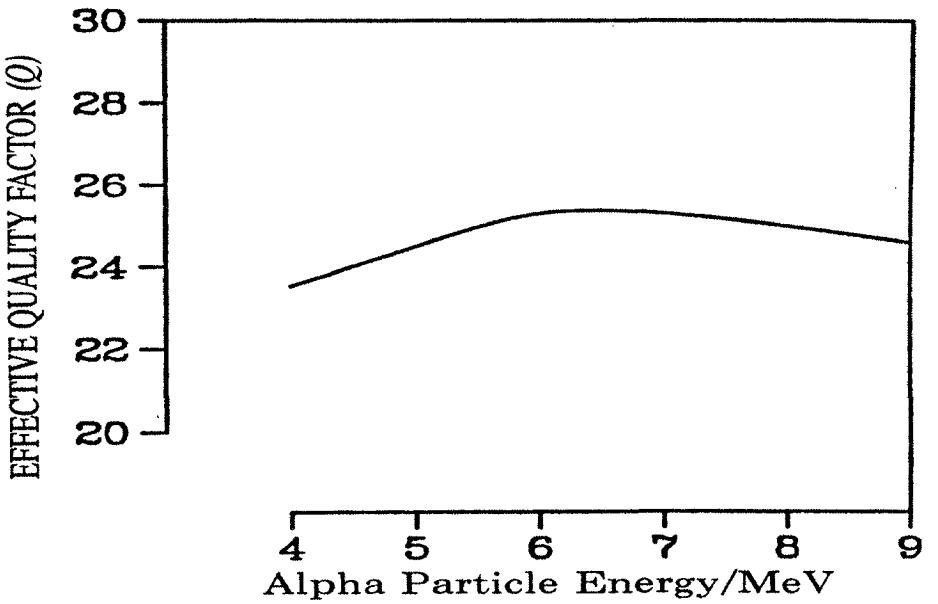

Fig. 14. Calculated effective quality factor, $\overline{Q}$, vs. alpha particle energy given in Fig. 5 of ICRU (1986). Values apply to entire range of alpha particles of given initial energy.

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).

---

[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

---

[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.

---

[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.

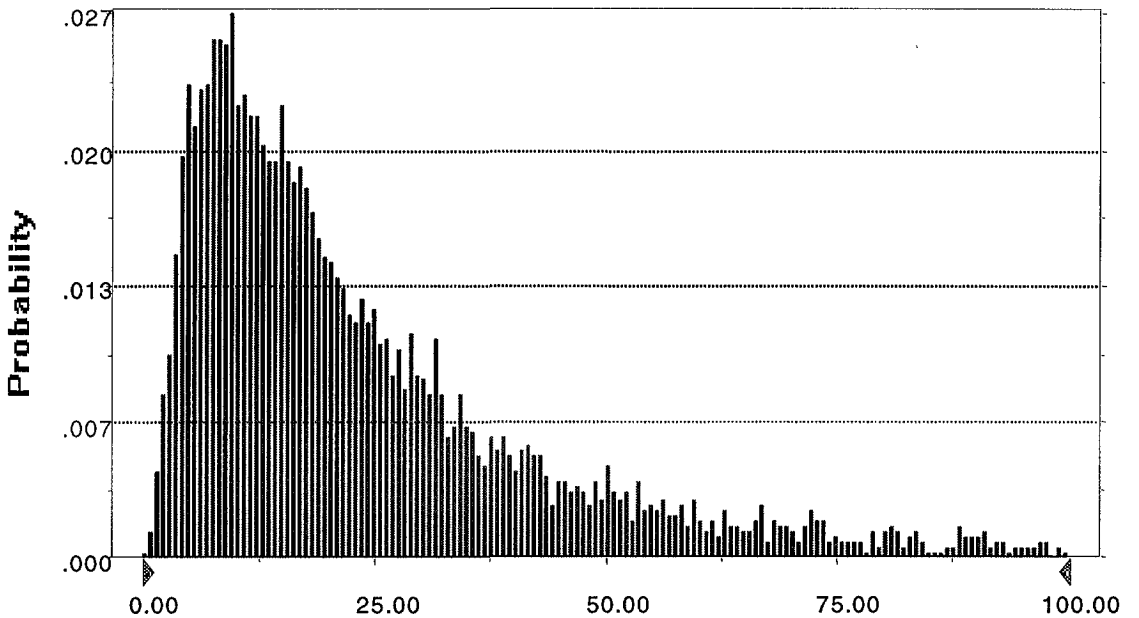

Fig. 15. Assumed probability distribution of REF_L for alpha particles and solid tumors modified by an enhancement factor representing an inverse dose-rate effect under conditions of chronic exposure. Median of distribution is at 18, and 95% confidence interval lies between 3.4 and 101; about 2.5% of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

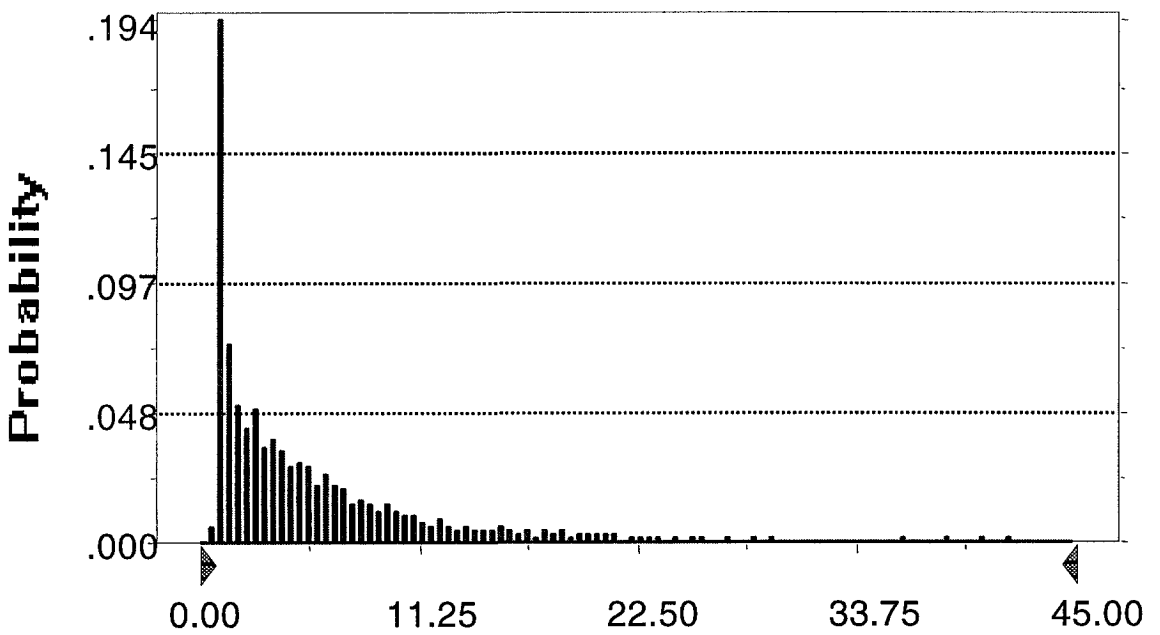

Fig. 16. Assumed probability distribution of REF_L for alpha particles and leukemias modified by an enhancement factor representing an inverse dose-rate effect under conditions of chronic exposure. Median of distribution is at 4.1, and 95% confidence interval lies between 1.0 and 42; about 2.1% of values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

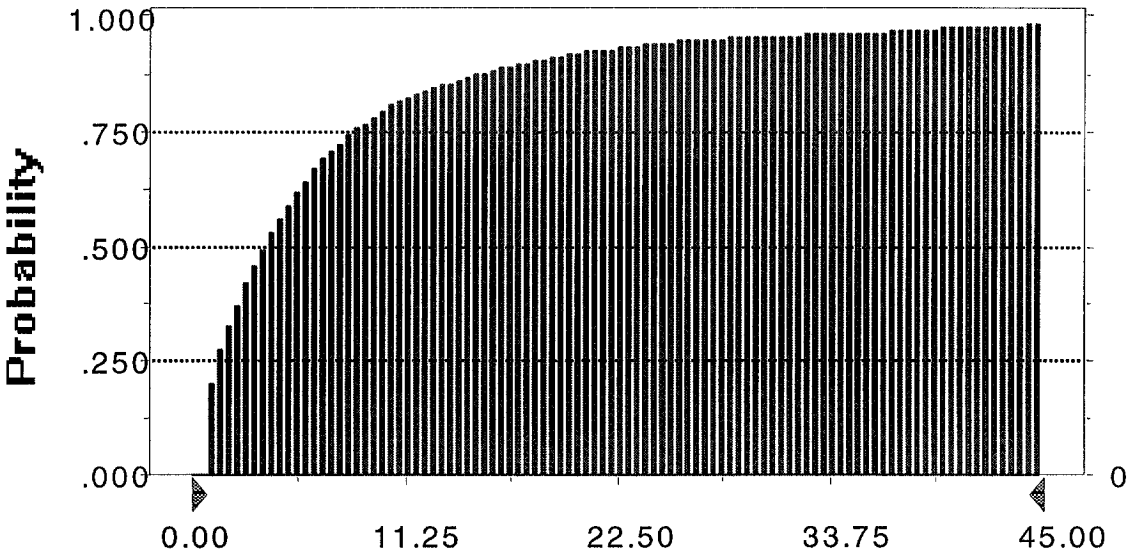

Fig. 17. Assumed probability distribution of REF_L for alpha particles and leukemias modified by an enhancement factor representing an inverse dose-rate effect under conditions of chronic exposure shown in Fig. 16 displayed as a cumulative distribution.

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