doses of fission neutrons reviewed by the NCRP (1990), the ICRP (1991), and CIRRPC (1995) show an enhancement in biological effectiveness by as much as a factor of about 3 when the same dose is delivered at lower dose rates. However, this effect is not seen in all studies of these endpoints at high doses, and it usually is not seen at lower doses.

Although it is not clear whether the mechanisms responsible for the observed inverse dose-rate effect for fission neutrons in some studies would apply in estimating cancer risks in humans, especially at low doses (CIRRPC, 1995), we apply a small correction to account for this effect. This correction, which we refer to as an enhancement factor, is applied only in cases of chronic exposure to neutrons of any energy; it does not apply to acute exposures.

Based on discussions and summaries of data on life-shortening and tumor induction in mice given in Sections 6 and 8 and Tables 6.2 and 8.2 of NCRP (1990), we assume a probability distribution for the enhancement factor representing an inverse dose-rate effect under conditions of chronic exposure to neutrons that ranges from 1 to 3 and is weighted toward lower values. Specifically, we assume a discrete probability distribution with 50% of the values at 1.0, 30% at 1.5, 15% at 2.0, and 5% at 3.0. The arithmetic mean of this distribution is 1.4. Assigning the

highest weight to the value 1.0 (i.e., an assumption of no inverse dose-rate effect) takes into account that the effect is not seen in all studies at high doses and usually is not seen at low doses of greatest interest in routine exposures of workers and the public.

Applying the assumed probability distribution representing the inverse dose-rate effect to the distributions of REFs shown in Figs. 6 and 10 results in the probability distributions under conditions of chronic exposure to neutrons shown in Figs. 11 and 12.

Summary

At any dose and dose rate of neutrons (n), cancer risks in humans are estimated using the following equations:

Solid tumors –

$$\Re_n = \mathrm{REF}_{n,\mathrm{H}} \times \mathrm{EF}_n \times R_{\gamma,\mathrm{H}} \times D_n \tag{7}$$

Leukemias –

$$\Re_n = a \times \mathrm{REF}_{n,\mathrm{L}} \times \mathrm{EF}_n \times D_n \tag{8}$$

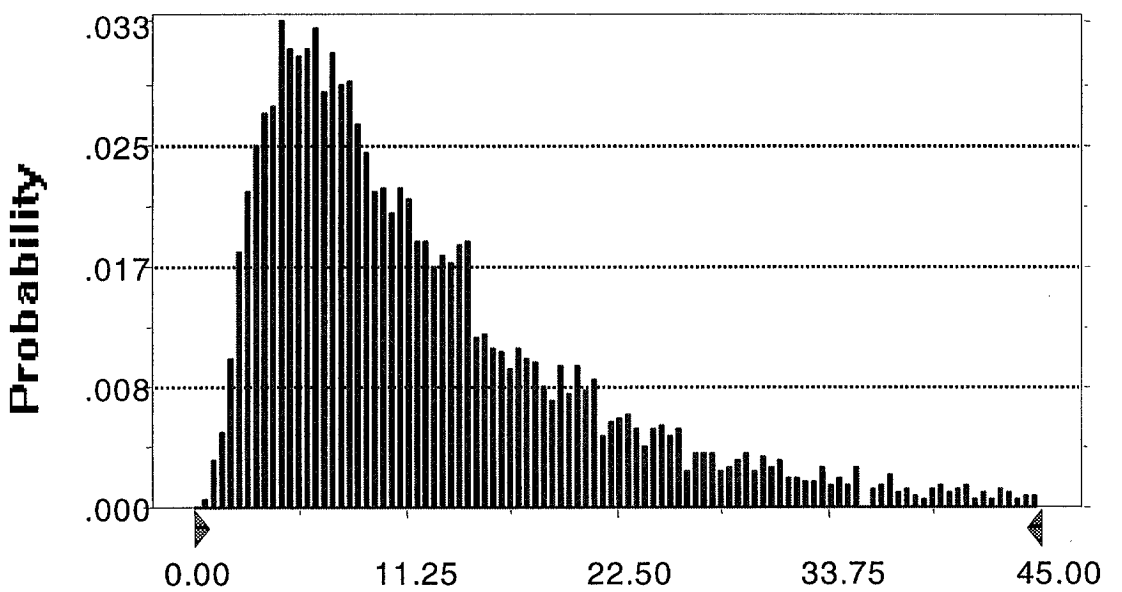

Fig. 11. Assumed probability distribution of $\mathrm{REF_H}$ for fission neutrons and solid tumors shown in Fig. 6 modified by enhancement factor representing inverse dose-rate effect under conditions of chronic exposure. Median of distribution is at 10, and 95% confidence interval lies between 2.4 and 47; about 3% of values lie beyond 45.

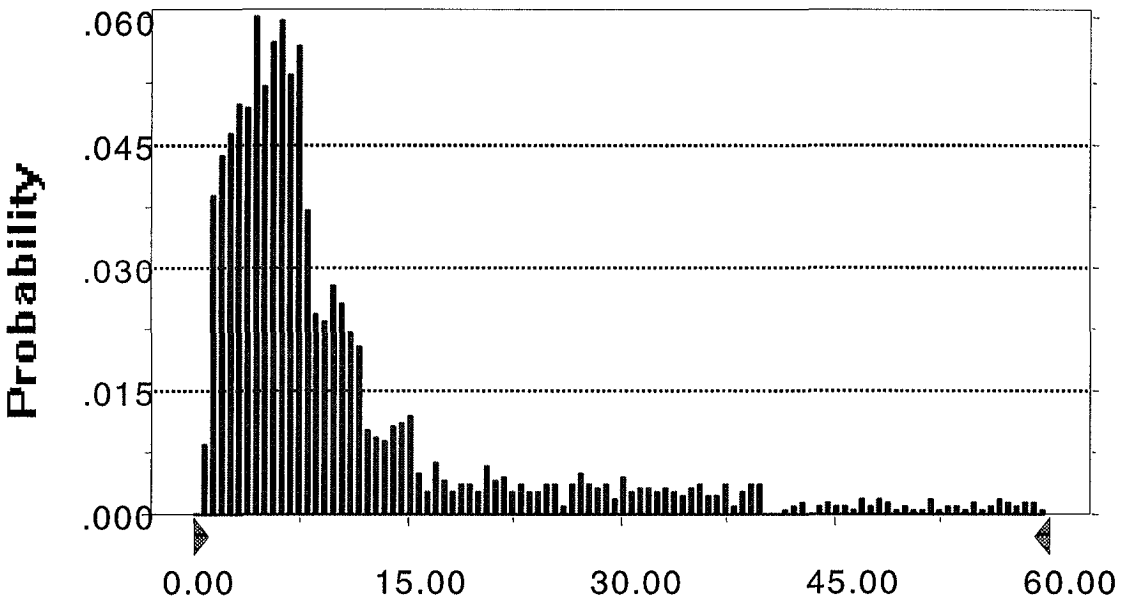

Fig. 12. Assumed probability distribution of REF_L for fission neutrons and leukemias shown in Fig. 10 modified by enhancement factor representing inverse dose-rate effect under conditions of chronic exposure. Median of distribution is at 7, and 95% confidence interval lies between 1.5 and 55; about 1.4% of values lie between 60 and 120.

where $REF_{n,H}$ and $REF_{n,L}$ are the radiation effectiveness factors at high doses and high dose rates and at low doses and dose rates of high-energy gamma rays, respectively, EF_n is the enhancement factor representing an inverse dose-rate effect under conditions of chronic exposure, $R_{\gamma,H}$ is the risk coefficient (ERR per Gy) at high acute doses of high-energy gamma rays for the solid tumor of concern, a is the coefficient of the linear term in the linear-quadratic dose-response relationship for leukemias at high acute doses of high-energy gamma rays, and D_n is the absorbed dose of neutrons in the organ or tissue of concern.

In addition to the distinction between solid tumors and leukemias, which is based on differences in RBEs for the two cancer types as well as the different assumptions about the form of the dose-response relationships at high acute doses of high-energy gamma rays, the REFs for neutrons are assumed to be energy dependent. REFs for five energy ranges are defined, and the energy ranges are those used by the ICRP to define the energy dependence of the radiation weighting factor for neutrons (see Fig. 7). When neutron energies are unknown, the REFs for fission neutrons (0.1-2 MeV) should be used.

The assumed probability distributions of REFs for neutrons and the enhancement factor representing the inverse dose-rate effect under conditions of chronic exposure to neutrons are summarized in Table 7.

Table 7. Summary of probability distributions of radiation effectiveness factors and enhancement factor for neutrons to be used in estimating cancer risks and probability of causation in accordance with eq. (7) or (8)

Cancer type/ Neutron energy	Probability distribution of radiation effectiveness factor (REF)
Solid tumors	
0.1-2 MeV[a]	Lognormal distribution of REF_H having a 95% confidence interval between 2.0 and 30
10-100 keV; 2-20 MeV	Piece-wise uniform distribution of REF_H with – 30% weight to interval from 1.0 to 3.0; 50% weight to interval from 3.0 to 5.0; 20% weight to interval from 5.0 to 20
< 10 keV; > 20 MeV	Piece-wise uniform distribution of REF_H with – 30% weight to interval from 1.0 to 1.6; 50% weight to interval from 1.6 to 2.4; 20% weight to interval from 2.4 to 12
Leukemias	
0.1-2 MeV[a]	Lognormal distribution of REF_L having a 95% confidence interval between 2.0 and 60
10-100 keV; 2-20 MeV	Piece-wise uniform distribution of REF_L with – 30% weight to interval from 1.0 to 4.0; 50% weight to interval from 4.0 to 8.0; 20% weight to interval from 8.0 to 40
< 10 keV; > 20 MeV	Piece-wise uniform distribution of REF_L with – 30% weight to interval from 1.0 to 2.3; 50% weight to interval from 2.3 to 3.5; 20% weight to interval from 3.5 to 25
Enhancement factor representing inverse dose-rate effect under conditions of chronic exposure	
	Discrete distribution with – 50% weight to value 1.0; 30% weight to value 1.5; 15% weight to value 2.0; 5% weight to value 3.0

[a]Energy range also applies to spectrum of fission neutrons. Distributions of REFs at energies of 0.1-2 MeV should be used when neutron energies are unknown.

In the assumed lognormal distributions of REFs for fission neutrons, there is only a small probability of values less than 1.0, and all values in the assumed piece-wise uniform distributions at other neutron energies are greater than 1.0. Thus, the distributions incorporate an assumption that the biological effectiveness of neutrons is greater than that of high-energy gamma rays. Nonetheless, we acknowledge that the REF could be less than 1.0 when most of the dose is delivered by 2.2-MeV gamma rays emitted following capture of thermalized neutrons by ^{1}H nuclei. This situation could occur when the incident neutron energy is less than about 10 keV, but should not be important at higher energies (NCRP, 1971). The possibility of an REF less than 1.0 at low neutron energies is based on the consideration that the biological effectiveness of 2.2-MeV gamma rays could be somewhat less than that of the reference ^{60}Co gamma rays of lower energies (1.2 and 1.3 MeV) used in radiobiological studies to estimate RBEs (Straume, 1995). However, we do not believe that this difference needs to be taken into account in estimating REFs for neutrons. The reduction in the biological effectiveness of 2.2-MeV gamma rays relative to ^{60}Co gamma rays presumably is less than a factor of 2 (Straume, 1995). This difference should be small compared with possible errors in estimating cancer risks that result from an assumption that the spectrum of photons to which the Japanese atomic-bomb survivors were exposed has the same biological effectiveness as ^{60}Co gamma rays. This assumption is implicit in the REFs for neutrons, and other radiations, developed in this report.

We also acknowledge that the assumed probability distributions of REFs for neutrons could tend to overestimate cancer risks in humans at energies greater than about 0.1 MeV (ICRP, 1997). In studies in small mammals used to estimate RBEs for fission neutrons, a substantial fraction of the dose to target tissues was delivered by high-LET radiations (e.g., recoil protons). In humans, however, more of the dose to deep-lying organs and tissues would be delivered by gamma rays produced by neutron interactions in tissue. Therefore, RBEs obtained from studies in small mammals should tend to overestimate the biological effectiveness of incident fission neutrons in many organs and tissues of humans (ICRP, 1997; Edwards, 1997; Edwards, 1999). We have not adjusted the probability distributions of REFs for neutrons to account for possible differences in biological effectiveness in humans compared with small mammals, mainly because calculations indicate that this difference depends in a complicated way on the neutron energy, the target tissue of concern, and the irradiation geometry (ICRP, 1997).

ALPHA PARTICLES

Approach to Estimating RBEs

Like neutrons, alpha particles are high-LET radiations that have been shown to be considerably more effective than low-LET radiations in inducing stochastic responses in biological systems. Alpha particles also are presumed to have linear dose-response relationships for any endpoints at doses below those where significant cell killing occurs. Thus, in principle, it would be desirable to estimate cancer risks in humans exposed to alpha particles based on estimates of RBE at high acute doses of high-energy gamma rays, RBE_H, in accordance with the

model in eq. (3), for example, as we have done for neutrons, to lessen the influence of variations in DDREFs of the reference radiations. The importance of DDREF is indicated by the pronounced increase in RBEs with decreasing dose of alpha particles in the studies summarized in Fig. 13. As is the case with neutrons, high estimates of RBE at low doses, RBE_M, may be due, at least in part, to high values of DDREF for the reference radiation.

As discussed below, however, most studies of the biological effectiveness of alpha particles did not use high acute doses of gamma rays as the reference radiation. Furthermore, an analysis to estimate RBEs of alpha particles at high acute doses of the reference radiation, similar to the analysis for neutrons by Edwards (1997; 1999), has not, to our knowledge, been performed. Such an analysis is not straightforward, due to the dependence of DDREF of the reference radiation on the chosen value of a high dose (see Fig. 5). Therefore, for alpha particles, we developed probability distributions of REFs at low doses and low dose rates of the reference radiation, REF_L, based on estimates of RBE_M obtained from various studies. As is the case with neutrons, the available data for alpha particles indicate that RBEs for leukemias are less than RBEs for solid tumors, and we have developed separate probability distributions of REF_L for solid tumors and leukemias based on RBEs for the two types of cancers.

Alpha particles are somewhat simpler than neutrons in that the range of energies that occur in radioactive decay is limited. A calculation of the energy dependence of the effective quality factor by the ICRU (1986), shown in Fig. 14, indicates that the biological effectiveness of alpha particles is nearly independent of energy over the energy range of concern. Therefore, we have assumed that the probability distributions of REF_L for solid tumors and leukemias can be applied to all alpha particles that occur in radioactive decay.

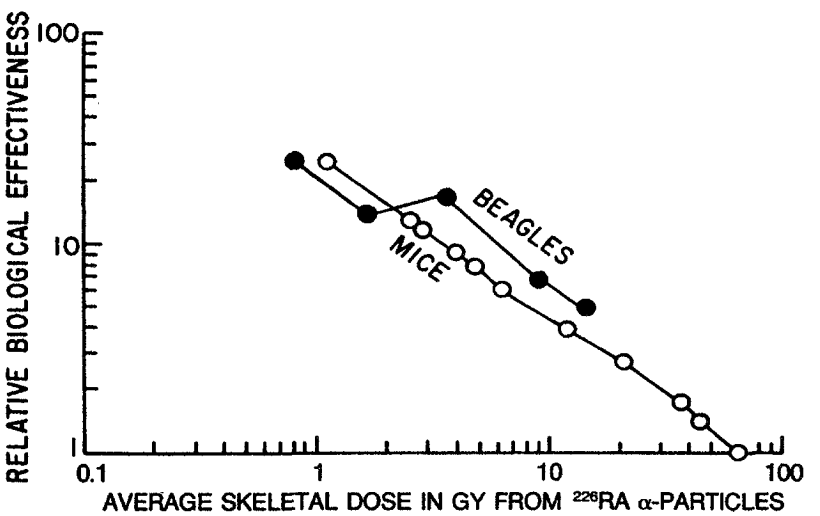

Fig. 13. Biological effectiveness of alpha particles emitted by ^{226}Ra, relative to beta particles emitted by ^{90}Sr and ^{90}Y, for induction of bone tumors in mammals given in Fig. 7.3 of NCRP (1990); curves show pronounced dependence of RBE on dose.

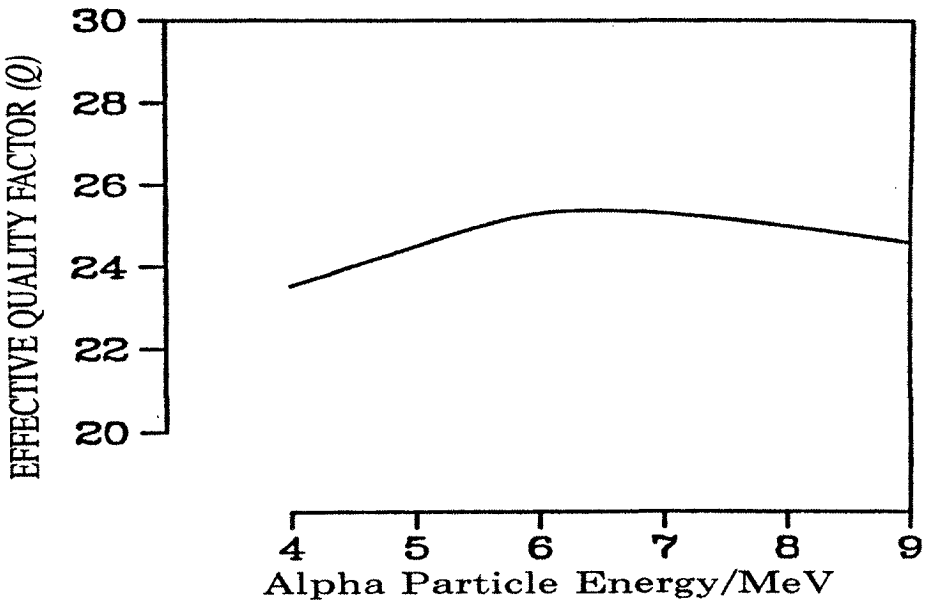

Fig. 14. Calculated effective quality factor, $\overline{Q}$, vs. alpha particle energy given in Fig. 5 of ICRU (1986). Values apply to entire range of alpha particles of given initial energy.

REF for Solid Tumors

Data on RBEs for alpha particles that are potentially relevant to induction of solid tumors in humans have been reviewed by the NCRP (1990) and the NRPB (Muirhead et al., 1993); see also Sinclair (1996). Compared with neutrons, a complicating factor in estimating RBEs for alpha particles is that the reference radiation in most studies was not high-energy gamma rays. In some studies in mammalian cells, the reference radiation was *X* rays, and in studies of bone or lung tumors in mammals, the reference radiation usually was the continuous spectrum of beta particles emitted in decay of ^{90}Sr and ^{90}Y, which have an average energy is 565 keV (Kocher, 1981), or other radionuclides. However, the difference between using electrons from beta decay and high-energy gamma rays as the reference radiation may not be significant, because studies discussed in Section 7.3 of NCRP (1990) indicated that beta particles from ^{144}Ce decay (average energy of 226 keV) and protracted ^{60}Co gamma rays are equally effective in producing chromosome aberrations in liver cells of hamsters.

The derivation of RBEs based on studies of induction of bone tumors in mammals by alpha-emitting radionuclides compared with beta-emitting ^{90}Sr and ^{90}Y is further complicated by differences in the distributions of the study and reference radionuclides in cortical and trabecular bone compared with bone surfaces. These differences are important because the radiosensitive tissues in bone are located near the surface and alpha particles and beta particles have short

ranges in tissue. For example, ^{239}Pu appears to be about 15 times more effective than ^{226}Ra in inducing bone tumors in mice and dogs when toxicity is estimated based on the average skeletal dose (NCRP, 1990). However, this difference is due mainly to the deposition of radium and strontium throughout the volume of bone, in contrast to plutonium which remains on bone surfaces. Similar effects are shown in studies of the toxicity of other alpha-emitting radionuclides in bone including, for example, ^{241}Am and ^{243,244}Cm (NCRP, 1990).

Estimates of RBE_M for alpha particles obtained from reviews and analyses by the NCRP (1990) and the NRPB (Muirhead et al., 1993) are summarized in Table 8. This summary also includes estimates obtained in an earlier analysis by the ICRP (1980). The RBEs in Table 8 are central estimates, and they vary from about 5 to nearly 100 (see footnote b). Based on these data, and taking into account that there is uncertainty in the central estimates, we assume a lognormal distribution of REF_L for alpha particles and solid tumors having a 95% confidence interval between 3 and 80. This distribution has a geometric mean (median) of about 15 and a geometric standard deviation of 2.3. A lognormal distribution was selected based mainly on the variability in estimates of RBE_M and the difficulty in judging a credible upper bound of possible values.

In a previous analysis of selected data, including consideration of estimated risks of lung cancer in underground miners who were exposed to alpha-emitting radon decay products (National Research Council, 1988) compared with estimated risks of lung cancer in Japanese atomic-bomb survivors who were exposed mainly to high-energy gamma rays (Shimizu et al., 1990), the EPA (1999) adopted a lognormal probability distribution of REF_L for alpha particles and solid tumors (referred to as an "RBE" by the EPA) having a 90% confidence interval between 5 and 40. The geometric mean of the EPA's distribution is 14 and the 95% confidence interval lies between 4.1 and 49. The lower confidence limit in our probability distribution is similar to the EPA's, except we have assumed a slightly lower value to account for uncertainties in the lowest estimates of RBE_M. The upper confidence limit in our probability distribution is substantially higher than in the EPA's; our assumption is based on the considerations that several estimates of RBE_M in Table 8 are in the range of about 20-40 and the early estimates for insoluble plutonium and lung cancer in mammals by the ICRP (1980) included values in the range of about 60-100. However, since the high estimates of RBE_M for insoluble plutonium and lung cancer have not been seen in more recent studies, only a small weight is given to values greater than 80 in our distribution.

With the exception of exposure of the lung to radon and its short-lived decay products noted in the Introduction, the assumed probability distribution of REF_L described above is used to estimate risks of solid tumors in humans at low doses and low dose rates of alpha particles in accordance with eq. (2). Since alpha-emitting radionuclides of concern in exposures of workers and the public, excluding radon, have half-lives of at least 0.5 years and are tenaciously retained in the body, acute exposure to alpha particles emitted by inhaled or ingested radionuclides should not be of concern. External exposure generally is not a concern for alpha particles emitted by radionuclides, due to the short range of these radiations in matter.

Table 8. Estimates of RBE_M for alpha particles obtained from reviews and analyses of selected studies by the NCRP (1990) and Muirhead et al. (1993)[a]

Endpoint	RBE_M	Reference
Lung tumors (various species)	30 (6-40)	ICRP (1980)[b]
Bone tumors (dogs)	26	NCRP (1990)[c]
Bone tumors (mice)	25	NCRP (1990)[c]
Lung tumors (dogs)	30-60	NCRP (1990)[d]
Bone tumors (dogs)	4-6	Griffith et al. (1991)
Lung tumors (rats)	25	Hahn et al. (1991)
Lung tumors (dogs)	36	Hahn et al. (1991)[e]
Cell transformation (C3H10T½ mouse cells)	10-25	Brenner (1990)
Cell mutation (Chinese hamster cells, V79)	Up to 18	Thacker et al. (1979)
Chromosome aberrations (liver cells of Chinese hamster)	15-20	Brooks et al. (1972); Brooks (1975)
Chromosome aberrations (human lymphocytes)	5-35	Edwards et al. (1980); Purrott et al. (1980)
Germ cell mutations (chromosome fragments, chromosome translocations, dominant lethals)	22-24	Searle et al. (1976)

[a]Adapted from data presented in Section 7 of NCRP (1990) and Table 7.3 of Muirhead et al. (1993). RBE_M is RBE at low doses and low dose rates of the reference radiation obtained by extrapolation of data on dose-response for alpha particles and the reference radiation at high doses. The reference radiation in all studies was either beta particles from decay of radionuclides, including $^{90}Sr/^{90}Y$ and ^{144}Ce, or high-energy gamma rays from decay of ^{60}Co.

[b]Range is based on analyses of dose-response at 10% and 40% lung tumor incidence for inhalation of soluble and insoluble alpha-emitting radionuclides combined; estimates based on analyses for inhalation of insoluble ^{239}Pu oxide only range from about 10 to about 60-100.

[c]Estimate based on re-analysis of preliminary data given in Mays and Finkel (1980).

[d]Range based on preliminary estimates given by Boecker et al. (1988) and Griffith et al. (1987); value toward upper end of range is not supported by subsequent analysis by Hahn et al. (1991), and value from Boecker et al. (1988) could be as low as 10.

[e]Estimate based on subsequent analysis of data given in Boecker et al. (1988) and Griffith et al. (1987).

REF for Leukemias

In contrast to the case of alpha particles and solid tumors discussed above, there are data in humans that can be used to infer an REF for alpha particles and leukemias. As discussed below, the data seem to indicate that the REF for leukemias is substantially less than the REF for solid tumors. However, interpretation of the available data is problematic, owing to difficulties in separating the issue of estimating absorbed doses of alpha particles in bone marrow from the issue of biological effectiveness. These issues are related to the question of where radiosensitive cells in bone marrow are located relative to the locations of alpha-emitting radionuclides on bone surfaces or within bone marrow.

Studies of medical patients who were administered Thorotrast[17] and experienced an excess of leukemias are a potentially important source of information on the REF for alpha particles. An REF can be inferred by comparing estimated risks of leukemia in Thorotrast patients with an estimated risk at low doses and low dose rates of gamma rays, as derived from data in the Japanese atomic-bomb survivors and an assumed DDREF. Based on an estimated lifetime risk of leukemia of (5-6) $\times 10^{-3}$ Gy^{-1} in Thorotrast patients (National Research Council, 1988) compared with an estimated risk of 5×10^{-3} Gy^{-1} at low doses and dose rates of gamma rays, the EPA initially concluded that the "effective RBE" for alpha particles and leukemia is essentially unity (EPA, 1994; Eckerman et al., 1999). The EPA also noted, however, that the lower than expected leukemia risk in Thorotrast patients may result from a nonuniform distribution of dose within bone marrow such that average doses to sensitive target cells are substantially lower than calculated average doses to bone marrow (EPA, 1994). That is, the low leukemia risk in the Thorotrast patients may reflect the use of models that overestimate dose to radiosensitive cells, rather than a low biological effectiveness of alpha particles.

Subsequent to the EPA's initial estimate of an "effective RBE" of unity for alpha particles and leukemia in Thorotrast patients, Hunacek and Kathren (1995) evaluated the data from several studies and noted that reported doses to bone marrow per unit activity of ^{232}Th administered vary by a factor of about 10. As a result, the estimated risk of leukemia in Thorotrast patients obtained from the various studies ranges from 5×10^{-3} to 6×10^{-2} Gy^{-1}; the best estimate adopted by Hunacek and Kathren is 3×10^{-2} Gy^{-1}. These risks, when compared with an estimated risk of 5×10^{-3} Gy^{-1} at low doses and dose rates of gamma rays, indicate that the REF for alpha particles and leukemia is likely to be substantially greater than unity; a central estimate of REF obtained from these risk estimates ranges from 1 to 12. Based on the analysis by Hunacek and Kathren, a subsequent uncertainty analysis of risk estimates in Thorotrast patients by Grogan et al. (2000; 2001), and taking into account data on RBE for fission neutrons and leukemias in mice (Ullrich and Preston, 1987), the EPA concluded that an RBE for alpha particles and leukemia in Thorotrast patients could be described by a lognormal probability distribution having a 95% confidence interval between 1 and 10 (EPA, 1999).

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[17]Thorotrast is a colloidal form of thorium oxide. Doses from administered Thorotrast are due mainly to alpha particles emitted by ^{232}Th and its decay products ^{228}Th and ^{224}Ra.

It is questionable, however, whether an REF for alpha particles and leukemia inferred from studies of Thorotrast patients can be applied to other exposures to alpha-emitting radionuclides. The difficulty is that Thorotrast occurs as colloidal particles that mostly remain suspended in bone marrow, whereas the various forms of alpha-emitting radionuclides normally encountered in the workplace or the environment are deposited on bone surfaces and, in some cases, are then distributed throughout the volume of cortical and trabecular bone (EPA, 1999). Thus, Thorotrast may be substantially more effective in irradiating radiosensitive cells in bone marrow than other forms of alpha-emitting radionuclides.

An indication that an REF for alpha particles and leukemia inferred from studies of Thorotrast patients may not apply to exposures to more common forms of alpha-emitting radionuclides is provided by the results of studies of other populations that were exposed to alpha emitters. Specifically, studies of radium dial painters who ingested ^{226}Ra and medical patients who were administered ^{224}Ra (National Research Council, 1988) have not shown an excess of leukemias in these populations. When dosimetry models developed by the ICRP are used to estimate an alpha dose to bone marrow from radium deposited in bone, an REF substantially greater than unity (e.g., a central estimate of about 6 based on the Thorotrast data) implies that the leukemia risk in these populations should have been comparable to the estimated risk of bone cancer (EPA, 1999), but no such risk has been seen.

Based on the absence of excess leukemias in populations exposed to radium, the EPA (1999) concluded that an "effective RBE" of about 1 is an upper bound for leukemia in cases of exposure to alpha-emitting radionuclides that deposit on bone surfaces or in bone, and that the uncertainty in this "effective RBE" could be described by a uniform probability distribution between 0 and 1. The EPA also emphasized, however, that this result does not imply that radiosensitive cells in bone marrow are less sensitive to alpha particles than to gamma rays. Rather, this result probably reflects the nonuniform distribution of alpha dose in bone marrow when an alpha emitter is deposited on bone surfaces or in bone.

Interpretation of the studies of leukemias in populations exposed to radium also has its difficulties. The high doses of alpha particles in some cases (e.g., the radium dial painters) may have resulted in substantial cell killing that masked any leukemia risk at lower doses. The potential importance of cell killing on the leukemia risk in Thorotrast patients was noted by Muirhead et al. (1993). Another difficulty is that both the observed incidence of leukemias in the exposed populations and the expected incidence in the absence of radiation exposure were low (about 10 cases or less). Therefore, there is considerable uncertainty in estimates of leukemia risk in these populations, and the possibility of a significant leukemia risk may not be completely ruled out by the data. Finally, some leukemias may have been missed in the radium dial painters, due to incomplete information on the identification of these workers and their causes of death, especially during the early years of the last century.

A third source of information on the REF for alpha particles and leukemias is data on RBEs for fission neutrons and leukemias in mice. These data are relevant because a large

difference in the biological effectiveness of alpha particles and fission neutrons is not expected and has not been demonstrated experimentally (ICRU, 1986; Sinclair, 1985). As noted above, selected data in mice were used by the EPA (1999) to support an assumption about biological effectiveness that applies to exposure situations represented by the Thorotrast patients, i.e., exposures to alpha emitters suspended in bone marrow.

Given the variety of information on the risk of leukemia from exposure to alpha particles discussed above, some of which is seemingly contradictory, we have taken the approach of developing a hybrid probability distribution of REF at low doses and dose rates of the reference radiation, REF_L, that gives some weight to all potentially relevant information. As discussed above, the sources of information include (1) data in the Thorotrast patients, (2) data in other populations exposed to alpha-emitting radionuclides, and (3) data for fission neutrons in mice. We also assume that there is only a small probability that alpha particles would be less effective than high-energy gamma rays in inducing leukemias.

Based on these considerations, we describe REF_L for alpha particles and leukemias by the following hybrid probability distribution:

[1] 50% weight to a lognormal distribution having a 95% confidence interval between 1.0 and 15, based on estimates of leukemia risk in Thorotrast patients;

[2] 25% weight to the value 1.0, based on the EPA's evaluation of leukemia risks in other populations and an assumption that the REF should not be less than 1.0;

[3] 25% weight to the lognormal probability distribution of REF_L for fission neutrons and leukemias, which has a 95% confidence interval between 2.0 and 60.

The median of this distribution is 3.6 and the 95% confidence interval lies between 1.0 and 33. This distribution clearly is a subjective representation of the current state of knowledge, rather than an expected frequency distribution of RBEs that would be obtained based on measurements.

The information on leukemia risks in populations exposed to radium discussed above indicates that the assumed probability distribution of REF_L could result in substantial overestimates of risk to individuals exposed to common forms of alpha-emitting radionuclides when alpha dose to bone marrow is estimated using dosimetry models developed by the ICRP. That is, the "effective RBE" in these cases may be substantially less than unity (EPA, 1999). However, we have given little weight to an assumption that the biological effectiveness of alpha particles is less than that of high-energy gamma rays, essentially because we believe that possible errors in estimating alpha dose to radiosensitive cells of bone marrow should not be incorporated in a representation of biological effectiveness; i.e., considerations of biological effectiveness should be separated from considerations of dosimetry. We have given some weight (25%) to an assumption that alpha particles and gamma rays are equally effective in inducing leukemias, but substantially more weight (75%) is given to an assumption that data in the Thorotrast patients

and RBEs for fission neutrons and leukemias in mice represent the biological effectiveness of alpha particles, given that the radiosensitive cells in bone marrow are irradiated.

Correction for Inverse Dose-Rate Effect

As in the case of neutrons discussed in the previous section, an additional consideration in estimating cancer risks at low doses and dose rates of alpha particles is the possibility of an inverse dose-rate effect, whereby the biological effectiveness at a given dose increases as the dose rate decreases. An analysis of data in humans (underground miners) who were exposed to elevated levels of radon has shown an inverse dose-rate effect that could be as much as a factor of 3 but is more likely less than a factor 2 (Lubin et al., 1995).

Arguments can be made both for and against the need to account for an inverse dose-rate effect in estimating cancer risks from chronic exposure to alpha particles. An argument in favor is that since an inverse dose-rate effect has been observed in some studies of neutrons, the effect, if it exists, should occur with other high-LET radiations. However, there are several opposing arguments. First, an inverse dose-rate effect has not been observed in underground miners at exposures to short-lived alpha-emitting radon decay products less than 50 Working Level Months (WLM) (Lubin et al., 1995).[18] Second, in contrast to studies of neutrons in small mammals, all studies of alpha-emitting radionuclides involved protracted exposures, and estimated RBEs obtained from these studies may already account for an inverse dose-rate effect. Finally, again in contrast to neutrons, RBEs for alpha particles are extrapolated values at low doses and dose rates, RBE_M, and the highest values, which correspond to the highest DDREFs of the reference low-LET radiations, may result in overestimates of cancer risks in humans.

We assume that the probability distributions of RBE_L for alpha particles described previously should be adjusted by a small factor representing a possible inverse dose-rate effect, to be consistent with a similar assumption in cases of chronic exposure to neutrons. However, we give less weight to a possible inverse dose-rate effect for alpha particles compared with neutrons based mainly on two considerations discussed above. First, the data in underground miners do not show an effect at low doses of concern in routine exposures of workers and the public. Second, the probability distributions of REF_L may already incorporate an inverse dose-rate effect when the relevant studies involved protracted exposures to alpha particles. Specifically, we assume a discrete probability distribution for the enhancement factor representing an inverse dose-rate effect for alpha particles with 70% of the values at 1.0, 20% at 1.5, 7.5% at 2.0, and 2.5% at 3.0. The arithmetic mean of this distribution is about 1.2.

As noted previously, all exposures to alpha particles emitted by radionuclides are assumed to be chronic. Therefore, the enhancement factor representing an inverse dose-rate

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[18]Based on conversion coefficients given in Table 4 of ICRP (1987) and Table 6 of ICRP (1993), an exposure to radon decay products of 50 WLM corresponds to an absorbed dose to the bronchial epithelium, where lung carcinomas in underground miners are observed to originate, of about 0.8 Gy.

effect for alpha particles is applied to the probability distributions of REF_L for solid tumors and leukemias in all cases. The resulting probability distributions are shown in Figs. 15 and 16. The result for leukemias in Fig. 16 also is shown as a cumulative probability distribution in Fig. 17. A cumulative distribution often is more informative when a single value is given a high weight relative to all other values. The assumed probability distributions of REF_L for alpha particles, when adjusted to account for an inverse dose-rate effect, encompass the recommended point values of the effective quality factor, $\overline{Q}$, and the radiation weighing factor, w_R, for alpha particles given Table 1.[19]

Summary

Except in cases of exposure of the lung due to inhalation of radon and its short-lived decay products, cancer risks in humans from exposure to alpha particles (α) emitted by radionuclides are estimated using the following equations:

Solid tumors –

$$\mathfrak{R}_\alpha = \mathrm{REF}_{\alpha,\mathrm{L}} \times \mathrm{EF}_\alpha \times \frac{R_{\gamma,\mathrm{H}}}{\mathrm{DDREF}_\gamma} \times D_\alpha \qquad (9)$$

Leukemias –

$$\mathfrak{R}_\alpha = a \times \mathrm{REF}_{\alpha,\mathrm{L}} \times \mathrm{EF}_\alpha \times D_\alpha \qquad (10)$$

where $REF_{\alpha,L}$ is the radiation effectiveness factor at low doses and low dose rates of high-energy gamma rays, EF_α is the enhancement factor representing an inverse dose-rate effect under conditions of chronic exposure, $R_{\gamma,H}$ is the risk coefficient (ERR per Gy) at high acute doses of high-energy gamma rays for the solid tumor of concern, a is the coefficient of the linear term in the linear-quadratic dose-response relationship for leukemias at high acute doses of high-energy gamma rays, $DDREF_\gamma$ is the dose and dose-rate effectiveness factor for gamma rays and other low-LET radiations, and D_α is the absorbed dose of alpha particles in the organ or tissue of concern. Since exposures to alpha-emitting radionuclides are assumed to be chronic, the enhancement factor, EF_α, is applied in all cases.

The assumed probability distributions of REFs for alpha particles and the enhancement factor representing an inverse dose-rate effect are summarized in Table 9.

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[19]The point values $w_R = 20$ and $\overline{Q} = 25$ in Table 1 are at about the 55th and 65th percentiles, respectively, of the probability distribution of REF_L for solid tumors, and lie between the 90th and 95th percentiles of the probability distribution of REF_L for leukemias. We also note that a best estimate of RBE_M for inhaled alpha-emitting radionuclides of 30 derived by the ICRP (1980) from studies in animals (see Table 8) is at about the 70th percentile of the distribution for solid tumors.

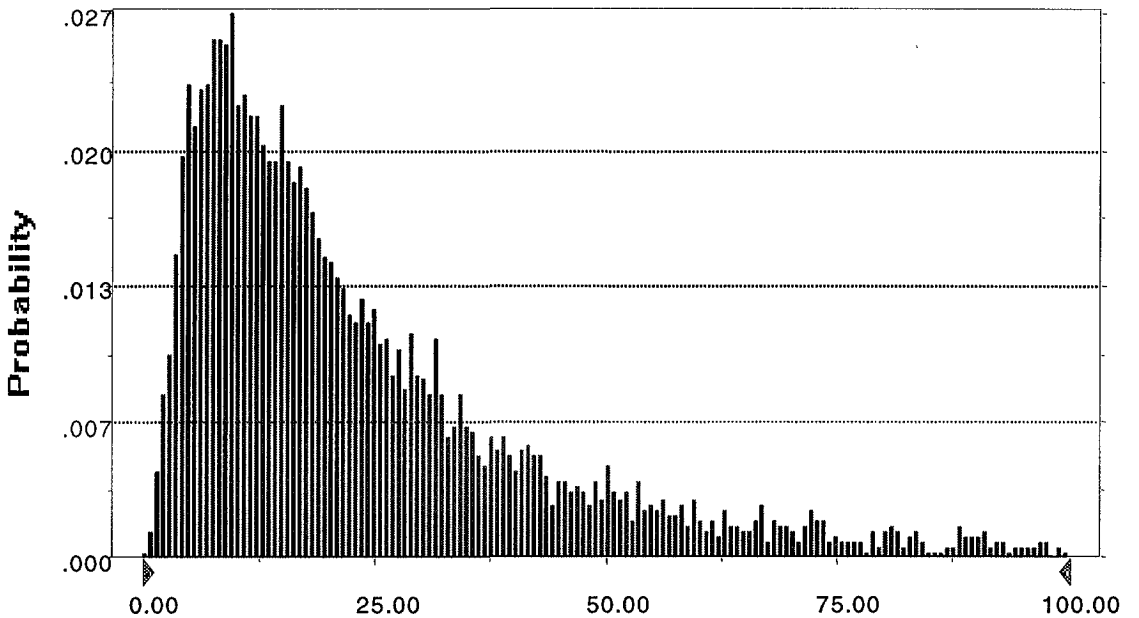

Fig. 15. Assumed probability distribution of REF_L for alpha particles and solid tumors modified by an enhancement factor representing an inverse dose-rate effect under conditions of chronic exposure. Median of distribution is at 18, and 95% confidence interval lies between 3.4 and 101; about 2.5% of values lie beyond 100.

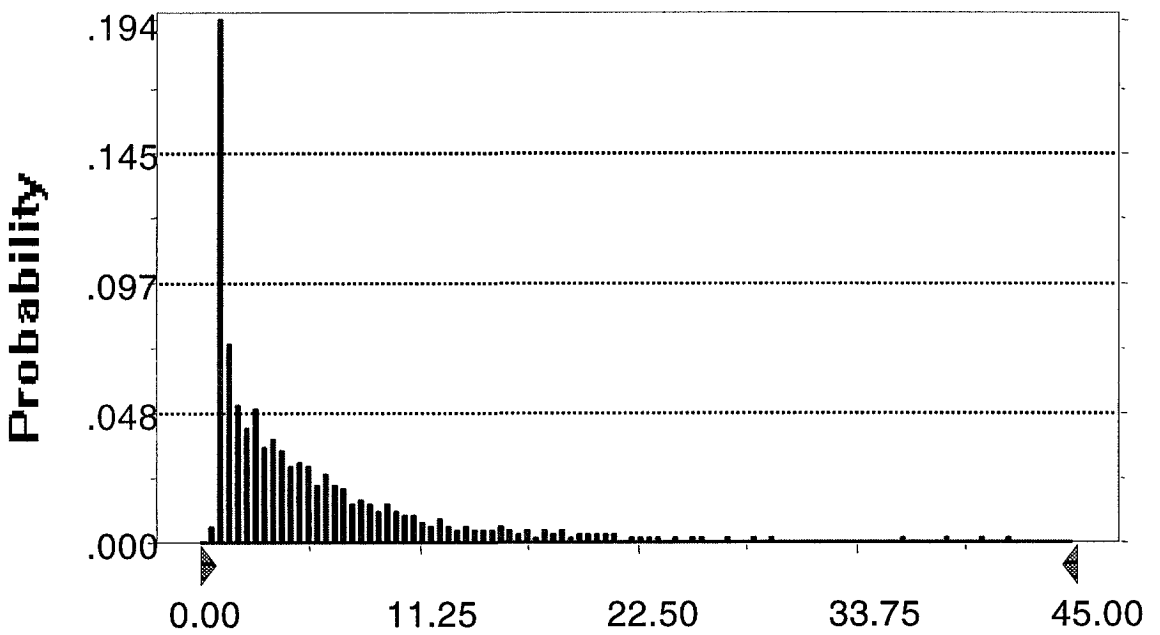

Fig. 16. Assumed probability distribution of REF_L for alpha particles and leukemias modified by an enhancement factor representing an inverse dose-rate effect under conditions of chronic exposure. Median of distribution is at 4.1, and 95% confidence interval lies between 1.0 and 42; about 2.1% of values lie beyond 45.

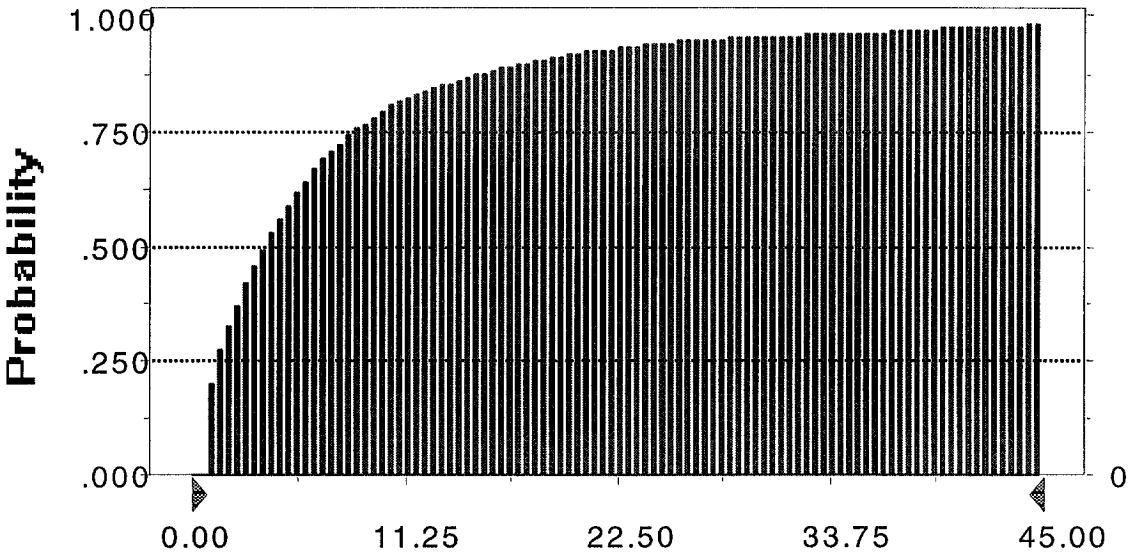

Fig. 17. Assumed probability distribution of REF_L for alpha particles and leukemias modified by an enhancement factor representing an inverse dose-rate effect under conditions of chronic exposure shown in Fig. 16 displayed as a cumulative distribution.

Table 9. Summary of probability distributions of radiation effectiveness factors and enhancement factor for alpha particles to be used in estimating cancer risks and probability of causation in accordance with eq. (9) or (10)

Cancer type	Probability distribution of radiation effectiveness factor (REF_L)
Solid tumors	Lognormal distribution having a 95% confidence interval between 3 and 80
Leukemias	Hybrid distribution with – 50% weight to lognormal distribution having a 95% confidence interval between 1.0 and 15; 25% weight to value 1.0; 25% weight to lognormal distribution having a 95% confidence interval between 2.0 and 60
Enhancement factor representing inverse dose-rate effect for all exposures to alpha particles[a]	
Discrete distribution with – 70% weight to value 1.0; 20% weight to value 1.5; 7.5% weight to value 2.0; 2.5% weight to value 3.0	

[a]All exposures to alpha particles emitted by radionuclides are assumed to be chronic.

PHOTONS

Approach to Estimating RBEs

Compared with neutrons and alpha particles discussed previously and beta particles from decay of ^{3}H discussed in the following section, there are few measurements of the biological effectiveness of orthovoltage *X* rays (and other lower-energy photons) relative to high-energy gamma rays. Furthermore, a review by the NCRP (1990) indicated that only a single stochastic endpoint in mammalian systems (induction of dicentric chromosomes in human lymphocytes) has been studied extensively in investigating the biological effectiveness of *X* rays. Nonetheless, we believe that the available data on chromosome aberrations, supplemented by information obtained from studies of other radiations discussed in this section, provide sufficient evidence to support an assumption that lower-energy photons have a substantially greater biological effectiveness than high-energy gamma rays. As noted in the Introduction, the ICRU (1986) reached the same conclusion. This assumption applies to orthovoltage *X* rays and other photons of similar energies including, for example, 60-keV gamma rays emitted in decay of ^{241}Am.

Cancer risks in humans from exposure to *X* rays and other lower-energy photons are estimated using an approach represented by eq. (2), (4), or (5); eq. (2) is used to estimate risks of solid tumors at any dose and dose rate of photons, and eq. (4) or (5) is used to estimate risks of leukemias under conditions of acute or chronic exposure, respectively. For a given photon energy, the same radiation effectiveness factor at low doses and low dose rates of the reference high-energy gamma rays, REF_L, is used for all cancer types. This approach to estimating cancer risks is based on assumptions that the dose-response relationships for solid tumors and leukemias are of the same form (linear or linear-quadratic) for photons of any energy, and that the same dose and dose-rate effectiveness factor (DDREF) applies to all photons in estimating risks of solid tumors.

Given the assumptions about the dose-response relationships and DDREF for photons of any energy described above, there is no apparent advantage to deriving an REF at high doses and high dose rates of reference high-energy gamma rays, REF_H, for use in the model represented by eq. (3). Furthermore, an analysis to estimate RBEs of *X* rays at high doses and dose rates has not, to our knowledge, been performed. An additional complication that discourages use of the approach to estimating risks represented by eq. (3) is that, in the various radiobiological studies, the reference gamma rays and *X* rays under study often exhibit non-linear dose-response relationships. As a consequence, the DDREFs for the two radiations in a given study often differ substantially from each other and from the nominal value of 2 normally used in radiation protection (ICRP, 1991; NCRP, 1993), and the DDREFs for the two radiations also vary from one study to another. The alternative approach to risk estimation involving use of REF_H is most appropriate when the dose-response relationship for the radiation under study is linear at any dose and dose rate and DDREF for the radiation is unity. The following discussion focuses on estimation of RBEs for lower-energy photons at low doses and low dose rates, RBE_M, and the derivation of probability distributions of REF_L based on these data.

REF Based on Estimated RBEs for *X* Rays and Data in Humans

Studies of the biological effectiveness of 220-250 kVp *X* rays in inducing dicentric chromosomes in human lymphocytes were reviewed and evaluated by the NCRP (1990). The average energy of *X*-rays in these studies was about 50-65 keV (Stanton et al., 1979; NCRP, 1985). The dose-response relationships for the *X* rays and reference gamma rays in these studies were assumed to be linear-quadratic; i.e., the response was assumed to be described by $\alpha D + \beta D^2$, where D is the absorbed dose and α and β are coefficients obtained from fits to the data. The data on dose-response for *X* rays and the reference gamma rays in the various studies are summarized in Table 10. Point estimates of RBE_M, calculated by the NCRP (1990) as α_X/α_γ using the central estimates of the two coefficients in Table 10, are given in Table 11. Similar values of RBE_M for *X* rays are indicated when estimates of RBE_M for neutrons and the same endpoint obtained in studies using *X* rays as the reference radiation are compared with estimates obtained using ^{60}Co gamma rays (Dobson et al., 1991; Schmid et al., 2000).

The NCRP's point estimates of RBE_M in Table 11 do not take into account the reported uncertainties in the coefficients α_X and α_γ in the dose-response relationships for *X* rays and gamma rays, respectively. We estimated the uncertainty in each value of RBE_M in the following way. We assumed that the central estimates and standard errors of α_X and α_γ given in Table 10 define 68% confidence intervals of lognormal probability distributions of these coefficients.[20] We then used random sampling methods to calculate a probability distribution of RBE_M as the ratio of the distributions of α_X and α_γ, and the 68% confidence interval of this distribution thus was obtained. These confidence intervals are given in parentheses in Table 11.

The estimates of RBE_M for *X* rays and their uncertainties summarized in Table 11 can be represented by a lognormal probability distribution having a 95% confidence interval between 1.0 and 6.5. However, information obtained from other radiobiological studies should be taken into account. This information is indirect, in that the radiation under study was not *X* rays or gamma rays but both of these radiations were used as reference radiations. Inferences about the biological effectiveness of *X* rays relative to gamma rays can be made by comparing RBEs for the radiation under study relative to *X* rays with RBEs relative to gamma rays, provided the RBEs apply to similar endpoints. Information obtained mainly from reviews of various studies by experts and expert groups is summarized below.

- A study of induced pink mutation events in stamen hairs of *Tradescantia* (Underbrink et al., 1970) discussed in Section 2.2.4 of NCRP (1990), in which the radiations under study were neutrons, indicated that the RBE of *X* rays was about 1.7.

[20]Uncertainties are described by lognormal probability distributions to avoid problems that arise in calculating ratios of two normal distributions when very small or negative values are randomly sampled from the distribution in the denominator.

Table 10. Dose-response relationships of *X* rays and reference high-energy gamma rays for induction of dicentric chromosomes in human lymphocytes[a]

Reference	Radiation	Dose range[b] (Gy)	$\alpha \pm SE^c$ ($\times 10^{-2}$ Gy^{-1})	$\beta \pm SE^c$ ($\times 10^{-2}$ Gy^{-2})
Bauchinger (1984)	220 kVp *X* rays	0.5-4	4.0 ± 0.3	5.98 ± 0.17
	^{60}Co γ rays	0.5-4	1.1 ± 0.4	5.55 ± 0.28
Fabry et al. (1985)	250 kVp *X* rays	0.05-2	4.4 ± 1.0	6.0 ± 1.1
	^{60}Co γ rays	0.05-2	3.0 ± 0.8	4.3 ± 1.0
Lloyd et al. (1986)	250 kVp *X* rays	0.05-6	3.6 ± 0.5	6.67 ± 0.22
	^{60}Co γ rays	0.05-6	1.4 ± 0.4	7.59 ± 0.27
Littlefield et al. (1989)	220 kVp *X* rays	0.25-3.75	4.3 ± 0.8	6.6 ± 0.4
	^{60}Co γ rays	0.25-4	1.6 ± 0.7	5.7 ± 0.3
Brewen and Luippold (1971)[d]	250 kVp *X* rays	0.5-4	9.1 ± 0.2	6.0 ± 0.7
Brewen et al. (1972)[d]	^{60}Co γ rays	0.5-4	3.9 ± 1.1	8.2 ± 0.4
Lloyd et al. (1975)	250 kVp *X* rays	0.05-8	4.8 ± 0.5	6.2 ± 0.3
	^{60}Co γ rays	0.25-8	1.6 ± 0.3	5.0 ± 0.2

[a]See Tables 2.6 and 2.7 of NCRP (1990).
[b]Doses were delivered acutely or over time period of about 10 minutes or less.
[c]α and β are coefficients of linear and quadratic terms in linear-quadratic dose-response relationship, respectively, and SE is the standard error.
[d]Results for *X* rays and gamma rays were reported separately.

- Studies of mutations in human diploid fibroplasts (Cox et al., 1977; Hei et al., 1988) summarized in Fig. 3.13 of NCRP (1990), in which the radiations under study included protons, deuterons, and heavy ions, indicated that the RBE of *X* rays was about 3 or less.

- A study of dominant lethal mutations in cells of mice (Pomerantseva, 1964) discussed in Section 4.1.1.1 of NCRP (1990), in which the radiation under study was high-energy protons, indicated that the RBE of *X* rays was about 1.5.

Table 11. Estimates of RBE_M for *X* rays and induction of dicentric chromosomes in human lymphocytes[a]

Reference	*X* rays	RBE_M (68% CI)[b]
Bauchinger (1984)	220 kVp	3.8 (2.5, 6.5)
Fabry et al. (1985)	250 kVp	1.5 (1.0, 2.2)
Lloyd et al. (1986)	250 kVp	2.6 (1.8, 3.8)
Littlefield et al. (1989)	220 kVp	2.8 (1.7, 5.1)
Brewen and Luippold (1971); Brewen et al. (1972)	250 kVp	2.3 (1.8, 3.3)
Lloyd et al. (1975)	250 kVp	3.0 (2.4, 3.8)

[a]RBE_M is RBE at low doses obtained by extrapolation of linear-quadratic dose-response relationships for *X* rays and reference ^{60}Co gamma rays.

[b]First entry is point estimate calculated by NCRP (1990) as α_X/α_γ, where α_X and α_γ are central estimates of coefficient of linear term in dose-response relationship for *X* rays and gamma rays, respectively, given in Table 10. Second entry in parentheses is 68% confidence interval based on standard errors in α coefficients given in Table 10 and calculated as described in text.

- A study of life-shortening in mice (Upton et al., 1967) summarized in Table 8.2 of NCRP (1990), in which the radiations under study were neutrons, indicated that the RBE at low doses and low dose rates of *X* rays was about 3 or less. A similar result was obtained from an analysis of these data by Edwards (1999) to obtain estimates of RBE for neutrons at high doses and high dose rates of the reference radiation, RBE_H (see Table 3).

- A study of mutations in human lung fibroplasts (Cox and Masson, 1979) summarized in Section 7, Paragraph 19, and Table 7.3 of Muirhead et al. (1993), in which the radiations under study were alpha particles, indicated that the RBE of *X* rays was about 2.5 when

compared with the results of a study of mutations in Chinese hamster cells (Thacker et al., 1979) summarized in Table 8.

- Several inferences can be made from studies of the biological effectiveness of beta particles from ^3H decay summarized by Straume and Carsten (1993) and discussed in the following section. Studies of carcinogenesis endpoints in mammals and mammalian cells indicated that the RBE of *X* rays was less than 2 (see Table 13). Studies of genetic endpoints in mammalian systems and fish lymphocytes indicated that the RBE of *X* rays was about 1.6 on average and did not exceed about 3.5 (see Table 14). A study of chromosome aberrations in human lymphocytes indicated that the 68% confidence interval of the RBE for *X* rays was (2.3, 3.9) (see Table 15); this estimate applies to the same endpoint as the results summarized in Table 11. Results of studies of reproductive effects in small mammals and fish summarized in Table 7 of Straume and Carsten (1993) are not considered, because these endpoints are deterministic and, thus, are not considered to be relevant in estimating cancer risks in humans.

- A study of tumor induction in rats (Wolf et al., 2000), in which the radiation under study was fission neutrons, indicated that the RBE of *X* rays at a dose of 2 Gy was about 3. This RBE should be especially relevant to estimating cancer risks in humans.

The indirect estimates of RBE for *X* rays suggest that a lognormal probability distribution of RBE_M for lower-energy photons having a 95% confidence interval between 1.0 and 6.5 gives too much weight to relatively high values. We believe this conclusion is reasonable even though uncertainties in the indirect estimates undoubtedly are substantial. We also note that the highest values of RBE_M in Table 11 have the largest uncertainties, which indicates that these values should be given less weight compared with the lower, and less uncertain, estimates of RBE_M for the same endpoint. Based on this information, we reduce the upper confidence limit of the lognormal probability distribution of RBE_M obtained from studies of dicentric chromosomes in human lymphocytes from 6.5 to 5.0.

Thus, the lognormal probability distribution of RBE_M that is assumed to describe all the radiobiological data discussed above has a 95% confidence interval between 1.0 and 5.0. The geometric mean (median) and geometric standard deviation of this distribution are 2.2 and 1.5, respectively. The assumed distribution assigns a small weight (2.5%) to an assumption that the biological effectiveness of *X* rays and other lower-energy photons is the same as, or lower than, that of high-energy gamma rays, and to an assumption that values greater than 5 are possible. Neither of these assumptions can be ruled out by the available radiobiological data.

We then investigated whether useful information on the biological effectiveness of *X* rays relative to high-energy gamma rays can be obtained from epidemiological studies of human populations. We compared estimated risks of thyroid cancer in children exposed to *X* rays with estimated risks of thyroid cancer in Japanese atomic-bomb survivors who were exposed in childhood mainly to high-energy gamma rays. In the atomic-bomb survivors, the following

central estimates and 95% confidence intervals (in parentheses) of the excess relative risk (ERR) of thyroid cancer per Gy in children have been reported:

- 4.7 (1.7, 11) – atomic-bomb survivors less than 15 years old at time of exposure, with a mean thyroid dose of gamma rays of 0.27 Gy (Ron et al., 1995);
- 9.5 (4.1, 19) – atomic-bomb survivors less than 10 years old at time of exposure, with the same mean thyroid dose (Thompson et al., 1994).

These estimates suggest that the risk to children of age less than 10 years at time of exposure is greater than the risk to children of age 10-15 years. For children exposed to *X* rays, the following estimates of the ERR of thyroid cancer per Gy have been reported (Ron et al., 1995):

- 9.1 (3.6, 29) – newborn children in Rochester, New York, treated for an enlarged thymus gland at ages less than 1 year, with a mean thyroid dose of *X* rays of 1.4 Gy;
- 33 (14, 57) – Israeli children treated for ringworm of the scalp at a mean age of 7 years, with a mean thyroid dose of *X* rays of 0.09 Gy;
- 2.5 (0.6, 26) – children in Chicago, Illinois, treated for enlarged tonsils and adenoids at ages 0-15 years (mean age of 4 years), with a mean thyroid dose of *X* rays of 0.59 Gy;
- 7.7 (2.1, 29) – pooled analysis of data on childhood exposures at ages 0-15 years, including data on the atomic-bomb survivors (result is dominated by data on childhood exposures to *X* rays at ages less than 10 years).

An RBE for *X* rays can be estimated from these results by assuming that the probability distribution of the estimated risk in each study is lognormal and calculating ratios of the probability distributions for *X* rays to a distribution for gamma rays. Since the average ages of children exposed to *X* rays were 7 years or less, we use the estimated risk in the atomic-bomb survivors of age less than 10 years at time of exposure to estimate RBEs. The 95% confidence intervals of RBEs obtained from the three studies of children exposed to *X* rays are (0.3, 4.2), (1.1, 9.2), and (0.06, 3.5), and the 95% confidence interval obtained using the results of the pooled analysis is (0.2, 4.0). If we assume that the biological effectiveness of *X* rays in humans should not be less than that of high-energy gamma rays, based on the effective quality factor shown in Fig. 1 (ICRU, 1986), these confidence intervals indicate that the RBE of *X* rays in inducing thyroid cancer in children most likely is in the range of about 1-4. However, the estimated risks in the different populations neither support nor refute an assumption that *X* rays are more effective than high-energy gamma rays in inducing thyroid cancer in children.

Additional information on the RBE for *X* rays and thyroid cancer can be obtained from a study of prepubescent rats exposed to *X* rays and beta particles emitted in ^{131}I decay (Lee et al., 1982). As discussed in a later section, the biological effectiveness of ^{131}I beta particles, which have an average energy of 182 keV (Kocher, 1981), should be similar to that of high-energy gamma rays. The following central estimates and 95% confidence intervals (in parentheses) of ratios of thyroid tumor incidence from exposure to *X* rays to tumor incidence from exposure to ^{131}I beta particles were obtained: 1.1 (0.32, 3.7) at a mean thyroid dose of 0.8 Gy, 1.2 (0.43, 3.2)

at 3.3 Gy, and 1.4 (0.24, 7.6) at 8.5 Gy. The average of the three confidence intervals is a distribution with a central estimate (50^{th} percentile) and 95% confidence interval of 1.4 (0.6, 3.6). Thus, although the uncertainties are large and an RBE for *X* rays as high as about 4 cannot be ruled out, the biological effectiveness of *X* rays and ^{131}I beta particles in inducing thyroid cancer in the study animals was about the same, on average.

Finally, we examined results obtained from epidemiological studies of cancers at other sites, including the colon, lung, skin, female breast, and bladder (UNSCEAR, 2000). The central estimate of the ERR per Gy in populations exposed to *X* rays often was comparable to or less than the central estimate in a similar age group in the atomic-bomb survivors, although some of the lower risks from *X* rays may be influenced by the much higher doses of *X* rays compared with the doses of gamma rays in the atomic-bomb survivors. In those few cases where a higher risk was observed in populations exposed to *X* rays, the difference was less than a factor of 2. In all cases, however, uncertainties in the risk estimates are sufficiently large that an RBE for *X* rays substantially greater than 1 cannot be ruled out. Thus, as in the case of thyroid cancer, the available data on other cancers in humans do not indicate whether *X* rays are biologically more effective than high-energy gamma rays or not.

The results of epidemiological studies described above lead to the following observations. First, there is no evident difference in the effectiveness of *X* rays in inducing thyroid cancers compared with cancers at other sites. Second, uncertainties in the results of epidemiological studies are sufficiently large that an upper confidence limit of REF_L as high as 5.0, as we have assumed based on radiobiological data, cannot be ruled out. Third, although uncertainties in the results of epidemiological studies are large, in no cases is a central estimate of an RBE for *X* rays as high as 4 obtained. Based on considerations of statistical uncertainties alone, an occasional high estimate of RBE would be expected. Finally, the epidemiological data do not rule out an assumption that the biological effectiveness *X* rays in inducing cancers in humans is the same as that of high-energy gamma rays.

Based on the evidence obtained from all the radiobiological and epidemiological studies discussed above and an assumption that the biological effectiveness of *X* rays should not be substantially less than that of high-energy gamma rays, we describe REF_L for orthovoltage *X* rays and other lower-energy photons by the following hydrid probability distribution:

[1] 75% weight to a lognormal distribution having a 95% confidence interval between 1.0 and 5.0, based on the results of radiobiological studies;

[2] 25% weight to the value 1.0, based on the lack of clear evidence of a difference between *X* rays and gamma rays in epidemiological data.

Thus, we use the results of epidemiological studies to modify the lognormal probability distribution that was based on the results of radiobiological studies by assigning a substantial weight to an assumption that *X* rays and other lower-energy photons have the same biological

effectiveness in humans as high-energy gamma rays. The resulting probability distribution of REF_L has a median of 1.9 and a 95% confidence interval between 1.0 and 4.7. The cumulative probability distribution of REF_L is shown in Fig. 18. The assumption that this distribution applies at photon energies of 30-250 keV is discussed below.

The weight to be given to an assumption that *X* rays and other lower-energy photons have the same biological effectiveness in humans as high-energy gamma rays clearly is a matter of subjective judgment. Our judgment is that the weight given to this assumption should be substantial but should not be much higher than 25% (e.g., 50% or higher). This judgment is based on two considerations. First, there are many and varied radiobiological studies which clearly indicate a greater biological effectiveness of *X* rays. Second, although the epidemiological data do not show clear evidence of a difference in biological effectiveness, the data are so uncertain that differences as large as a factor of 3 cannot be ruled out.

Energy Dependence of REF

Based on the energy dependence of the effective quality factor shown in Fig. 1 (ICRU, 1986), we assume that the probability distribution of REF_L for orthovoltage *X* rays and other lower-energy photons described above applies at energies of 30-250 keV; the effective quality factor is essentially independent of energy over much of this range. We also note that the effective quality factor at these energies is approximately twice the value at the energies of ^{60}Co gamma rays; by our reading of the curve in Fig. 1, the difference is a factor of 2.3. The ICRU's calculation thus supports our assumed distribution of REF_L.

An assumption that the distribution of REF_L applies at photon energies as low as 30 keV is supported by calculations of the biological effectiveness of 60- and 80-kVp *X* rays relative to gamma rays from the Hiroshima and Nagasaki atomic bombs for a number of specific endpoints, including chromosomal aberrations in human lymphocytes, induction of mutations in human fibroblasts, and oncongenic transformation in C3H10T½ mouse cells (Brenner, 1999). RBEs at low doses between 1.6 and 2.0 were calculated. The differences between these values and the value of 2.3 inferred from the calculation in Fig. 1 are due, in part, to differences in the assumed responses as a function of lineal energy and to an assumption that the average energies of gamma rays from the atomic bombs were somewhat less than the energies of ^{60}Co gamma rays.

The effective quality factor shown in Fig. 1 also indicates that the biological effectiveness of photons increases as the energy decreases below 30 keV. For example, based on the calculation in Fig. 1, Brenner and Amols (1989) estimated that 23 kVp *X* rays should be approximately 1.3 times more effective than 44-250 kVp *X* rays in inducing breast cancer. Thus, we assume that the probability distribution of REF_L for photons of energy 30-250 keV should be increased when the energy is less than 30 keV. We represent this increase by a factor which is described by a triangular probability distribution having a lower bound of 1.0, a mode of 1.3, and an upper bound of 1.6. The resulting probability distribution of REF_L at photon energies less than 30 keV is shown in Fig. 19.

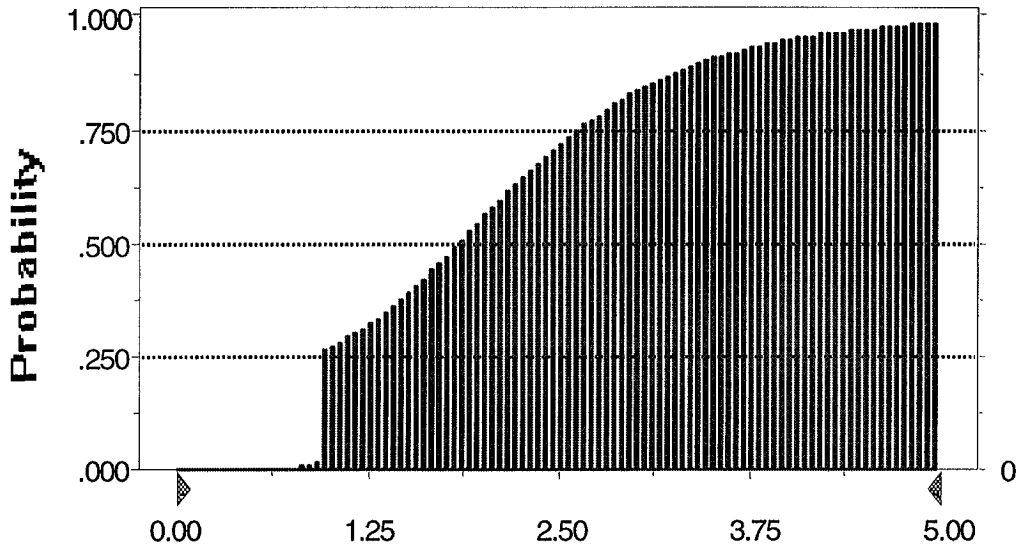

Fig. 18. Assumed probability distribution of REF_L for photons of energy 30-250 keV (25% weight to value 1.0; 75% weight to lognormal probability distribution having a 95% confidence interval between 1.0 and 5.0) displayed as a cumulative distribution; distribution applies to all cancers and at any dose and dose rate. Median of distribution is 1.9, and 95% confidence interval lies between 1.0 and 4.7; about 1.8% of values lie beyond 5.0.

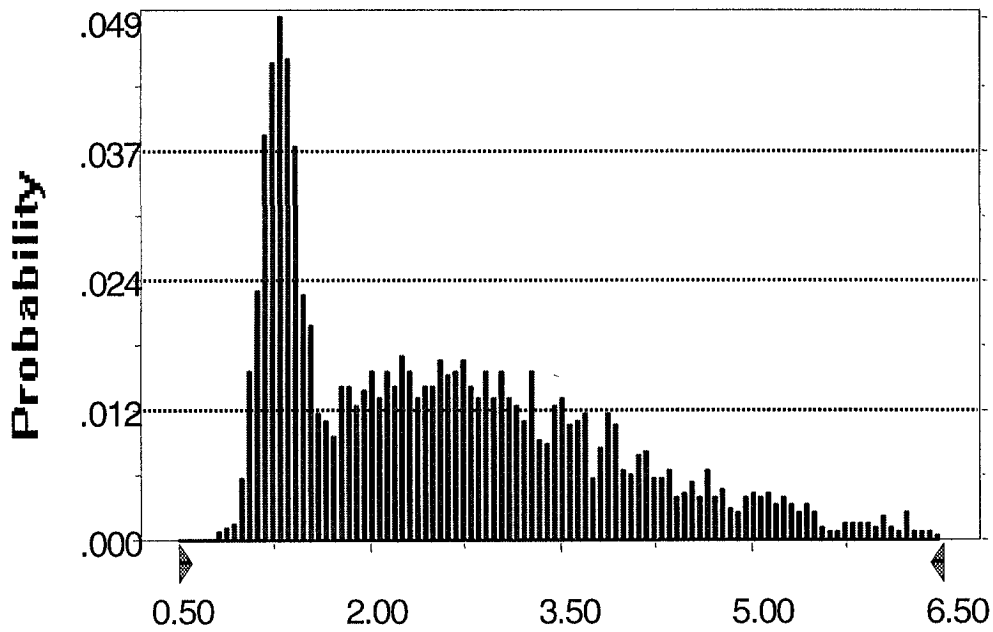

Fig. 19. Assumed probability distribution of REF_L for photons of energy less than 30 keV; distribution applies to all cancers and at any dose and dose rate. Median of distribution is 2.4 and 95% confidence interval lies between 1.1 and 6.1; about 1.8% of values lie beyond 6.5.

Summary

The biological effectiveness of lower-energy photons relative to high-energy gamma rays is assumed to be independent of dose and dose rate under similar conditions of exposure to the two radiations. Cancer risks in humans from exposure to photons (γ) are estimated using the following equations:

Solid tumors (any dose and dose rate) –

$$\Re_\gamma = \mathrm{REF}_{\gamma,\mathrm{L}} \times \mathrm{AF}_\gamma \times \frac{R_{\gamma,\mathrm{H}}}{\mathrm{DDREF}_\gamma} \times D_\gamma \qquad (11)$$

Leukemias (acute exposure) –

$$\Re_\gamma = a(\mathrm{REF}_{\gamma,\mathrm{L}} \times \mathrm{AF}_\gamma \times D_\gamma) + b(\mathrm{REF}_{\gamma,\mathrm{L}} \times \mathrm{AF}_\gamma \times D_\gamma)^2 \qquad (12)$$

Leukemias (chronic exposure) –

$$\Re_\gamma = a \times \mathrm{REF}_{\gamma,\mathrm{L}} \times D_\gamma \qquad (13)$$

where $\mathrm{REF}_{\gamma,\mathrm{L}}$ is the radiation effectiveness factor at low doses and low dose rates that applies at photon energies of 30-250 keV, AF_γ is an adjustment factor representing an increase in biological effectiveness at photon energies less than 30 keV, $R_{\gamma,\mathrm{H}}$ is the risk coefficient (ERR per Gy) at high acute doses of high-energy gamma rays for the solid tumor of concern, a and b are the coefficients of the linear and quadratic terms in the linear-quadratic dose-response relationship for leukemias at high acute doses of high-energy gamma rays, DDREF_γ is the dose and dose-rate effectiveness factor for gamma rays and other low-LET radiations, and D_γ is the absorbed dose of photons in the organ or tissue of concern. The value of REF_L for all photons of energy greater than 250 keV is assumed to be unity. The probability distribution of REF_L at a given photon energy is applied to all cancers.

A single probability distribution of DDREF_γ is applied in estimating risks of solid tumors under conditions of chronic exposure. Under conditions of acute exposure, DDREF_γ depends on the magnitude of the dose. At acute doses greater than 0.2 Gy, DDREF_γ is assumed to be unity. At acute doses less than 0.2 Gy, a DDREF_γ that can exceed unity is applied, and the distribution of possible values approaches the probability distribution of DDREF_γ under conditions of chronic exposure as the dose approaches zero (Land et al., 2002).

The assumed probability distributions of REF_L for photons of different energies are summarized in Table 12.

Table 12. Summary of probability distributions of radiation effectiveness factors for photons to be used in estimating cancer risks and probability of causation in accordance with eq. (11), (12), or (13)[a]

Photon energy	Probability distribution of radiation effectiveness factor (REF_L)
> 250 keV	Single-valued at 1.0 (higher-energy photons are assumed reference radiation)
30-250 keV	Hybrid distribution with – 75% weight to lognormal distribution having a 95% confidence interval between 1.0 and 5.0; 25% weight to value 1.0;
< 30 keV	Product of two distributions – (1) hybrid distribution for photons of energy 30-250 keV; and (2) triangular distribution with minimum of 1.0, mode of 1.3, and maximum of 1.6

[a]Probability distributions apply to all cancers and at any dose and dose rate.

ELECTRONS

With the exception of low-energy electrons emitted in beta decay of ^3H, there have been few studies of the biological effectiveness of electrons relative to gamma rays or *X* rays. In this section, we develop a probability distribution of an REF for beta particles emitted in ^3H decay; these electrons have an average energy of 5.7 keV and a maximum energy of 18.6 keV (Kocher, 1981). We then consider the biological effectiveness of other electrons, including low-energy Auger electrons.

REF for Tritium Beta Particles

Many studies have shown that beta particles emitted in decay of ^3H are biologically more effective than gamma rays in inducing stochastic effects (NCRP, 1990; Straume and Carsten, 1993). Estimates of RBE obtained from studies reviewed by Straume and Carsten (1993), including studies in which the reference radiation was *X* rays, are summarized in Tables 13-16.

For purposes of developing an REF for ^3H beta particles that is consistent with the REFs for the other radiation types, the relevant studies are those in which the reference radiation was gamma rays. In most studies using gamma rays, the reference radiation was delivered chronically to match the conditions of exposure to ^3H beta particles. Thus, cancer risks in humans from

exposure to ^3H beta particles are estimated using the models represented in eqs. (2) and (5), which apply at low doses and low dose rates. If we assume that DDREF for ^3H beta particles in the various studies is about the same as DDREF for the reference radiation, RBEs obtained under conditions of chronic exposure in Tables 13-16 provide estimates of RBE_M.

Based on the data under conditions of chronic or sub-acute exposure to gamma rays in Tables 13-16, but excluding the data for tritiated thymidine, central estimates of RBE_M are in the range of about 1.5-3. When uncertainties in these estimates are considered, the range presumably is about 1.2-4. The data on RBE for tritiated thymidine are not included based on the consideration that this compound has a different distribution within the body than other chemical forms of ^3H that would be encountered in the workplace or the environment.

Estimates of RBE_M under conditions of chronic exposure to *X* rays also are relevant. In three of the five such determinations, the central estimate of RBE_M is about 2-3. If we assume a nominal biological effectiveness of *X* rays relative to gamma rays of 2, based on the probability distribution of REF_L for *X* rays developed in the previous section, these data indicate that RBE_M for ^3H beta particles relative to gamma rays is as high as about 4-6.

Table 13. Estimates of RBE of tritium beta particles for carcinogenesis endpoints[a]

Effect	Radiation and conditions	RBE	Reference
Mammary tumors in S-D rats	HTO and chronic *X* rays	1.2 ± 0.3	Gragtmans et al. (1984)
Leukemia in CBA/H mice	HTO and chronic *X* rays	1.2 ± 0.3	Myers and Johnson (1991)
Tumors in C57B1/6N × C3H/He mice	HTO and acute gamma rays	~1[b]	Yokoro et al. (1989)
Transformation in hamster cells *in vitro*	HTO and acute *X* rays	~1	Suzuki et al. (1989)
Transformation in mouse cells *in vitro*	HTO and acute *X* rays	1-2	Little (1986)
Transformation in 10T½ cells	HTO and subacute gamma rays	1.4-1.8	Yamaguchi et al. (1985)

[a]See Table 1 of Straume and Carsten (1993).
[b]Authors did not provide estimate of RBE but state that biological effectiveness of HTO and gamma rays was not very different.

Table 14. Estimates of RBE of tritium beta particles for genetic endpoints[a]

Effect	Radiation and conditions	RBE	Reference
6-Thioguanine resistance in mouse cells *in vitro*	HTO and chronic gamma rays	2.9	Ueno et al. (1989)
6-Thioguanine resistance in mouse cells *in vitro*	^{3}H-amino acid and chronic gamma rays	2.6	Ueno et al. (1989)
6-Thioguanine resistance in mouse cells *in vitro*	Tritiated thymidine (^{3}H-Tdr)[b] and chronic gamma rays	5.9	Ueno et al. (1989)
6-Thioguanine resistance in mouse cells *in vitro*	HTO and gamma rays at 10^{-5} mutant frequency		Nakamura et al. (1985)
	acute	1.5	
	chronic	2.4	
Chromosome aberrations in human sperm *in vitro*	HTO and chronic *X* rays	3	Kamiguchi et al. (1990)
Chromosome aberrations in fish lymphocytes *in vitro*	HTO and chronic gamma rays	1.9	Suyama and Etoh (1985)
Chromosome aberrations in mouse zygotes	HTO and chronic gamma rays	1.8	Matsuda et al. (1985)
Chromosome aberrations in CBA/H mice			Chopra and Heddle (1988)
lymphocytes	HTO and *X* rays	1.1	
spermatogonia	HTO and *X* rays	1.2	
Micronuclei in mammalian cells	HTO and chronic gamma rays	2.0 2.7	Ueno et al. (1982) Kashima et al. (1985)
Mutations in *Drosophila* spermatozoa	HTO and gamma rays	2.7	Byrne and Lee (1989)
Mutations in mice *in vivo*	HTO and chronic gamma rays	2.7	Nomura and Yamamoto (1989)

Table is continued on following page.

Table 14. Estimates of RBE of tritium beta particles for genetic endpoints (continued)[a]

Effect	Radiation and conditions	RBE	Reference
Dominant lethals in male mice	HTO and chronic gamma rays	2.5	Searle (1984)
		1-2	Carsten and Commerford (1976)
Dominant lethals in female mice	HTO and chronic gamma rays	2.5	Xiang-yan et al. (1986)
Specific locus mutations in male mice	HTO and chronic gamma rays	2.0	UNSCEAR (1982)

[a]See Table 2 of Straume and Carsten (1993).
[b]Use of methyl-^{3}H-Tdr resulted in identical RBEs.

Table 15. Estimates of RBE of tritium beta particles for chromosome aberrations in human lymphocytes[a]

Radiation and conditions	RBE	Reference
HTO and acute *X* rays	1.9 ± 0.7	Bocian et al. (1977), as refit by Prosser et al. (1983)
HTO and subacute gamma rays	1.49 ± 0.21	Morimoto et al. (1989)
HTO and acute *X* rays	1.13 ± 0.18	Prosser et al. (1983)
HTO and acute gamma rays	3.4 ± 0.6	Prosser et al. (1983) and Lloyd et al. (1975)
HTO and subacute *X* rays	2.6	Vulpis (1984)
HTO and low dose *X* rays	2.0	Estimated from Prosser et al. (1983) and Lloyd et al. (1988)

[a]See Table 3 of Straume and Carsten (1993).

Table 16. Estimates of RBE of tritium beta particles for developmental and related effects[a]

Effect	Radiation and conditions	RBE	Reference
Mouse embryo, two-cell to blastocyte *in vitro*	HTO and chronic gamma rays	1.7	Yamada et al. (1982)
Teratogenic effects in rat embryos	HTO and chronic gamma rays	2.6	Satow et al. (1989)
Cell killing *in vitro*	HTO and chronic gamma rays	1.3	Ueno et al. (1989)
	^{3}H-amino acids and chronic gamma rays	1.7	
	Tritiated thymidine (^{3}H-Tdr)[b] and chronic gamma rays	3.5	

[a]See Table 4 of Straume and Carsten (1993).
[b]Use of methyl-^{3}H-Tdr resulted in an identical RBE.

Taking into account the data on RBE relative to gamma rays and *X* rays, we describe the REF for ^{3}H beta particles at low doses and low dose rates, REF_L, by a lognormal probability distribution having a 95% confidence interval between 1.2 and 5.0. This distribution has a geometric mean (median) and geometric standard deviation of 2.4 and 1.4, respectively. Based on discussions presented below and except as noted, the probability distribution of REF_L for ^{3}H beta particles is assumed to apply to any electrons of energy less than 15 keV.

In a previous analysis by *SENES* Oak Ridge (Thomas and Hoffman, 2000), the biological effectiveness of ^{3}H beta particles was described by a triangular probability distribution having a lower bound of 1.0, a mode of 2.0, and an upper bound of 5.0. The lognormal probability distribution described above is similar to the previous assumption. However, the data summarized in Tables 13-16 indicate that an REF_L greater than 5 cannot be ruled out. The upper tail of the lognormal probability distribution represents an assumption that REF_L could be 5 or greater, and that a reasonable upper bound cannot be determined with certainty. The small probability assigned to an REF_L of 4 or greater (about 10%) also is intended to take into account that RBEs for organically-bound tritium appear to be 2-3 times higher than RBEs for HTO or ^{3}H incorporated into amino acids (see Tables 14 and 16). This is a potentially important consideration when some HTO taken into the body becomes organically-bound before it is excreted (Straume and Carsten, 1993).

In a recent analysis by Harrison et al. (2002) of the NRPB, the biological effectiveness of ^{3}H beta particles relative to high-energy gamma rays was described by a uniform probability distribution between 1.0 and 2.5; this distribution has a median of 1.75. The analysis by Harrison et al. differs from the analysis in this report mainly in two respects. First, these investigators evaluated RBEs for ^{3}H beta particles relative to high-energy gamma rays and RBEs relative to lower-energy *X* rays together without taking into account that *X* rays probably have a greater biological effectiveness than gamma rays. As discussed above, we have assumed that RBEs for ^{3}H beta particles relative to *X* rays should be increased by a factor representing the biological effectiveness of *X* rays to provide a proper comparison with RBEs relative to gamma rays. This adjustment by a factor of about two results in a median and upper confidence limit in our probability distribution of REF_L that are substantially higher than assumed by Harrison et al. Second, the uniform probability distribution developed by Harrison et al. incorporates an assumption that the biological effectiveness of ^{3}H beta particles relative to gamma rays could not exceed 2.5. In contrast, we believe that the data on RBE are consistent with values as high as about 5, and that an upper bound near 5 cannot be established with certainty. These assumptions are incorporated in the lognormal probability distribution of REF_L developed in this report.

The assumed lognormal probability distribution of REF_L for ^{3}H beta particles having a 95% confidence interval between 1.2 and 5.0 is nearly the same as the probability distribution of REF_L for photons of energy less than 30 keV discussed in the previous section. This consistency is expected when, as discussed below, the energies of electrons that deliver an absorbed dose are similar in the two cases.

Consideration of Energy Dependence of REF

Since the energies of ^{3}H beta particles are very low, we also considered whether other electrons, especially those of higher energy, should have an REF greater than unity. In radiation protection, all such electrons generally are assumed to have the same biological effectiveness as high-energy gamma rays (see Table 1). A study of the biological effectiveness of *X* rays and beta particles from ^{131}I decay in inducing thyroid cancer in rats by Lee et al. (1982) discussed previously is the only study we are aware of that was designed to investigate the biological effectiveness of higher-energy electrons. In the absence of extensive radiobiological data, we address this question using the following arguments.

In the previous section, data on the biological effectiveness of *X* rays and a calculation of the energy dependence of the effective quality factor for photons shown in Fig. 1 were used to develop a probability distribution of REF_L with a median greater than 1.0 for photons of energy as high as 250 keV. Since the absorbed dose from irradiation by photons is due almost entirely to energetic secondary electrons produced by interactions of the incident photons in tissue, information on the biological effectiveness of photons can be used to infer the biological effectiveness of electrons. That is, an REF for photons of a given energy essentially describes the biological effectiveness of the secondary electrons produced by the first interactions of the photons in tissue.

The energies of secondary electrons produced by interactions of photons in tissue generally decrease with decreasing photon energy. Therefore, electrons produced by interactions of 250-keV photons in tissue are at the highest energies for which the biological effectiveness should be the same as that of lower-energy photons. In tissue, which has an average atomic number of 7 (Shleien et al., 1998), Compton scattering is the dominant interaction at a photon energy of 250 keV [see Fig. A.1 of NCRP (1991) and Figs. 5.1 and 5.2 of Shleien et al. (1998)]. At this energy, the continuous spectrum of secondary electrons produced by Compton scattering has a maximum energy of 124 keV and an average energy of 60 keV (Turner, 1995). In contrast, the energy of secondary electrons produced by the photoelectric effect in tissue at this energy is nearly 250 keV, since the binding energies of electrons in atoms of the elements comprising tissue are about 3 keV or less (Shleien et al., 1998). At 250 keV, however, photoelectrons are produced in only about 0.1% of all interactions [see Fig. 5.2 of Shleien et al. (1988)] and, thus, have little effect on the average energy of secondary electrons.

As the incident photon energy decreases below 250 keV, the photoelectric effect increases in importance relative to Compton scattering and becomes the dominant interaction in tissue at energies less than about 30 keV (Schleien et al., 1998; NCRP, 1991). At this photon energy, the average and maximum energies of secondary electrons produced in Compton scattering are about 1.5 and 3 keV, respectively, and the average energy of photoelectrons is nearly 30 keV. Thus, the average energy of secondary electrons produced by 30-keV photons is about 15 keV. This result is of interest because we have assumed, based on the calculated energy dependence of the effective quality factor shown in Fig. 1, that the biological effectiveness of photons of energy less than 30 keV is higher than at 30-250 keV. Thus, the same increase in biological effectiveness should apply to electrons of energy less than about 15 keV. As the photon energy decreases below 30 keV, the average energy of secondary electrons produced in tissue approaches the incident photon energy, due to the increasing importance of the photoelectric effect and the low binding energies of atomic electrons. At a photon energy of 20 keV, for example, the energies of secondary electrons are little different from the incident photon energy.

Three conclusions can be drawn from the analysis described above. First, at energies greater than about 60 keV, the biological effectiveness of electrons should be essentially the same as that of the reference high-energy gamma rays (i.e., unity). Second, at energies in the range of about 15-60 keV, the biological effectiveness of electrons should be the same as that of photons of energy 30-250 keV. Third, at energies less than about 15 keV, but possibly excluding Auger electrons as discussed below, the biological effectiveness of electrons should be the same as that of photons of energy less than 30 keV.

We use the conclusions about the biological effectiveness of electrons of various energies in the following way. First, the assumed probability distribution of REF_L for beta particles from ^3H decay is applied to any electrons of energy less than 15 keV. In general, this REF_L should be applied to electrons from beta decay when the average energy of the spectrum of beta particles is less than 15 keV. Use of the average energy of beta particles is reasonable when the argument to assume an REF_L greater than 1.0 at energies less than 15 keV was based in part on the average

energy of the spectrum of secondary electrons in Compton scattering. The assumed REF_L also should be applied to discrete internal conversion electrons of energy less than 15 keV emitted in radioactive decay.[21] In these cases, however, an increased biological effectiveness needs to be taken into account only when the average energy of low-energy internal conversion electrons per decay of a radionuclide is significant compared with the average energies per decay of other radiations that have a short range in tissue, including internal conversion electrons of energy greater than 15 keV, beta particles, and alpha particles. Application of the assumed REF_L to Auger electrons is discussed below.

Second, we have not adopted an increased biological effectiveness of 15-60 keV electrons relative to high-energy photons, even though the calculations described above indicate that REF_L for electrons in this energy range should be the same as that for 30-250 keV photons. This decision was based on two considerations noted previously. First, we are not aware of any data on RBE for 15-60 keV electrons. Second, the assumed REF_L for 30-250 keV photons is based on studies in which the average energies of *X* rays was about 50-65 keV and relatively few *X* rays had energies above 100 keV, and the assumption that RBEs for such *X* rays apply at photon energies up to 250 keV was based on a calculation of the energy dependence of the effective quality factor shown in Fig. 1. Thus, adoption of an REF_L greater than unity for 15-60 keV electrons would be based on two assumptions for which there is no experimental evidence. In general, we have assumed that probability distributions of REFs should be developed only when there is some basis in radiobiological data.

Biological Effectiveness of Auger Electrons

Radionuclides that emit Auger electrons[22] require special consideration, due to the very low energies of these radiations (often a few keV or less) and their short range in matter (less than 0.1 μm). The ICRP (1991) and the NCRP (1993) recommend that Auger electrons emitted by radionuclides that are incorporated into DNA should not be assigned a radiation weighting factor of 1 (see Table 1), since it is unreasonable to average the absorbed dose over the whole mass of DNA. Techniques of microdosimetry are considered more appropriate in such cases.

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[21]Internal conversion is the process by which the energy difference between an initial and final state in an atomic nucleus is transferred directly to a bound atomic electron, which is then ejected from the atom (NCRP, 1985). Emission of internal conversion electrons competes with emission of gamma rays, and it increases in importance as the atomic number increases and the transition energy decreases.

[22]The emission of Auger electrons competes with the emission of *X* rays as a means of carrying off the energy released when a vacancy in an inner atomic shell of electrons, created by an electron capture or internal conversion electron event, is filled by an electron from an outer shell (NCRP, 1985). In the Auger process, the filling of a vacant inner shell is accompanied by the simultaneous ejection of one or more electrons from an outer shell. Auger electrons are important compared with other radiations having a short range in matter (beta particles, internal conversion electrons, and alpha particles) mainly when a radionuclide decays by electron capture or an isomeric transition (Kocher, 1981).

Limited data on the biological effectiveness of low-energy Auger electrons are summarized by the ICRP (1991). When an Auger-emitting radionuclide penetrates a cell but is not incorporated into DNA, estimated RBEs for a number of endpoints, including cell killing, are in the range of 1.5-8. These RBEs are similar to estimates for low-energy beta particles emitted in ^{3}H decay discussed previously. When Auger emitters, such as ^{125}I, are incorporated into DNA, RBEs in the range of 20-40 have been estimated for such endpoints as cell transformation. These high RBEs are supported by calculated patterns of energy deposition.

When information on whether an Auger-emitting radionuclide is incorporated into DNA of an exposed individual is lacking, we believe that Auger electrons should be treated in the same way as other low-energy electrons. Thus, for example, when the energy of Auger electrons is less than 15 keV, the probability distribution of REF_L that applies to low-energy beta particles emitted in decay of ^{3}H should be used. When Auger electrons are important compared with other low-energy electrons, their energies are nearly always less than 15 keV (Kocher, 1981).

When an Auger-emitting radionuclide is known to be incorporated into DNA, however, we do not believe that a credible probability distribution of REF_L can be developed based on available information. Although REF_L in such cases should be substantially higher than the REF_L that applies to ^{3}H beta particles, there are potentially important uncertainties including, for example, the fraction of the activity that is incorporated into DNA, the dependence of RBE on the energy of Auger electrons, and the dependence of RBE on dose when cell killing could occur. Thus, we support the recommendation of the ICRP (1991) and the NCRP (1993) that the biological effectiveness of Auger emitters that are incorporated into DNA should be handled as special cases using techniques of microdosimetry.

Summary

The biological effectiveness of low-energy electrons relative to high-energy gamma rays is assumed to be independent of dose and dose rate under similar conditions of exposure to the two radiations. Cancer risks in humans from exposure to electrons (e) are estimated using the following equations:

Solid tumors (any dose and dose rate) –

$$\Re_e = \mathrm{REF}_{e,\mathrm{L}} \times \frac{R_{\gamma,\mathrm{H}}}{\mathrm{DDREF}_{\gamma}} \times D_e \qquad (14)$$

Leukemias (acute exposure) –

$$\Re_e = a(\mathrm{REF}_{e,\mathrm{L}} \times D_e) + b(\mathrm{REF}_{e,\mathrm{L}} \times D_e)^2 \qquad (15)$$

Leukemias (chronic exposure) –

$$\Re_e = a \times \mathrm{REF}_{e,\mathrm{L}} \times D_e \qquad (16)$$

where $\mathrm{REF}_{e,\mathrm{L}}$ is the radiation effectiveness factor at low doses and low dose rates, $R_{\gamma,\mathrm{H}}$ is the risk coefficient (ERR per Gy) at high acute doses of high-energy gamma rays for the solid tumor of concern, a and b are the coefficients of the linear and quadratic terms in the linear-quadratic dose-response relationship for leukemias at high acute doses of high-energy gamma rays, DDREF_γ is the dose and dose-rate effectiveness factor for gamma rays and other low-LET radiations, and D_e is the absorbed dose of electrons in the organ or tissue of concern. A probability distribution of REF_L based on RBEs for beta particles emitted in decay of ^{3}H is applied at all electron energies less than 15 keV (i.e., when the average energy of beta particles or the energy of discrete electrons is less than 15 keV), except the distribution does not apply when an Auger-emitting radionuclide is known to be incorporated into DNA. The probability distribution of REF_L for low-energy electrons is applied to all cancers. The value of REF_L for all electrons of energy greater than 15 keV is assumed to be unity.

As described previously in the summary for photons, a single probability distribution of DDREF_γ is applied in estimating risks of solid tumors under conditions of chronic exposure to electrons, and DDREF_γ under conditions of acute exposure depends on the magnitude of the dose (Land et al., 2002). Acute exposure to beta particles and other electrons emitted by radionuclides is not expected to be of concern. For example, given the residence half-time of tritiated water in soft tissues of about 10 days (ICRP, 1979) and the longer half-life of ^{3}H (12.3 years), exposures to beta particles emitted by ^{3}H generally should be chronic. Acute exposure to electrons presumably is a concern only in situations involving unusual external exposures.

The assumed REF_L for low-energy electrons would be important in calculating cancer risks and probability of causation whenever intakes of radionuclides that emit low-energy beta particles, internal conversion electrons, or Auger electrons contribute significantly to estimated doses to an organ or tissue of concern. Examples of potentially important radionuclides include, in addition to ^{3}H, the beta-emitting radionuclides ^{106}Ru and ^{107}Pd and the Auger-emitting radionuclides ^{51}Cr, ^{55}Fe, ^{57}Co, ^{58}Co, ^{65}Zn, and ^{125}I (Kocher, 1981).

Based on considerations of the energies of secondary electrons produced by interactions of photons in tissue and the assumed REF_L for photons of energy 30-250 keV, REF_L also should be greater than unity at electron energies of 15-60 keV. However, such an REF_L is not adopted in this work, due to the lack of supporting radiobiological data.

The assumed probability distributions of REF_L for electrons of different energies are summarized in Table 17.

Table 17. Summary of probability distributions of radiation effectiveness factors for electrons to be used in estimating cancer risks and probability of causation in accordance with eq. (14), (15), or (16)[a]

Electron energy	Probability distribution of radiation effectiveness factor (REF_L)
> 15 keV	Single-valued at 1.0 (assumption that such electrons have same biological effectiveness as reference high-energy gamma rays)[b]
< 15 keV[c]	Lognormal distribution having a 95% confidence interval between 1.2 and 5.0

[a]Probability distributions apply to all cancers and at any dose and dose rate.

[b]Based on considerations of the energies of secondary electrons produced by photon interactions in tissue, 15-60 keV electrons should have the same REF_L as 30-250 keV photons (see Table 12). However, a distribution of REF_L greater than unity for 15-60 keV electrons is not adopted in this work, due to the lack of supporting radiobiological data.

[c]Probability distribution of REF_L is based on data on RBE for beta particles emitted in decay of ^3H. Distribution does not apply to Auger-emitting radionuclides that are incorporated into DNA.

SUMMARY OF REFs FOR DIFFERENT RADIATIONS

Based on evaluations of information on the biological effectiveness of various types of ionizing radiation, including neutrons, alpha particles, lower-energy photons, and lower-energy electrons, relative to high-energy photons, we have developed radiation effectiveness factors (REFs) for the different radiation types for use in calculating the probability of causation of specific cancers in humans. The REFs developed in this report are applied to estimates of cancer risk in specific organs or tissues at high acute doses of high-energy gamma rays, which are obtained mainly from studies in the Japanese atomic-bomb survivors.

The REFs developed in this report are expressed as probability distributions. These distributions are intended to represent the current state of knowledge of the biological effectiveness of different radiation types in inducing cancers in humans, taking into account uncertainties in data on relative biological effectiveness (RBE) obtained from relevant radiobiological studies and any other judgments involved in evaluating the available information. The REFs for the different radiations considered in this report are summarized as follows.

Neutrons

The assumed probability distributions of REFs for neutrons are summarized previously in Table 7. Separate distributions of REFs are developed for solid tumors and leukemias. The distributions for solid tumors are REFs that represent data on RBE at high acute doses of the reference high-energy gamma rays, REF_H, whereas the distributions for leukemias are REFs that

represent data on RBE at low doses and low dose rates, REF_L. When REF_H is used to estimate risks of solid tumors at any dose and dose rate of neutrons, a dose and dose-rate effectiveness factor (DDREF) for high-energy gamma rays is not used. REFs at high acute doses of the reference radiation are not used in estimating cancer risks for any other radiation type.

The probability distributions of REF_H for solid tumors and REF_L for leukemias are assumed to depend on neutron energy. Based on the energy dependence of the radiation weighting factor recommended by the ICRP (see Fig. 7), probability distributions of REFs are developed for three groups of energies: 0.1-2 MeV (including fission neutrons), 10-100 keV and 2-20 MeV, and less than 10 keV and greater than 20 MeV.

Under conditions of chronic exposure to neutrons, a small correction representing an inverse dose-rate effect is applied to the probability distributions of REFs for solid tumors and leukemias. This correction is assumed to be independent of neutron energy.

The 50^{th} percentile (median) and the 95% confidence interval (2.5^{th} and 97.5^{th} percentiles) of the assumed probability distributions of REFs for neutrons are given in Tables 18 and 19.

Alpha Particles

The assumed probability distributions of REFs for alpha particles are summarized previously in Table 9. As in the case of neutrons, separate distributions of REFs are developed for solid tumors and leukemias, except the distribution for solid tumors is not applied in estimating risks of lung cancer due to inhalation of radon and its short-lived decay products. The distribution for each cancer type is the REF at low doses and low dose rates of the reference high-energy gamma rays, REF_L. The separate probability distributions of REF_L for solid tumors and leukemias are applied at all energies of alpha particles emitted by radionuclides.

In all cases of exposure to alpha particles emitted by radionuclides, a small correction representing an inverse dose-rate effect under conditions of chronic exposure is applied to the probability distributions of REF_L for solid tumors and leukemias. Acute exposure to alpha particles emitted by radionuclides is assumed not to occur.

The 50^{th} percentile (median) and the 95% confidence interval (2.5^{th} and 97.5^{th} percentiles) of the assumed probability distributions of REF_L for alpha particles are given in Table 20.

Table 18. Summary of 95% confidence intervals of probability distributions of radiation effectiveness factors for neutrons and solid tumors[a]

		95% confidence interval of REF_H[b]		
Neutron energy	Exposure	2.5th percentile	50th percentile	97.5th percentile
0.1-2 MeV[c]	Acute	2.0	7.7	30
	Chronic	2.4	10	47
10-100 keV; 2-20 MeV	Acute	1.2	3.8	18
	Chronic	1.4	4.7	28
< 10 keV; > 20 MeV	Acute	1.1	1.9	11
	Chronic	1.1	2.4	16

[a]Summary description of probability distributions is given in Table 7.
[b]REF_H is radiation effectiveness factor at high acute doses of reference high-energy gamma rays.
[c]REFs for this energy range apply to fission neutrons.

Table 19. Summary of 95% confidence intervals of probability distributions of radiation effectiveness factors for neutrons and leukemias[a]

		95% confidence interval of REF_L[b]		
Neutron energy	Exposure	2.5th percentile	50th percentile	97.5th percentile
0.1-2 MeV[c]	Acute	2.0	11	60
	Chronic	2.5	14	91
10-100 keV; 2-20 MeV	Acute	1.3	5.6	36
	Chronic	1.5	7.1	55
< 10 keV; > 20 MeV	Acute	1.1	2.8	22
	Chronic	1.2	3.4	34

[a]Summary description of probability distributions is given in Table 7.
[b]REF_L is radiation effectiveness factor at low doses and low dose rates of reference high-energy gamma rays.
[c]REFs for this energy range apply to fission neutrons.

Table 20. Summary of 95% confidence intervals of probability distributions of radiation effectiveness factors for alpha particles[a]

		95% confidence interval of REF_L[c]		
Cancer type	Exposure[b]	2.5th percentile	50th percentile	97.5th percentile
Solid tumors	Chronic	3.4	18	101
Leukemias	Chronic	1.0	4.1	42

[a]Summary description of probability distributions is given in Table 9.
[b]All exposures to alpha particles emitted by radionuclides are assumed to be chronic.
[c]REF_L is radiation effectiveness factor at low doses and low dose rates of reference high-energy gamma rays.

Photons

The assumed probability distributions of REFs for photons at low doses and low dose rates, REF_L, are summarized previously in Table 12. The biological effectiveness of photons of energy greater than 250 keV is assumed to be the same as that of high-energy gamma rays, and probability distributions of REF_L greater than unity are applied at energies of 30-250 keV and less than 30 keV. The assumed distributions of REF_L are applied to all cancer types.

The 50th percentile (median) and the 95% confidence interval (2.5th and 97.5th percentiles) of the assumed probability distributions of REF_L for photons are given in Table 21.

Electrons

The assumed probability distributions of REFs for electrons at low doses and low dose rates, REF_L, are summarized previously in Table 17. The biological effectiveness of electrons of energy greater than 15 keV is assumed to be the same as that of high-energy gamma rays, and a probability distribution of REF_L greater than unity is applied at energies less than 15 keV, except Auger-emitting radionuclides that are incorporated into DNA are excluded. The assumed distribution of REF_L at low energies is applied to all cancer types.

The 50th percentile (median) and the 95% confidence interval (2.5th and 97.5th percentiles) of the assumed probability distributions of REF_L for electrons are given in Table 22.

Table 21. Summary of 95% confidence intervals of probability distributions of radiation effectiveness factors for photons[a]

		95% confidence interval of REF_L[b]		
Photon energy	Exposure	2.5th percentile	50th percentile	97.5th percentile
> 250 keV	Acute or chronic	–	1.0	–
30-250 keV	Acute or chronic	1.0	1.9	4.7
< 30 keV	Acute or chronic	1.1	2.4	6.1

[a]Summary description of probability distributions is given in Table 12. Probability distributions of REF_L apply to all cancers.

[b]REF_L is radiation effectiveness factor at low doses and low dose rates of reference high-energy gamma rays.

Table 22. Summary of 95% confidence intervals of probability distributions of radiation effectiveness factors for electrons[a]

		95% confidence interval of REF_L[b]		
Electron energy	Exposure	2.5th percentile	50th percentile	97.5th percentile
> 15 keV	Acute or chronic	–	1.0	–
< 15 keV[c]	Acute or chronic	1.2	2.4	5.0

[a]Summary description of probability distributions is given in Table 17. Probability distributions of REF_L apply to all cancers.

[b]REF_L is radiation effectiveness factor at low doses and low dose rates of reference high-energy gamma rays.

[c]Auger-emitting radionuclides that are incorporated into DNA are excluded. Beta-emitting radionuclides are included if average energy of continuous spectrum of beta particles is less than 15 keV.

REFERENCES

Bauchinger, M., 1984. "Cytogenetic Effects in Human Lymphocytes As a Dosimetry System," p. 15 in *Biological Dosimetry*, ed. by W.G. Eisert and M.L. Mendelsohn, Springer-Verlag, Berlin, Germany.

Bocian, E., Ziembia-Zak, E.B., Rosiek, O., and Sablinski, J., 1977. "Chromosome Aberration in Human Lymphocytes Exposed to Tritiated Water *in Vitro*," *Curr. Topics Radiat. Res. Q.* 12, 168-181.

Boecker, B.B., Hahn, F.F., Muggenburg, B.A., Guilmette, R.A., Griffith, W.C., and McClellan, R.O., 1988. "The Relative Effectiveness of Inhaled Alpha and Beta Emitting Radionuclides in Producing Lung Cancer," p. 1059 in *Radiation Protection Practice, Proceedings of the Seventh International Congress of IRPA*, Vol. II, Pergamon Press, Sydney, Australia.

Brenner, D.J., 1990. "The Microdosimetry of Radon Daughters and Its Significance," *Radiat. Prot. Dosim.* 31, 399-403.

Brenner, D.J., 1999. "Does Fractionation Decrease the Risk of Breast Cancer Induced by Low-LET Radiation?," *Radiat. Res.* 151, 225-229.

Brenner, D.J., and Amols, H.I., 1989. "Enhanced Risk from Low-Energy Screen-Film Mammography X Rays," *Brit. J. Radiol.* 62, 910-914.

Brewen, J.G., and Luippold, H.E., 1971. "Radiation-Induced Human Chromosome Aberrations: *In Vitro* Dose Rate Studies," *Mutat. Res.* 12, 305.

Brewen, J.G., Preston, R.L., and Littlefield, L.G., 1972. "Radiation Induced Human Chromosome Aberrations. III. Aberration Yields Following an Accidental Whole-Body Exposure to ^{60}Co γ-Rays," *Radiat. Res.* 49, 647.

Broerse, J.J., van Bekkum, D.W., Zoetelief, J., and Zurcher, C., 1991. "Relative Biological Effectiveness for Neutron Carcinogenesis in Monkeys and Rats," *Radiat. Res.* 128, S128-S135.

Brooks, A.L., 1975. "Chromosome Damage in Liver Cells from Low Dose Rate Alpha, Beta, and Gamma Irradiation: Derivation of RBE," *Science* 190, 1090.

Brooks, A.L., Mewhinney, J.A., and McClellan, R.O., 1972. "The *in Vivo* Cytogenetic Effects of ^{252}Cf on Liver and Bone Marrow of the Chinese Hamster," *Health Phys.* 22, 701-706.

Byrne, B.J., and Lee, W.R., 1989. "Relative Biological Effectiveness of Tritiated Water to Gamma Radiation for Germ Line Mutations," *Radiat. Res.* 117, 469-479.

Carnes, B.A., Grahn, D., and Thompson, J.F., 1989. "Dose Response Modeling of the Life Shortening in a Retrospective Analysis of the Combined Data from the JANUS Program at Argonne National Laboratory," *Radiat. Res.* 119, 39-56.

Carsten, A.L., and Commerford, S.L., 1976. "Dominant Lethal Mutations in Mice Resulting from Chronic Tritiated Water (HTO) Ingestion," *Radiat. Res.* 66, 609-614.

Chopra, C., and Heddle, J.A., 1988. *Cytogenetic Measurements of the Relative Biological Effectiveness of Tritium*, INFO-0287, Atomic Energy Control Board, Ottawa, Ontario, Canada.

CIRRPC (Committee on Interagency Radiation Research and Policy Coordination), 1995. *Neutron Quality Factor*, ORAU 95/F-29, CIRRPC, Washington, DC.

Coggle, J.E., 1988. "Lung Tumour Induction in Mice after X-Rays and Neutrons," *Int. J. Radiat. Biol.* 53, 585-598.

Coppola, M., 1993. "Specification of Fast Neutron Radiation Quality from Cell Transformation Data," *Radiat. Prot. Dosim.* 46, 211-212.

Cox, R., and Masson, W.K., 1979. "Mutation and Activation of Cultured Mammalian Cells Exposed to Beams of Accelerated Heavy Ions. III. Human Diploid Fibroplasts," *Int. J. Radiat. Biol.* 36, 149-160.

Cox, R., Thacker J., Goodhead, D.T., and Munson, R.J., 1977. "Mutation and Inactivation of Mammalian Cells by Various Ionizing Radiations," *Nature* 267, 425.

Dobson, R.L., Straume, T., Carrano, A.V., Minkler, J.L., Deaven, L.L., Littlefield, L.G., and Awa, A.A., 1991. "Biological Effectiveness of Neutrons from Hiroshima Bomb Replica: Results of a Collaborative Cytogenetic Study," *Radiat. Res.* 142-149.

DOE (U.S. Department of Energy), 1993. "10 CFR Part 835—Occupational Radiation Protection," Final Rule, *Fed. Registr.* 58, 65458-65512; see also Title 10 of *Code of Federal Regulations*, which is published annually by U.S. Government Printing Office, Washington, DC.

Eckerman, K.F., Leggett, R.W., Nelson, C.B., Puskin, J.S., and Richardson, A.C.B., 1999. *Cancer Risk Coefficients for Environmental Exposure to Radionuclides*, Federal Guidance Report No. 13, EPA 402-R-99-001, U.S. Environmental Protection Agency, Washington, DC.

Edwards, A.A., 1997. "Relative Biological Effectiveness of Neutrons for Stochastic Effects," *Documents of the NRPB* 8, No. 2, National Radiological Protection Board, Chilton, U.K.

Edwards, A.A., 1999. "Neutron RBE Values and Their Relationship to Judgements in Radiological Protection," *J. Radiol. Prot.* 19, 93-105.

Edwards, A.A., Lloyd, D.C., and Prosser, J.S., 1985. "The Induction of Chromosomal Aberrations in Human Lymphocytes by Accelerated Charged Particles," *Radiat. Prot. Dosim.* 13, 205-209.

Edwards, A.A., Lloyd, D.C., and Prosser, J.S., 1990. "The Induction of Chromosomal Aberrations in Human Lymphocytes by 24 keV Neutrons," *Radiat. Prot. Dosim.* 31, 265-268.

Edwards, A.A., Purrott, R.J., Prosser, J.S., and Lloyd, D.C., 1980. "The Induction of Chromosome Aberrations in Human Lymphocytes by Alpha-Radiation," *Int. J. Radiat. Biol.* 38, 83-91.

EPA (U.S. Environmental Protection Agency), 1994. *Estimating Radiogenic Cancer Risks*, EPA 402-R-93-076, EPA, Washington, DC.

EPA (U.S. Environmental Protection Agency), 1999. *Estimating Radiogenic Cancer Risks. Addendum: Uncertainty Analysis*, EPA 402-R-99-003, EPA, Washington, DC.

Fabry, L., Leonard, A., and Wambersie, A., 1985. "Induction of Chromosome Aberrations in G_0 Human Lymphocytes by Low Doses of Ionizing Radiations of Different Quality," *Radiat. Res.* 103, 122.

Gragtmans, N.J., Myers, D.K., Johnson, J.R., Jones, A.R., and Johnson, L.D., 1984. "Occurrence of Mammary Tumors in Rats After Exposure to Tritium Beta Rays and 200-kVp X-Rays," *Radiat. Res.* 99, 636-650.

Grahn, D., Lombard, L. S., and Carnes, B. A., 1992. "The Comparative Tumorigenic Effect of Fission Neutrons and Cobalt-60 γ-rays in the B6CF1 Mouse, *Radiat. Res.* 129, 19-36.

Griffith, W.C., Boecker, B.B., Cuddihy, R.G., Guilmette, R.A., Hahn, F.F., McClellan, R.O., Muggenberg, B.A., and Snipes, M.B., 1987. "Preliminary Radiation Risk Estimates of Carcinoma Incidence in the Lung as a Function of Cumulative Radiation Dose Using Proportional Tumor Incidence Rates," p. 196 in *Inhalation Toxicology Research Institute Annual Report*, LMF-120, National Technical Information Service, Springfield, VA.

Griffith, W.C., Boecker, B.B., Gillett, N.A., et al., 1991. "Comparison of Risk Factors for Bone Cancer Induced by Inhaled $^{90}SrCl_2$ and $^{238}PuO_2$," in *Proceedings of EULEP/DOE Joint*

Bone Radiobiology Workshop, UDC-472-136, U.S. Department of Energy, Washington, DC.

Grogan, H.A., Sinclair, W.K., and Voillequé, P.G., 2000. *Assessing Risks of Exposure to Plutonium*, Revision 2, RAC Report No. 5-CDPHE-RFP-1998-FINAL(Rev. 2), Radiological Assessments Corporation, Neeses, South Carolina.

Grogan, H.A., Sinclair, W.K., and Voillequé, P.G., 2001. "Risks of Fatal Cancer from Inhalation of ^{239,240}Plutonium by Humans: A Combined Four-Method Approach with Uncertainty Evaluation," *Health Phys.* 80, 447.

Hahn, F.F., Griffith, W.C., Boecker, B.B., Muggenberg, B.A., and Lundgren, D.L., 1991. "Comparison of the Effects of Inhaled $^{239}PuO_2$ and β-Emitting Radionuclides on the Incidence of Lung Carcinomas in Laboratory Animals," pp. 916-919 in *Proceedings of IRPA8: Worldwide Achievement in Public and Occupational Health Protection Against Radiation*, 8th International Congress of the International Radiation Protection Association, Vol. I, Pergamon Press, London.

Harrison, J.D., Khursheed, A., and Lambert, B.E., 2002. "Uncertainties in Dose Coefficients for Intakes of Tritiated Water and Organically Bound Forms of Tritium by Members of the Public," *Radiat. Prot. Dosim.* 98, 299.

Hei, T.K., Chen, D.J., and Hall, E.J., 1988. "Mutation Induction by Charged Particles of Defined LET," *Carcinogenesis* 9, 1233.

Hunacek, M.M., and Kathren, R.L., 1995. "Alpha Radiation Risk Coefficients for Liver Cancer, Bone Sarcomas, and Leukemia," *Health Phys.* 68, 41-49.

ICRP (International Commission on Radiological Protection), 1960. *Recommendations of the International Commission on Radiological Protection. Report of Committee II on Permissible Dose for Internal Radiation (1959)*, Pergamon Press, Oxford, U.K.

ICRP (International Commission on Radiological Protection), 1979. *Limits for Intakes of Radionuclides by Workers*, ICRP Publication 30, Part 1, *Ann. ICRP* 2, No. 3/4.

ICRP (International Commission on Radiological Protection), 1980. *Biological Effects of Inhaled Radionuclides*, ICRP Publication 31, *Ann. ICRP* 4, No. 1-2.

ICRP (International Commission on Radiological Protection), 1987. *Lung Cancer Risk from Indoor Exposures to Radon Daughters*, ICRP Publication 50, *Ann. ICRP* 17, No. 1.

ICRP (International Commission on Radiological Protection), 1991. *1990 Recommendations of the International Commission on Radiological Protection*, ICRP Publication 60, *Ann. ICRP* 21, No. 1-3.

ICRP (International Commission on Radiological Protection), 1993. *Protection Against Radon-222 at Home and at Work*, ICRP Publication 65, *Ann. ICRP* 23, No. 2.

ICRP (International Commission on Radiological Protection), 1997. *Conversion Coefficients for Use in Radiological Protection Against External Radiation*, ICRP Publication 74, *Ann. ICRP* 26, No. 3/4.

ICRU (International Commission on Radiation Units and Measurements), 1986. *The Quality Factor in Radiation Protection*, ICRU Report 40, ICRU, Bethesda, MD.

Kamiguchi, M., Tateno, H., and Mikamo, K., 1990. "Dose-Response Relationship for the Induction of Structural Chromosome Aberrations in Human Spermatozoa After *in Vitro* Exposure to Tritium Beta-Rays," *Mutat. Res.* 228, 125-131.

Kashima, M., Joshima, H., and Fukutsu, K., 1985. "Induction of Micronuclei and Some Other Abnormalities in Mouse Bone Marrow Following Tritium Exposure," p. 246-257 in *Proceedings of the Second Workshop on Tritium Radiobiology and Health Physics*, ed. by H. Matsudaira, T. Yamaguchi, and H. Etoh, NIRS-M-52, National Institute of Radiological Sciences, Chiba, Japan.

Kocher, D.C., 1981. *Radioactive Decay Tables*, DOE/TIC-11026, National Technical Information Service, Springfield, VA.

Land, C., Gilbert, E., Smith, J., Hoffman, F.O., Apostoaei, I., Thomas, B., and Kocher, D.C., 2002. *Report of the NCI-CDC Working Group to Revise the 1985 NIH Radioepidemiological Tables* (in preparation).

Lee, W., Chiacchierini, R.P., Shleien, B., and Telles, N.C., 1982. "Thyroid Tumors Following ^{131}I or Localized X Irradiation to the Thyroid and Pituitary Glands in Rats," *Radiat. Res.* 92, 307-319.

Little, J.B., 1986. "Induction of Neoplastic Transformation by Low-Dose-Rate Exposure to Tritiated Water," *Radiat. Res.* 107, 225-233.

Littlefield, L.G., Joiner, E.E., and Hubner, K.F., 1989. "Cytogenetic Techniques in Biological Dosimetry: Overview and Example of Dose Estimation in 10 Persons Exposed to Gamma Radiation in the 1984 Mexican ^{60}Co Accident," in *Medical Management of Radiation Accidents*, ed. by F.A. Mettler, Jr., C.A. Kelsey, and R.C. Ricks, CRC Press, Boca Raton, Florida.

Lloyd, D.C., Edwards, A.A., Leonard, A., Deknudt, G., Natarajan, A., Obe, G., Palitti, F., Tanzarella, C., and Tawn, E.J., 1988. "Frequencies of Chromosome Aberrations Induced in Human Blood Lymphocytes by Low Doses of X Rays," *Int. J. Radiat. Biol.* 53, 49-55.

Lloyd, D.C., Edwards, A.A., and Prosser, J.S., 1986. "Chromosome Aberrations Induced in Human Lymphocytes by *in Vitro* Acute X and Gamma Radiation," *Radiat. Prot. Dosim.* 15, 83.

Lloyd, D.C., Purrott, R.J., Dolphin, G.W., Bolton, D., Edwards, A.A., and Corp, M., 1975. "The Relationship Between Chromosome Aberrations and Low-LET Radiation Dose to Human Lymphocytes," *Int. J. Radiat. Biol.* 28, 75-90.

Lubin, J.H., Boice, J.D., Jr., Edling, C., Hornung, R.W., Howe, G., Kunz, E., Kusiak, R.A., Morrison, H.I., Radford, E.P., Samet, J.M., Tirmarche, M., Woodward, A., and Yao, S.X., 1995. "Radon-Exposed Underground Miners and Inverse Dose-Rate (Protraction Enhancement) Effects," *Health Phys.* 69, 494-500.

Mays, C.W., and Finkel, M.P., 1980. "RBE of α-Particles vs. β-Particles in Bone Sarcoma Induction," p. 401 in *Proceedings of the 5th International Congress of IRPA*, Vol. II, Israel Health Physics Society, Jerusalem, Israel.

Matsuda, Y., Yamada, T., and Tobari, I., 1985. "Chromosomal Effects of Tritium in Mouse Zygotes Fertilized *in Vitro*," p. 193-206 in *Proceedings of the Second Workshop on Tritium Radiobiology and Health Physics*, ed. by H. Matsudaira, T. Yamaguchi, and H. Etoh, NIRS-M-52, National Institute of Radiological Sciences, Chiba, Japan.

Miller, R.C., Geard, C.R., Brenner, D.J., Komatsu, K., Marino, S.A., and Hall, E.J., 1989. "Neutron-Energy-Dependent Oncogenic Transformation of C3H10T½ Mouse Cells," *Radiat. Res.* 117, 114-127.

Miller, R.C., Marino, S.A., Napoli, J., Shah, H., Hall, E.J., Geard, C.R., and Brenner, D.J., 2000. "Oncogenic Transformation in C3H10T½ Cells by Low-Energy Neutrons," *Int. J. Radiat. Biol.* 76, 327-333.

Mole, R.H., and Davids, J.A.G., 1982. "Induction of Myeloid Leukaemia and Other Tumours in Mice by Irradiation with Fission Neutrons," pages 31-42 in *Neutron Carcinogenesis*, Commission of the European Communities, Luxembourg.

Mole, R.H., Papworth, D.G., and Corp, M.J., 1983. "The Dose Response X-Ray Induction of Myeloid Leukaemia in Male CBA/H Mice, *Br. J. Cancer* 47, 285-291.

Morimoto, K., Ogawa, Y., Okayama, A., Shirakawa, T., and Miura, K., 1989. "Development of the Monitoring System for Human Exposure to Tritium: Chromosome Aberrations in

Human Lymphocytes Exposed to HTO," p. 137-142 in *Tritium Radiobiology and Health Physics*, Proceedings of the Third Japan-U.S. Workshop, ed. by S. Okada, IPPJ-REV-3, Institute of Plasma Physics, Nagoya University, Nagoya, Japan.

Muirhead, C.R., Cox, R., Stather, J.W., MacGibbon, B.H., Edwards, A.A., and Haylock, R.G.E., 1993. "Relative Biological Effectiveness," pages 126-139 in *Documents of the NRPB* 4, No. 4, National Radiological Protection Board, Chilton, U.K.

Myers, D.K., and Johnson, J.R., 1991. *Toxicity and Dosimetry of Tritium: A Review*, Atomic Energy Control Board, Ottawa, Ontario, Canada; see also Myers, D.K., and Johnson, J.R., 1990. *RBE of Tritium and Induction of Myeloid Leukemia and CBA/H Mice*, INFO-0360, Atomic Energy Control Board, Ottawa, Ontario, Canada.

Nakamura, N., Morikawa, N., and Okada, S., 1985. "Dose Rate Effects of Mutation Induction by Tritiated Water in Mouse Leukemia Cells," p. 95-100 in *Proceedings of the Second Workshop on Tritium Radiobiology and Health Physics*, ed. by H. Matsudaira, T. Yamaguchi, and H. Etoh, NIRS-M-52, National Institute of Radiological Sciences, Chiba, Japan.

National Research Council, 1988. *Health Risks of Radon and Other Internally Deposited Alpha-Emitters*, BEIR IV, National Academy Press, Washington, DC.

NCRP (National Council on Radiation Protection and Measurements), 1971. *Protection Against Neutron Radiation*, Second Edition, NCRP Report No. 38, NCRP, Bethesda, MD.

NCRP (National Council on Radiation Protection and Measurements), 1985. *A Handbook of Radioactivity Measurements Procedures*, Second Edition, NCRP Report No. 58, NCRP, Bethesda, MD.

NCRP (National Council on Radiation Protection and Measurements), 1990. *The Relative Biological Effectiveness of Radiations of Different Quality*, NCRP Report No. 104, NCRP, Bethesda, MD.

NCRP (National Council on Radiation Protection and Measurements), 1991. *Conceptual Basis for Calculations of Absorbed-Dose Distributions*, NCRP Report No. 108, NCRP, Bethesda, MD.

NCRP (National Council on Radiation Protection and Measurements), 1993. *Limitation of Exposure to Ionizing Radiation*, NCRP Report No. 116, NCRP, Bethesda, MD.

Nomura, T., and Yamamoto, O., 1989. "*In Vivo* Somatic Mutation in Mice Induced by Tritiated Water," p. 230-233 in *Tritium Radiobiology and Health Physics*, Proceedings of the

Third Japan-U.S. Workshop, ed. by S. Okada, IPPJ-REV-3, Institute of Plasma Physics, Nagoya University, Nagoya, Japan.

NRC (U.S. Nuclear Regulatory Commission), 1991. "10 CFR Part 20 et al.—Standards for Protection Against Radiation," *Fed. Registr.* 56, 23360-23474; see also Title 10 of *Code of Federal Regulations*, which is published annually by U.S. Government Printing Office, Washington, DC.

Pomerantseva, M.D., 1964. "The Genetic Activity of Various Types of Ionizing Radiation," *Radiobiologiya* 4, 13.

Prosser, J.S., Lloyd, D.C., Edwards, A.A., and Stather, J.W., 1983. "The Induction of Chromosome Aberrations in Human Lymphocytes by Exposure to Tritiated Water *in Vitro*," *Radiat. Protect. Dosim.* 4, 21-26.

Purrott, R.J., Edwards, A.A., Lloyd, D.C., and Stather, J.W., 1980. "The Induction of Chromosome Aberrations in Human Lymphocytes by *in Vitro* Irradiation with α-Particles from Plutonium-239," *Int. J. Radiat. Biol.* 38, 277-284.

Ron, E., Lubin, J.H., Shore, R.E., Mabuchi, K., Modan, B., Pottern, L.M., Scheider, A.B., Tucker, M.A., and Boice, J.D., Jr., 1995. "Thyroid Cancer after Exposure to External Radiation: A Pooled Analysis of Seven Studies," *Radiat. Res.* 141, 259-277.

Satow, Y., Lee, J., and Sawada, S., 1989. "Teratogenic Effect of Tritium Water and Tritium Simulator on Rat Embryos," p. 280-286 in *Tritium Radiobiology and Health Physics*, Proceedings of the Third Japan-U.S. Workshop, ed. by S. Okada, IPPJ-REV-3, Institute of Plasma Physics, Nagoya University, Nagoya, Japan.

Schmid, E., Regulla, D., Guldbakke, S., Schlegel, D., and Bauchinger, M., 2000. "The Effectiveness of Monoenergetic Neutrons at 565 keV in Producing Dicentric Chromosomes in Human Lymphocytes at Low Doses," *Radiat. Res.* 154, 307-312.

Searle, A.G., 1984. "Genetic Effects of Tritium in Mammals," p. 303-310 in *Proceedings of the European Seminar on the Risks from Tritium Exposure*, EUR 9056 EN, Commission of the European Communities, Mol, Belgium.

Searle, A.G., Beechey, C.V., Green, D., and Humphreys, E.R., 1976. "Cytogenetic Effects of Protracted Exposures to Alpha Particles from ^{239}Pu and to Gamma Rays from ^{60}Co Compared in Male Mice," *Mutat. Res.* 41, 297-310.

Sevan'kaev, A.V., Zherbin, E.A., Luchnik, N.V., Obaturov, G.M., Kozloo, G.M., Tayatte, E.G., and Kapchigasher, S.P., 1979. "Neutron-Induced Cytogenetic Effects in Lymphocytes of Human Peripheral Blood *in Vitro*. I. Dose Dependence of the Effects of Neutrons of

Different Energies on Various Types of Chromosome Aberrations," *Genetika* 15, 1046-1060.

Shimizu, Y., Kato, H., and Schull, W.J., 1990. "Studies of the Mortality of A-Bomb Survivors: 9. Mortality, 1950-1985: Part 2. Cancer Mortality Based on the Revised Doses (DS86)," *Radiat. Res.* 121, 120.

Shleien, B., Slaback, L.A., Jr., and Birky, B.K. (eds.), 1998. *Handbook of Health Physics and Radiological Health*, Third Edition, Williams & Wilkins, Baltimore, MD.

Sinclair, W.K., 1985. "Experimental RBE Values of High-LET Radiations at Low Doses and the Implications for Quality Factor Assignment," *Radiat. Prot. Dosim.* 13, 319-326.

Sinclair, W.K., 1996. "The Present System of Quantities and Units for Radiation Protection," *Health Phys.* 70, 781-786.

Stanton, L., Day, J.L., Lightfoot, D.A., Villafana, T., and Rauch, P.L., 1979. "Rapid Computation of Diagnostic X-Ray Bremsstrahlung Spectra," *Radiol.* 130, 477-484.

Storer, J.B., Serrano, L.J., Darden, E.B., Jr., Jernigan, M.C., and Ullrich, R.L., 1979. "Life shortening in RFM and BALB/c Mice as a Function of Radiation Quality, Dose and Dose Rate," *Radiat. Res.* 78, 122-161.

Storer, J.B., and Ullrich, R.L., 1983. "Life Shortening in BALB/c Mice Following Brief, Protracted or Fractionated Exposures to Neutrons," *Radiat. Res.* 96, 335-347.

Straume, T., and Carsten, A.L., 1993. "Tritium Radiobiology and Relative Biological Effectiveness," *Health Phys.* 65, 657-672.

Straume, T., 1995. "High-Energy Gamma Rays in Hiroshima and Nagasaki: Implications for Risk and w_R," *Health Phys.* 69, 954-956.

Suyama, I., and Etoh, H., 1985. "Chromosome Effects of Tritium on Lymphocytes of the Telost, *Umbra Limi*," p. 146-156 in *Proceedings of the Second Workshop on Tritium Radiobiology and Health Physics*, ed. by H. Matsudaira, T. Yamaguchi, and H. Etoh, NIRS-M-52, National Institute of Radiological Sciences, Chiba, Japan.

Suzuki, F., Mori, T., Nikaida, O., Suzuki, K., and Watanabe, M., 1989. "Neoplastic Transformation and Chromosome Aberration Induced by Tritiated Water in Golden Hamster Embryo Cells," p. 211-216 in *Tritium Radiobiology and Health Physics*, Proceedings of the Third Japan-U.S. Workshop, IPPJ-REV-3, Institute of Plasma Physics, Nagoya University, Nagoya, Japan.

Thacker, J., Stretch, A., and Stephens, M.A., 1979. "Mutation and Inactivation of Cultured Mammalian Cells Exposed to Beams of Accelerated Heavy Ions. II. Chinese Hamster V79 Cells," *Int. J. Radiat. Biol.* 36, 137-148.

Thomas, B.A., and Hoffman, F.O., 2000. *The Estimate of Excess Lifetime Risk of Cancer Incidence Associated with Discrete Routine Releases of Tritiated Water Vapor (HTO) from the National Tritium Labelling Facility at Lawrence Berkeley National Laboratory*, SOR/TR-003-900, SENES Oak Ridge, Inc., Oak Ridge, TN.

Thompson, D.E., Mabuchi, K., Ron, E., Soda, M., Tokunaga, M., Ochikubo, S., Sugimoto, S., Ikeda, T., Terasaki, M., Izumi, S., and Preston, D.L., 1994. "Cancer Incidence in Atomic Bomb Survivors. Part II: Solid Tumors, 1958-1987," *Radiat. Res.* 137, S17-S67.

Turner, J.E., 1995. *Atoms, Radiation, and Radiation Protection*, Second Edition, John Wiley & Sons, New York.

Ueno, A.M., Furuno-Fukushi, I., and Matsudaira, H., 1982. "Induction of Cell Killing, Micronuclei and Mutation to 6-Thioguanine Resistance After Exposure to Low Dose-Rate Gamma Rays and Tritiated Water in Cultured Mammalian Cells (L5178Y)," *Radiat. Res.* 91, 447-456.

Ueno, A.M., Furuno-Fukushi, I., and Matsudaira, H., 1989. "Cell Killing and Mutation to 6-Thioguanine Resistance After Exposure to Tritiated Amino Acids and Tritiated Thymidine in Cultured Mammalian Cells," p. 200-210 in *Tritium Radiobiology and Health Physics*, Proceedings of the Third Japan-U.S. Workshop, ed. by S. Okada, IPPJ-REV-3, Institute of Plasma Physics, Nagoya University, Nagoya, Japan.

Ullrich, R.L., 1980. "Effects of Split Doses of X-Rays or Neutrons on Lung Tumor Formation in RFM Mice," *Radiat. Res.* 83, 138-145.

Ullrich, R.L., 1984. "Tumor Induction in BALB/c Mice after Fractionated or Protracted Exposures to Fission Spectrum Neutrons," *Radiat. Res.* 97, 587-597.

Ullrich, R.L., Jernigan, M.C., Cosgrove, G.E., Satterfield, L.C., Bowles, N.D., and Storer, J.B., 1976. "The Influence of Dose and Dose Rate on the Incidence of Neoplastic Disease in RFM Mice after Neutron Irradiation," *Radiat. Res.* 68, 115-131.

Ullrich, R.L., Jernigan, M.C., and Storer, J.B., 1977. "Neutron Carcinogenesis Dose and Dose-Rate Effects in BALB/c Mice," *Radiat. Res.* 72, 487-498.

Ullrich, R.L., Jernigan, M.C., and Adams, L.M., 1979. "Induction of Lung Tumors in RFM Mice after Localized Exposures to X-Rays or Neutrons," *Radiat. Res.* 80, 464-473.

Ullrich, R.L., and Preston, R.J., 1987. "Myeloid Leukemia in Male RFM Mice Following Irradiation with Fission Spectrum Neutrons or γ-Rays," *Radiat. Res.* 109, 165-170.

Underbrink, A.G., Sparrow, R.C., Sparrow, A.H., and Rossi, H.H., 1970. "RBE of X Rays and 0.43 MeV Monoenergetic Neutrons on Somatic Mutations and Loss of Reproductive Integrity in *Tradescantia* Stamen Hairs," p. 373 in *Symposium on Neutrons in Radiobiology*, CONF-691106, Oak Ridge National Laboratory, Oak Ridge, Tennessee; see also *Radiat. Res.* 44, 187.

UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation), 1982. *Ionizing Radiation: Sources and Biological Effects*, Report to the General Assembly, with Annexes, United Nations, New York.

UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation), 2000. "Epidemiological Evaluations of Radiation-Induced Cancer," Annex I in *Sources and Effects of Ionizing Radiation*, Vol. II, pp. 298-450, United Nations, New York.

Upton, A.C., Randolph, M.L., Conklin, J.W., Kastenbaum, M.A., Slater, M., Melville, G.S.J., Conte, F.P., and Sproul, J.A., Jr., 1967. "Late Effects of Fast Neutrons and Gamma Rays in Mice as Influenced by the Dose Rate of Irradiation: Life Shortening," *Radiat. Res.* 32, 493-509.

Upton, A.C., Randolph, M.L., and Conklin, J.W., 1970. "Late Effects of Fast Neutrons and Gamma-Rays in Mice as Influenced by the Dose Rate of Irradiation: Induction of Neoplasia," *Radiat. Res.* 41, 467-491.

Vulpis, N., 1984. "The Induction of Chromosome Aberrations in Human Lymphocytes by *in Vitro* Irradiation with Beta Particles from Tritiated Water," *Radiat. Res.* 97, 511-518.

Wolf, C., Lafuma, J., Masse, R., Morin, M., and Kellerer, A.M., 2000. "Neutron RBE for Induction of Tumors of High Lethality in Sprague-Dawley Rats," *Radiat. Res.* 154, 412-420.

Xiang-yan, Z., Jin-chan, D., Xin-sheng, G., and Lu-xin, W., 1986. "Tritium Beta-Ray and ^{60}Co Gamma-Ray Caused Dominant Lethal Mutation in Mice," *Chinese Med. J.* 99, 420-423.

Yamada, T., Yukawa, O., Asami, K., and Nakazawa, T., 1982. "Effect of Chronic HTO Beta or ^{60}Co Gamma-Radiation on Pre-implantation Mouse Development *in Vitro*," *Radiat. Res.* 93, 359-369.

Yamaguchi, T., Yasukawa, M., Terasima, T., and Matsudaira, H., 1985. "Malignant Cell Transformation Induced by Tritiated Water in Mouse 10T½ Cells," p. 136-145 in *Proceedings of the Second Workshop on Tritium Radiobiology and Health Physics*, ed. by

H. Matsudaira, T. Yamaguchi, and H. Etoh, NIRS-M-52, National Institute of Radiological Sciences, Chiba, Japan.

Yokoro, K., Yamamoto, O., Seyama, T., Nitta, Y., and Niwa, O., 1989. "Carcinogenic Effect of Tritiated Water (HTO) in Mice in Comparison with Those of Fission Neutrons and Gamma-Rays," p. 233-238 in *Tritium Radiobiology and Health Physics*, Proceedings of the Third Japan-U.S. Workshop, ed. by S. Okada, IPPJ-REV-3, Institute of Plasma Physics, Nagoya University, Nagoya, Japan.