

ENERGY DEPENDENCE OF DOSE AND DOSE-RATE EFFECTIVENESS FACTOR FOR LOW-LET RADIATIONS: POTENTIAL IMPORTANCE TO ESTIMATION OF CANCER RISKS AND RELATIONSHIP TO BIOLOGICAL EFFECTIVENESS

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Abstract—A dose and dose-rate effectiveness factor (DDREF) for low-linear energy transfer (LET) radiations (photons and electrons) is used in cancer risk assessments to represent an assumption that risks at low doses and low dose rates may be less than estimates that are based mainly on linear extrapolations of observed risks at higher acute doses. DDREF generally is assumed to be independent of energy. However, a variety of radiobiological data reviewed in this paper suggest that DDREF may decrease with decreasing energy. This effect, which parallels increases in biological effectiveness with decreasing energy of photons and electrons that have been observed in many radiobiological studies, has received little attention. The importance of an overestimation of DDREF at low energies of photons and electrons is that cancer risks at low doses and low dose rates could be underestimated. This paper also discusses (1) the link between DDREF and the usual assumption of a linear-quadratic dose-response relationship for low-LET radiations and (2) concerns about the validity of estimates of DDREF and biological effectiveness used in cancer risk assessments that are raised by results of recent studies that cast doubt on whether the underlying radiobiological data can be represented by a simple linear-quadratic model. *Health Phys.* 93(1):17–27; 2007

Key words: relative biological effectiveness; radiation risk; radiation effects; DDREF

INTRODUCTION

METHODS OF estimating cancer risks from exposure to low-LET radiations (photons and electrons) require assumptions about a dose and dose-rate effectiveness factor (DDREF), which takes into account that risks at low doses and low dose rates of those radiations may be less than estimates that are based on linear extrapolations of observed risks at higher acute doses. In radiation protection, for example, nominal cancer risks at low doses and

low dose rates are estimated by reducing estimated risks per unit dose in Japanese atomic-bomb survivors, who mainly received acute doses of high-energy photons, by a DDREF of 2 (ICRP 1991).

In radiation protection and in estimating cancer risks to exposed individuals, DDREF for low-LET radiations generally is assumed to be independent of energy. However, a variety of radiobiological data suggest that DDREF may decrease with decreasing energy in a manner that parallels increases in biological effectiveness with decreasing energy of photons and electrons that have been observed in many radiobiological studies. The primary purpose of this paper is to review data on an energy dependence of DDREF for low-LET radiations and to discuss its potential importance in cancer risk assessments.

We also consider the link between DDREF and the usual assumption of a linear-quadratic dose-response relationship for low-LET radiations. Recent studies that cast doubt on the use of a simple linear-quadratic model to represent radiobiological data for the purpose of estimating DDREF and biological effectiveness are discussed. We believe that those studies raise important concerns about the validity of using estimates of DDREF and biological effectiveness derived on the basis of a linear-quadratic model to estimate cancer risks at low doses and low dose rates.

It is not our intent to propose an energy dependence of DDREF for low-LET radiations that should be used in cancer risk assessments, nor do we attempt to resolve questions about use of a linear-quadratic dose-response model to estimate DDREF or the biological effectiveness of lower-energy photons and electrons. Rather, the central message of this paper is that further work to address these issues is needed because of their importance to cancer risk assessment.

USE OF DDREF IN ESTIMATING CANCER RISKS

We discuss DDREF in the context of methods of estimating cancer risks from known radiation exposures

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(Manuscript accepted 7 December 2006)

0017-9078/07/0

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of specific individuals that were developed by Land et al. (2003). Models to estimate cancer risks from exposure to low-LET radiations can be represented as follows.

Solid tumors (including lymphomas and multiple myelomas):

$$R = \text{REF}_L \times \frac{R_{\gamma,H}}{\text{DDREF}} \times D. \quad (1)$$

Leukemia:

$$R = \alpha(\text{REF}_L \times D) + \beta(\text{REF}_L \times D)^2, \text{ acute exposure}, \quad (2)$$

$$R = \alpha \times \text{REF}_L \times D, \text{ chronic exposure}. \quad (3)$$

In these equations:

- R is the excess relative risk (ERR) of a given cancer type associated with a given absorbed dose, D , of photons or electrons;
- $R_{\gamma,H}$ is the risk coefficient (ERR per Gy) for a given solid tumor at high acute doses (H) of high-energy photons (γ), as estimated from epidemiological studies;[†]
- REF_L is the so-called radiation effectiveness factor (Kocher et al. 2002, 2005), which represents the effectiveness of photons or electrons of various energies in inducing cancer in humans at low doses and low dose rates (L) relative to high-energy photons;
- DDREF is the dose and dose-rate effectiveness factor for photons or electrons; and
- α and β are coefficients of the linear and quadratic terms, respectively, in the assumed linear-quadratic dose-response relationship for leukemia under conditions of acute exposure to high-energy photons.

Fits to data on dose-response for leukemia in Japanese atomic-bomb survivors indicated that the coefficients α and β in eqn (2) are about equal (Land et al. 2003). The model to estimate risks of leukemia from acute exposure to low-LET radiations then reduces to the following.

Leukemia, acute exposure:

$$R = \alpha \times [(\text{REF}_L \times D) + (\text{REF}_L \times D)^2]. \quad (4)$$

Assumptions about the energy dependence of REF_L for photons or electrons were developed by Kocher et al. (2002, 2005) mainly on the basis of estimates of relative biological effectiveness (RBE) at low doses and low dose rates of reference high-energy photons that were obtained from radiobiological studies of various endpoints.

[†] An acute dose is considered “high” if a statistically significant increase in cancers has been observed at that dose in Japanese atomic-bomb survivors or other exposed populations. Thus, a “high” acute dose in humans is on the order of 0.1 Gy or higher.

Table 1. Summary of radiation effectiveness factors (REFs) for induction of cancer in humans by photons and electrons developed by Kocher et al. (2002, 2005).^a

Radiation type/energy	REF_L^b	
	Median	95% credibility interval
Photons		
>250 keV ^c	1.0	—
30–250 keV	1.9	(1.0, 4.7)
<30 keV	2.4	(1.1, 6.1)
Electrons		
>15 keV ^d	1.0	—
<15 keV	2.4	(1.2, 5.0)

^a Probability distributions of REFs are incorporated in cancer risk models developed by Land et al. (2003) and apply in estimating risks of any cancer type; see eqns (1–4).

^b Radiation effectiveness factor at low doses and low dose rates of reference radiation.

^c Reference radiation with defined REF of unity.

^d Electrons of energy greater than 15 keV are assumed to have the same biological effectiveness as reference high-energy photons. Electrons of energy 15–60 keV should have about the same REF_L as photons of energy 30–250 keV (Kocher et al. 2002, 2005), but probability distribution of REF_L with median greater than unity is not adopted for those radiations, due to lack of supporting radiobiological data.

Assumed probability distributions of REF_L s for photons and electrons, which are subjective representations of uncertainty, are summarized in Table 1. It is seen that the effectiveness of low-LET radiations in inducing cancer in humans is assumed to increase with decreasing energy.

DDREFs developed by Land et al. (2003) are the same for photons and electrons and, in contrast to REF_L s for those radiations, are assumed to be independent of energy. Under conditions of chronic exposure at any dose,[‡] assumed probability distributions of DDREFs in the risk model for solid tumors in eqn (1) are summarized as follows:

- breast and thyroid cancer—mean DDREF of 1.6, range of (0.5, 4); and
- all other solid tumors (including lymphomas and multiple myelomas)—mean DDREF of 1.8, range of (0.5, 5).

Under conditions of acute exposure, DDREFs for all solid tumors are assumed to depend on dose. At acute doses above an uncertain reference value that varies between 0.03 and 0.2 Gy, DDREF is assumed to be 1, without uncertainty. As an acute dose decreases below the uncertain reference value, DDREF is phased in and approaches the appropriate DDREF for chronic exposure summarized above as the dose approaches zero (Land et al. 2003).

For leukemia, a DDREF is implicit in the assumed dose-response relationships in eqns (2) and (3). When a

[‡] An exposure is considered chronic if the absorbed dose rate, averaged over a period of a few hours, is less than 6 mGy h⁻¹ or the exposure is protracted over a period of more than 1 d (Land et al. 2003).

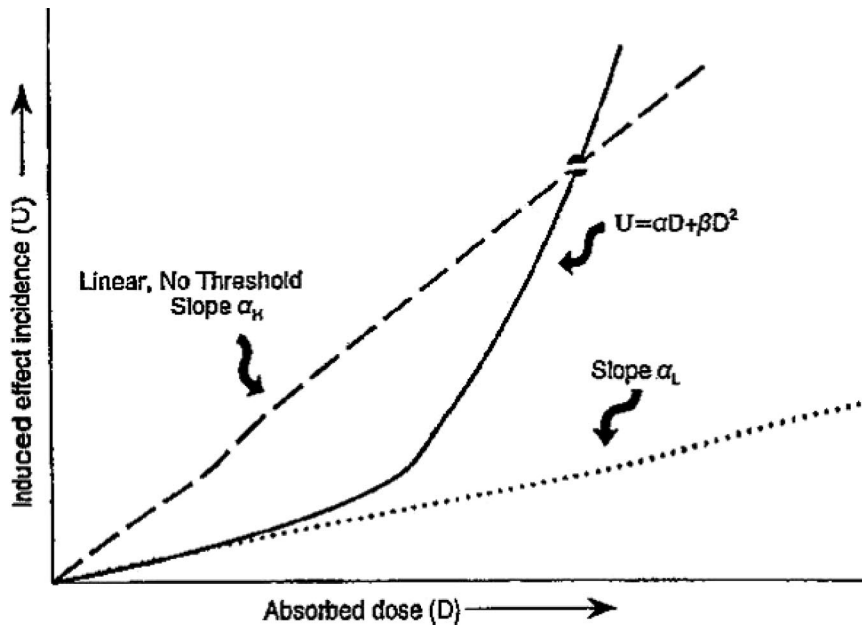


Fig. 1. Representation of linear-quadratic dose-response relationship for low-LET radiations given in Fig. 2 of CIRRPC (1995). Dose and dose-rate effectiveness factor (DDREF) is ratio of linear extrapolation at high doses, α_H , to slope of dose-response relationship at low doses, α_L .

linear-quadratic dose-response of the form $\alpha D + \beta D^2$ is assumed, and as indicated in Fig. 1, DDREF is the ratio of a linear extrapolation at high doses to the dose-response at low doses and, thus, is a function of dose given by

$$\text{DDREF} = (\alpha D + \beta D^2)/\alpha D = 1 + (\beta/\alpha)D, \quad (5)$$

where β/α describes the degree of upward curvature in the dose-response. For example, in the risk model for leukemia under conditions of acute exposure in eqn (4), DDREF is 2 at 1 Gy. This DDREF also is implicit in the model that applies at low dose rates [see eqns (3) and (4)].

DATA ON ENERGY DEPENDENCE OF DDREF

This section presents radiobiological data for various endpoints that provide information on a possible energy dependence of DDREF for low-LET radiations. These data were obtained in studies that were undertaken primarily for the purpose of investigating increases in RBEs with decreasing energy of photons or electrons.

Energy dependence of DDREF for photons

Recent reviews and analyses of radiobiological data suggest an energy dependence of DDREF for photons over a wide range of energies of interest in estimating cancer risks.

Schmid et al. (2002) presented data on induction of dicentric chromosome aberrations in human lymphocytes in blood obtained from the same donor as a function of

photon energy under conditions of acute exposure. Table 2 gives reported α and β coefficients that were obtained by fitting a linear-quadratic dose-response model to the data, reported maximum values of RBE, denoted by RBE_M , relative to reference high-energy ^{60}Co gamma rays that were calculated as ratios of α coefficients to represent the expected responses at doses sufficiently low that the quadratic terms in the dose-response relationships are negligible, and DDREFs at 1 Gy that we calculated using eqn (5).[§] These results show a clear trend of decreasing DDREF with decreasing photon energy, as well as increasing RBE_M .^{**}

Guerrero-Carbajal et al. (2003) presented additional data on induction of dicentric chromosome aberrations in human lymphocytes under conditions of acute exposure that were obtained by various investigators (Lloyd et al.

[§] Means and standard errors of DDREFs were calculated by assuming that all α and β coefficients are lognormally distributed with means and standard errors as given in Table 2.

^{**} Two cautions about interpreting these results are warranted. First, estimates of DDREF and RBE_M in the studies using x rays, which involved continuous spectra of photons over a range of energies (e.g., 8–29 keV in the case of 29 kVp x rays), may differ from estimates that would be obtained if monoenergetic photons of the indicated mean energies were used. Second, to keep all irradiation times about the same, doses were administered at a rate that increased with increasing dose from 0.009 to 0.140 Gy min⁻¹ (Schmid et al. 2002). Therefore, estimates of DDREF could incorporate effects of dose rate, as well as dose, on the dose-responses. We also note, however, that the lowest dose rate is about two orders of magnitude higher than the average dose rate of 6 mGy h⁻¹ above which exposures of humans that occur over a period of a few hours or less are assumed to be acute (Land et al. 2003).

Table 2. Estimates of coefficients in linear-quadratic dose-response relationship, RBE_M , and DDREF for induction of dicentric and acentric chromosome aberrations in human lymphocytes in blood from the same donor under conditions of acute exposure to photons of various energies.^a

Radiation quality	Mean energy (keV)	$\alpha \pm SE^b$ ($\times 10^{-2} \text{ Gy}^{-1}$)	$\beta \pm SE^b$ ($\times 10^{-2} \text{ Gy}^{-2}$)	$RBE_M \pm SE^c$	DDREF at 1 Gy $\pm SE^d$
(a) Dicentric chromosome aberrations					
29 kVp x rays ^e	17.4	6.6 ± 1.0	3.5 ± 0.8	6.1 ± 2.5	1.55 ± 0.15
60 kVp x rays ^f	48	4.4 ± 0.7	2.1 ± 0.8	4.2 ± 1.7	1.48 ± 0.19
220 kVp x rays ^g	96	4.0 ± 0.3	5.98 ± 0.17	3.7 ± 1.5	2.50 ± 0.12
220 kVp x rays ^g	135	2.2 ± 0.4	4.36 ± 0.24	2.1 ± 0.9	3.1 ± 0.4
¹³⁷ Cs γ rays ^h	662	1.5 ± 0.5	4.7 ± 0.3	1.4 ± 0.7	4.5 ± 1.2
⁶⁰ Co γ rays ⁱ	1,250	1.1 ± 0.4	5.5 ± 0.3	—	6.9 ± 2.3
(b) Acentric chromosome aberrations					
29 kVp x rays ^e	17.4	7.2 ± 1.0	1.3 ± 0.8	3.0 ± 0.6	1.18 ± 0.11
60 kVp x rays ^f	48	4.5 ± 1.3	3.4 ± 1.4	1.9 ± 0.6	1.8 ± 0.4
220 kVp x rays ^g	96	5.3 ± 0.3	5.15 ± 0.28	2.2 ± 0.4	1.98 ± 0.12
220 kVp x rays ^g	135	6.4 ± 0.6	2.99 ± 0.27	2.6 ± 0.4	1.47 ± 0.06
¹³⁷ Cs γ rays ^h	662	2.9 ± 0.6	3.31 ± 0.20	1.2 ± 0.4	2.20 ± 0.25
⁶⁰ Co γ rays ⁱ	1250	2.4 ± 0.3	4.46 ± 0.18	—	2.87 ± 0.25

^a Adapted from Table 4 of Schmid et al. (2002). Data for Cr K-shell x rays with mean energy of 5.4 keV are omitted because sample was irradiated as a monolayer, rather than whole blood as in irradiations at all other energies.

^b α and β are coefficients of linear and quadratic terms in assumed linear-quadratic dose-response relationship, respectively, and SE is standard error of the mean.

^c RBE at low doses of indicated radiations relative to reference ⁶⁰Co gamma rays obtained as a ratio of α coefficients.

^d Calculated as $1 + \beta/\alpha$ by assuming that coefficients are lognormally distributed with given means and standard errors (see text).

^e Data reported by Schmid et al. (2002).

^f Data reported by Regulla et al. (2001).

^g Data reported by Schmid et al. (1984).

^h Data reported by Schmid et al. (1995).

ⁱ Data reported by Bauchinger et al. (1983).

1975, 1986; Guerrero-Carbajal et al. 2003). Values of RBE_M for 80–220 kVp x rays, with mean energies of 58–90 keV, relative to reference high-energy ⁶⁰Co gamma rays and values of DDREF at 1 Gy that we calculated from the reported α and β coefficients are broadly consistent with estimates in Table 2. However, these results may be less reliable when blood was obtained from different donors.

It is important to note that data on induction of dicentric chromosome aberrations in human lymphocytes by ⁶⁰Co gamma rays and 220 or 250 kVp x rays provided the primary basis for assumed probability distributions of REF_L at photon energies less than 250 keV given in Table 1 (Kocher et al. 2002, 2005). More generally, studies of dicentric chromosome aberrations in human lymphocytes have long been considered the most reliable and repeatable method of investigating biological responses for a wide range of doses and radiation qualities (Lloyd and Edwards 1983; NCRP 1990; Guerrero-Carbajal et al. 2003), and results from such studies have been important in developing assumptions about cancer induction in humans used in radiation protection, including the form of dose-response relationships (linear-quadratic), the biological effectiveness of different radiation types, and DDREF (Goodhead 2000).

Schmid et al. (2002) also presented data on induction of acentric chromosome aberrations in human lymphocytes that were obtained in the studies of dicentric chromosome

aberrations discussed above; these data also are given in Table 2. Estimates of DDREF and RBE_M for acentric chromosome aberrations show the same trends with decreasing photon energy as the estimates for dicentrics, although the effects are less pronounced.

Finally, Heyes and Mill (2004) presented data on induction of neoplastic transformations in CGL1 human hybrid cells by 29 kVp x rays and various reference radiations, including 200 and 220 kVp x rays, high-energy beta particles from decay of ⁹⁰Sr and ⁹⁰Y, and an atomic-bomb photon spectrum, under conditions of acute exposure. Data obtained from the different studies that were considered are given in Table 3. Estimates of DDREF for 29 kVp x rays show a decrease compared with estimates for the high-energy reference radiations, and estimates of RBE_M show an increase although uncertainties are large. These relationships are more evident in estimates derived from data obtained by Göggemann et al. (2003) and Heyes and Mill (2004), which have smaller uncertainties than data obtained by Frankenburg et al. (2002).^{††}

^{††} We also acknowledge, however, that dose-responses for neoplastic transformations in CGL1 human hybrid cells and other cell lines that are abnormal (i.e., immortalized) can be complex and difficult to interpret, and that the relevance of data on such transformations in already transformed cell lines to transformation of normal non-immortalized cells in vivo has not been established (e.g., see NCRP 2001; NRC 2006).

Table 3. Estimates of coefficients in linear-quadratic dose-response relationship, RBE_M , and DDREF for induction of neoplastic transformations in CGL1 human hybrid cells under conditions of acute exposure to photons and electrons of various energies.^a

Reference	Radiation	$\alpha \pm SE^b$ (Gy ⁻¹)	$\beta \pm SE^b$ (Gy ⁻²)	$RBE_M \pm SE^c$	DDREF at 1 Gy $\pm SE^d$
Frankenburg et al. (2002)	29 kVp x rays	0.52 \pm 0.25	0.07 \pm 0.06	4.7 \pm 3.9	1.17 \pm 0.18
	200 kVp x rays	0.11 \pm 0.08	0.026 \pm 0.018	—	1.4 \pm 0.4
Göggelmann et al. (2003)	29 kVp x rays	1.41 \pm 0.27	-0.01 \pm 0.07	3.6 \pm 1.8	\approx 1
	220 kVp x rays	0.39 \pm 0.18	0.15 \pm 0.05	—	1.47 \pm 0.27
Heyes and Mill (2004)	29 kVp x rays	0.61 \pm 0.13	0.012 \pm 0.028	5.2 \pm 3.5 ^e	1.02 \pm 0.05
				4.0 \pm 2.3 ^f	
				4.4 \pm 2.0 ^g	
	⁹⁰ Sr/ ⁹⁰ Y beta particles	0.12 \pm 0.08	0.075 \pm 0.017	—	1.9 \pm 0.6
	A-bomb γ spectrum	0.15 \pm 0.08	0.079 \pm 0.019	—	1.7 \pm 0.4
	Combined beta and γ sources	0.14 \pm 0.06	0.075 \pm 0.013	—	1.63 \pm 0.28

^a Adapted from Tables 3 and 7 of Heyes and Mill (2004).^b α and β are coefficients of linear and quadratic terms in assumed linear-quadratic dose-response relationship, respectively, and SE is standard error of the mean.^c RBE at low doses of 29 kVp x rays relative to indicated reference radiations obtained as ratio of α coefficients.^d Calculated as $1 + \beta/\alpha$ by assuming that coefficients are lognormally distributed with given means and standard errors (see text).^e Value relative to ⁹⁰Sr/⁹⁰Y beta particles.^f Value relative to atomic-bomb photon spectrum.^g Value relative to combined beta and photon sources.

Energy dependence of DDREF for electrons

Information on the energy dependence of DDREF for electrons can be obtained from a study by Gragtmans et al. (1984) of induction of mammary tumors in female Sprague-Dawley rats by tritium beta particles under conditions of chronic exposure to HTO and by 200 kVp x rays under conditions of chronic and acute exposure. Endpoints studied include cumulative incidence of tumors per 100 animals at risk, cumulative percent of animals with tumors, and decrease in the time required to develop a tumor in 50% of the animals at risk. Data at doses up to 2 Gy were fitted with a linear dose-response model; data for tritium beta particles at 3.85 Gy were excluded, due to observed departures from linearity (Gragtmans et al. 1984).

Table 4 gives reported slopes of the linear dose-response relationships for each radiation type and endpoint studied, reported RBEs for tritium beta particles and acute x rays relative to reference chronic x rays that were calculated as ratios of slopes of the dose-responses for each endpoint, and DDREFs for tritium beta particles relative to values for acute x rays that we calculated as ratios of RBEs for tritium beta particles to the corresponding RBEs for acute x rays. It is seen that, on average, DDREF for tritium beta particles is about 20% less than DDREF for acute 200 kVp x rays. We also note that the average RBE for tritium beta particles relative to chronic 200 kVp x rays of about 1.2, when increased by a factor of about 2 to account for the greater biological effectiveness of x rays compared with high-energy photons, was taken into account in developing the assumed probability distribution of REF_L at electron energies less than 15 keV given in Table 1 (Kocher et al. 2002, 2005).

DISCUSSION OF RADIOBIOLOGICAL DATA

Increases in biological effectiveness with decreasing energy of photons have long been observed in radiobiological studies, especially studies of dicentric chromosome aberrations in human lymphocytes; e.g., see ICRU (1986), NCRP (1990), and Hill (2004). Such increases have received considerable attention in recent years, due

Table 4. Estimates of coefficients in linear dose-response relationship, RBE, and DDREF for induction of mammary tumors in female Sprague-Dawley rats by tritium beta particles and 200 kVp x rays.^a

Radiation type	$\alpha \pm SE^b$ (Gy ⁻¹)	RBE ^c	DDREF ^d
(a) Cumulative tumor incidence per 100 animals at risk			
Tritium beta particles	53 \pm 5	1.17 \pm 0.18	0.70 \pm 0.17
Acute 200 kVp x rays	78 \pm 10	1.7 \pm 0.3	
Chronic 200 kVp x rays	46 \pm 5	—	
(b) Cumulative percent animals with tumors			
Tritium beta particles	33.6 \pm 0.8	1.35 \pm 0.13	0.83 \pm 0.09
Acute 200 kVp x rays	40.5 \pm 0.4	1.63 \pm 0.10	
Chronic 200 kVp x rays	24.8 \pm 2.4	—	
(c) Decrease in time required to develop tumor in 50 percent of animals at risk			
Tritium beta particles	-125 \pm 12 ^e	1.12 \pm 0.18	0.87 \pm 0.19
Acute 200 kVp x rays	-148 \pm 12 ^e	1.32 \pm 0.20	
Chronic 200 kVp x rays	-112 \pm 14 ^e	—	

^a Adapted from data at doses of 2 Gy or less in Tables III and IV of Gragtmans et al. (1984). Results that include data for tritium beta particles at dose of 3.85 Gy are omitted, due to departure from linearity in dose-response relationships (Gragtmans et al. 1984).^b Slope of linear dose-response relationship; assumption of linearity gave better fit to data than assumption of linear-quadratic dose-response relationship.^c RBE relative to reference chronic x rays obtained as ratio of α coefficients; RBE is independent of dose when dose-response relationships are linear.^d DDREF for tritium beta particles relative to value for acute x rays calculated as a ratio of RBE for tritium beta particles to RBE for acute x rays.^e Unit of slope of dose-response relationship is d Gy⁻¹.

primarily to their potential importance in estimating risks of breast cancer in women who undergo mammography x-ray exams; e.g., see Frankenburg et al. (2002), Schmid et al. (2002), Guerrero-Carbajal et al. (2003), Heyes and Mill (2004), and Hill (2004). As indicated in eqns (1–4) and Table 1, an energy dependence of REF_L for photons that is intended to represent data on RBE at low doses and low dose rates is incorporated in cancer risk models developed by Land et al. (2003). The possibility of an increased effectiveness of x rays in inducing cancers in humans relative to high-energy photons also has been acknowledged by the International Commission on Radiological Protection (ICRP 2003) and the BEIR VII committee (NRC 2006). However, such increases are not yet incorporated in recommendations on radiation protection by the former (ICRP 2003, 2006) or in cancer risk models preferred by the latter (NRC 2006).

Increases in biological effectiveness of low-energy tritium beta particles relative to 180–250 kVp x rays and high-energy ^{137}Cs or ^{60}Co gamma rays also have been observed in many radiobiological studies of various endpoints, including induction of cancer in rats and mice (Straume and Carsten 1993). As indicated in eqns (1–4) and Table 1, an REF_L for low-energy electrons that is intended to represent data on RBE at low doses and low dose rates is incorporated in cancer risk models developed by Land et al. (2003). An increase in biological effectiveness of tritium beta particles by a factor of 1.7 was incorporated in early ICRP recommendations on radiation protection (ICRP 1960), but no such increase has been incorporated in subsequent revisions (ICRP 1977, 1991, 2003, 2006).

In contrast, possible decreases in DDREF with decreasing energy of photons and electrons have received little attention in radiobiology, radiation protection, and cancer risk assessment. For example: reviews and analyses of radiobiological data that we used to investigate the energy dependence of DDREF (Schmid et al. 2002; Guerrero-Carbajal et al. 2003; Heyes and Mill 2004; Gragtman et al. 1984) did not include estimates of DDREF; ICRP (1991, 2006) has not considered an energy dependence of DDREF in its recommendations on radiation protection; the BEIR VII committee (NRC 2006) did not include an energy dependence of DDREF in its preferred cancer risk models;^{‡‡} and an energy

dependence of DDREF is not incorporated in cancer risk models developed by Land et al. (2003).

Of the studies considered in this paper, only those by Guerrero-Carbajal et al. (2003) and Hill (2004), which were concerned mainly with investigating the energy dependence of RBE_M for photons, noted that large increases in RBE_M with decreasing photon energy are associated with “a large reduction in response with the higher energy photons of the reference radiation, with a much lower reduction observed for lower energy photons” (Hill 2004); i.e., DDREFs at low photon energies were less than at higher energies.^{§§} That observation was interpreted as indicating that when a DDREF of 2 is assumed, as recommended by ICRP (1991), it is more likely that nominal cancer risk estimates at low doses and low dose rates recommended by ICRP (1991) apply to low-energy photons (e.g., 30 keV) and, thus, that risks at high photon energies (e.g., 1 MeV) are overestimated (Guerrero-Carbajal et al. 2003; Hill 2004). However, we believe that this interpretation is plausible only if high DDREFs for high-energy photons that have been observed in studies of dicentric chromosome aberrations in human lymphocytes (see Table 2) apply to cancer induction in humans. Modeled dose-response relationships for cancer incidence in Japanese atomic-bomb survivors do not indicate that a DDREF much greater than 2 applies under conditions of acute exposure to high-energy photons (NRC 2006).

IMPORTANCE OF POSSIBLE ENERGY DEPENDENCE OF DDREF

Radiobiological data for various endpoints reviewed in this paper suggest that DDREF for photons and electrons may decrease with decreasing energy in a manner that parallels increases in RBE_M with decreasing energy that have been observed in many studies. An energy dependence of DDREF for low-LET radiations seems plausible when DDREFs for high-LET radiations are essentially 1 (ICRP 1991; NCRP 2001), RBE_M s for high-LET radiations are high (ICRU 1986; NCRP 1990; Muirhead et al. 1993; Edwards 1997, 1999), and LET is substantially higher at low photon energies than at high energies (ICRP 2003). The potential importance of a possible overestimation of DDREF at lower energies of photons and electrons is that current cancer risk models could underestimate risks at low doses and low dose rates of those radiations.

We also believe that there are more general concerns about the validity of DDREFs for photons and electrons

^{‡‡} The BEIR VII committee did note, however, that since the modeled dose-response relationship for incidence of solid tumors in Japanese atomic-bomb survivors is nearly linear at doses up to 2 Gy, the much larger curvature in the dose-response for induction of dicentric chromosome aberrations by ^{60}Co gamma rays compared with 29 kVp x rays reported by Schmid et al. (2002) and indicated in Table 2 may not apply to induction of solid tumors in humans (NRC 2006). If there is little curvature in the dose-response for high-energy photons, there should be little energy dependence of DDREF for photons.

^{§§} Neither Guerrero-Carbajal et al. (2003) nor Hill (2004) quantified DDREF and its energy dependence on the basis of data on dose-response they presented.

used in cancer risk assessments, as well as REF_L s for those radiations that are based on estimates of RBE at low doses and low dose rates (Table 1). These concerns, which are related to an assumption that radiobiological data used to estimate DDREFs and RBEs for low-LET radiations can be represented by a simple linear-quadratic dose-response model, are discussed in the following section.

VALIDITY OF DDREFS AND REF_L S USED IN CANCER RISK ASSESSMENTS

As indicated in Fig. 1 and eqn (5), estimation of a DDREF on the basis of radiobiological or epidemiological data is linked to an assumption of a linear-quadratic dose-response relationship for low-LET radiations. Similarly, REF_L s for photons and electrons given in Table 1 are based on RBEs at low doses and low dose rates (RBE_M) that are estimated by assuming a linear-quadratic model (e.g., see Tables 2 and 3). Thus, DDREF and RBE_M are interrelated through their dependence on α coefficients in a linear-quadratic dose-response model. For example, as the α coefficient for a reference radiation decreases, RBE_M for a radiation type of concern and DDREF for the reference radiation both increase (CIRRPC 1995). Largely on the basis of data on dose-response for chromosome aberrations, augmented by data for mutations in mammalian cells and induction of cancers in animals, the linear-quadratic model has long been the standard paradigm used in cancer risk assessment and radiation protection.

The usual interpretation of the linear-quadratic model is that the linear term represents the production of pairs of chromosome breaks by a single charged-particle track that then undergo exchange and illegitimate rejoining, whereas the quadratic term represents the production of break pairs by two uncorrelated tracks, with repair between the two events described by an exponential reduction over time in the number of breaks that are available for potential exchange formation; e.g., see Goodhead (2000), Cornforth et al. (2002), and NRC (2006). If this interpretation is correct, the linear term should be important at any dose and dose rate but independent of dose rate, whereas the quadratic term should be important only at high doses and high dose rates. We also emphasize that use of a linear-quadratic model to represent data on dose-response involves an implicit assumption that the data apply to a single endpoint.

The relationships between DDREF, REF_L , and a linear-quadratic dose-response model for low-LET radiations and the implications of using a linear-quadratic model described above are important in light of results of

recent studies of dose-responses for chromosome aberrations using multi-fluor fluorescence in situ hybridization (mFISH). This technique of chromosome painting provides a means of visualizing intricacies of the chromosome exchange process in response to radiation damage that cannot be seen, for example, when dicentric chromosome aberrations are scored by conventional Giemsa staining, as in the studies summarized in Table 2. Studies using mFISH led to two observations that cast doubt on the use of a linear-quadratic model to represent the dose-response for chromosome aberrations.

First, a study of induction of chromosome aberrations in human lymphocytes at high acute doses of high-energy gamma rays using mFISH (Loucas and Cornforth 2001) showed that the upward curvature in the dose-response, as indicated by the data in Table 2, is due mainly to the competing influences of multiple endpoints—i.e., simple chromosome exchanges involving 2 break pairs, which are important at any dose, plus complex exchanges that arise from 3 or more breakpoints distributed among 2 or more chromosomes, which are important only at high doses—rather than a curvature in the dose-response for a single endpoint (simple exchanges). Furthermore, the dose-response for simple exchanges was nearly linear, with only slight upward curvature. These results appeared to verify earlier predictions from a study by Simpson and Savage (1995) and other studies using FISH reviewed by Loucas and Cornforth (2001) that the dose-response for simple dicentrics and translocations is nearly linear and that most of the upward curvature in the dose-response for dicentric chromosome aberrations that are scored by conventional Giemsa staining is due to complex exchanges.

In a later paper, Loucas et al. (2004) also noted that the apparent linearity in the acute dose-response for simple exchanges might result from competition between simple and complex exchanges for the same available chromosome breaks during the rejoining process that results in a distortion (i.e., saturation) of the acute dose-response for simple exchanges at high doses compared with the dose-response that would be seen if complex exchanges were unimportant. As a consequence, “the acute dose-response for the production of simple exchanges does not owe its apparent linear shape to a one-track/one-lesion mechanism” (Loucas et al. 2004), as would be expected if a simple linear-quadratic relationship were valid. Rather, Loucas et al. argued that the near-linearity in the dose-response for simple exchanges can be explained in terms of the more traditional two-lesion paradigm as a consequence of “warping” of an otherwise curvilinear dose-response into one that may appear to be linear over a limited range of doses. Although available data are insufficient to resolve such

questions, Loucas et al. (2004) concluded that “it is naïve to expect that any upward curvature in [the shape of the acute dose-response for simple exchanges] would obey kinetics described by a second-order polynomial, even though, statistically, it may provide an adequate fit to the data” and, therefore, that “fitting the high dose rate data . . . to the relationship $\alpha D + \beta D^2$, to extract from it the initial slope, may well produce misleading results.”

The importance of multiple endpoints in the dose-response for dicentric chromosome aberrations and the apparent near-linearity in the dose-response for simple exchanges contradicted a previous assumption that the dose-response in studies in which conventional Giemsa staining was used is due mainly to a single endpoint (simple exchanges) and, therefore, that the dose-response for that endpoint exhibits considerable upward curvature. A consequence of these results is that fitting of acute dose-response data for chromosome aberrations that represent multiple endpoints using a simple linear-quadratic model, as in Table 2, may give α and β coefficients that are misleading for the purpose of estimating DDREF.

The second important observation resulted from a study of induction of chromosome aberrations in human fibroblasts by high-energy gamma rays using mFISH (Loucas et al. 2004). Dose-response data for simple aberrations were obtained under conditions of chronic exposure at low dose rates, as well as acute exposure. As in the study by Loucas and Cornforth (2001) discussed above, the acute dose-response for simple aberrations was nearly linear and showed little upward curvature. The dose-response also was linear under conditions of chronic exposure at dose rates sufficiently low that damage should be produced by a single charged-particle track, but the slope of the dose-response was a factor of 5 to 6 less than at high dose rates. As noted previously, if the usual interpretation of the linear-quadratic model were valid, the slope of the linear dose-response for simple chromosome exchanges should be independent of dose rate, rather than highly dependent on dose rate.

However, the observation of a significant dose-rate effect in the study by Loucas et al. (2004) would be consistent with the explanation they offered for the quasi-linear shape of the acute dose-response for simple exchange aberrations, which is that an otherwise curvilinear shape of that dose-response has been warped into a shape that appears to be linear by competition between processes with different dose-responses. Regardless of the proper interpretation of empirical data from mFISH studies, the large dose-rate effects observed by Loucas et al. (2004) cannot be explained by applying a simple linear-quadratic relationship to their acute exposure data

to predict the response at low dose rates. This is indicated, for example, by differences between the linear α coefficients obtained from fitting the acute and chronic dose-responses for total simple aberrations in Figs. 2 and 4 of their paper. Loucas et al. argued that the best estimate of the initial slope is given by the dose-response at low dose rates, rather than the dose-response under conditions of acute exposure.

The mFISH data for chromosome exchange aberrations reported by Loucas et al. (2004) may help explain the significant dose-rate effects that were observed in studies of carcinogenesis and life-span shortening in animals, in which dose-response relationships under conditions of acute exposure also appeared to be linear.*** This effect is illustrated by differences in the linear dose-responses for mammary tumors in female Sprague-Dawley rats induced by acute and chronic exposure to 200 kVp x rays given in Table 4 (Gragtmans et al. 1984). NCRP (1993) and CIRRPC (1995) both cautioned that the apparently linear acute dose-responses in studies of whole animals or humans should not be interpreted to mean that significant dose-rate effects could be ruled out, as would be predicted by a simple linear-quadratic relationship. In regard to the dose-responses for most types of solid tumors in Japanese atomic-bomb survivors, for example, NCRP (1993) concluded that “the fact that the linear fit appears appropriate for the data over a broad range of doses does not preclude a dose-rate effect.”

A potentially important implication of the strong dependence of the linear dose-responses on dose rate in the study by Loucas et al. (2004) is that a dose-rate effectiveness factor (DREF) under conditions of chronic or highly fractionated exposure could be substantially greater than a low-dose effectiveness factor (LDEF) under conditions of acute exposure; i.e., an assumption that DREF and LDEF are the same at low doses and can be combined into a DDREF, which is implicit in the use of a linear-quadratic model to estimate DDREFs, may not be valid. For example, if a DREF that applies to cancer induction in humans were substantially greater than an LDEF, a DDREF of 1.5, with a 95% credibility interval of (0.8, 2.7), that was derived by the BEIR VII committee on the basis of a modeled dose-response relationship for incidence of solid tumors in Japanese atomic-bomb survivors augmented by data on cancer induction in animals (NRC 2006) would apply only to acute exposures and would result in overestimates of

*** See, for example, Upton et al. (1970), Ullrich and Storer (1979a, 1979b, 1979c), Gragtmans et al. (1984), Ullrich and Preston (1987), Carnes et al. (1989), Edwards (1992), NCRP (1993, 2001), and CIRRPC (1995).

cancer risks from chronic or highly fractionated exposures.

Results described above are of interest to this paper when we used data on induction of chromosome aberrations in human lymphocytes that were obtained using conventional Giemsa staining to investigate a possible energy dependence of DDREF. Dose-responses for simple chromosome exchanges in human lymphocytes and fibroblasts at acute doses of high-energy photons obtained in studies using mFISH (Loucas and Cornforth 2001; Loucas et al. 2004) are consistent with a DDREF (or LDEF) at 1 Gy of no more than about 1.2 to 1.3. Such a DDREF is much lower than DDREFs for high-energy photons that are derived when a linear-quadratic model is used to represent the dose-response for induction of simple and complex exchanges combined in studies of dicentric chromosome aberrations, as in Table 2 or reported elsewhere (e.g., NCRP 1990; Guerrero-Carbajal et al. 2003). If the DDREFs were close to 1 for high-energy photons, there should be no reduction with decreasing energy.^{†††}

Similar concerns apply to the use of data on induction of chromosome aberrations to investigate the energy dependence of RBE_M for photons. Results of studies using mFISH discussed above cast doubt on the validity of estimates of RBE_M that are derived from α coefficients in a linear-quadratic model that is assumed to represent dose-responses for simple and complex exchanges combined. As noted previously, such estimates provided the primary basis for estimates of REF_L for low-energy photons in Table 1.

CONCLUSION

DDREF and RBE_M generally have been estimated by assuming a simple linear-quadratic dose-response model. Since DDREF and RBE_M are interrelated through their dependence on α coefficients in that model, REF_Ls for low-energy photons that are based on RBE_Ms obtained in studies of dicentric chromosome aberrations using conventional Giemsa staining would be overestimated if DDREFs for high-energy photons obtained in those studies are too high. Thus, if the high DDREFs for high-energy photons obtained in studies of dicentric chromosome aberrations are considered to be implausible on the basis of the near-linearity in the modeled dose-response relationship for incidence of solid tumors

^{†††} Such a conclusion would not rule out the possibility of a supralinear dose-response for low-energy photons, whereby the response at low acute doses is higher than predicted by a linear model, or an inverse dose-rate effect similar to that reported for neutrons (CIRRPC 1995; ICRP 1991; NCRP 1990) and alpha particles (Lubin et al. 1995), whereby the response increases with decreasing dose rate at the same dose.

in Japanese atomic-bomb survivors (NRC 2006), the high values of RBE_M obtained in those studies also would have to be questioned. On the other hand, if the high RBE_Ms obtained in conventional studies of dicentric chromosome aberrations are considered to apply to induction of cancers in humans, the high DDREFs for high-energy photons obtained in those studies also should be considered plausible.

It is not our intent to resolve questions about the validity of the linear-quadratic model or the most appropriate values of DDREF and REF_L for low-LET radiations that should be used in cancer risk assessments. Rather, our intent is to emphasize the need for further investigations of DDREFs and RBEs in studies of endpoints of relevance to cancer induction in humans (e.g., cancer induction in animals). Given that mammography (about 29 kVp) and higher-energy (180–250 kVp) x rays are commonly used in medical diagnosis and that estimated cancer risks from those radiations can vary by as much as an order of magnitude depending on assumptions about DDREF and REF_L,^{***} we believe that further investigation of the energy dependence of DDREF and REF_L for low-LET radiations is an important area of research.

Acknowledgments—This study was funded by the National Institute for Occupational Safety and Health (NIOSH) under contract number 200-2001-08006.

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^{***} For example, if we assume an REF_L for mammography (29 kVp) x rays of about 6, as suggested by data on dicentric chromosome aberrations given in Table 2, and a DDREF for those radiations of about 1, as suggested by the low DDREF for induction of solid tumors in Japanese atomic-bomb survivors (NRC 2006) and reductions in DDREF with decreasing photon energy indicated in Tables 2 and 3, estimated risks would be more than a factor of 10 higher than risks obtained by assuming an REF_L of 1 and a DDREF of 2 for those radiations, as recommended by ICRP (1991, 2003, 2006) for purposes of radiation protection.

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