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Reference radiation selection is confirmed as a significant source of relative biological effectiveness variation for neutrons

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ABSTRACT

Purpose: To confirm that the selection of a reference radiation affects the magnitude and range of the relative biological effectiveness (RBE) evaluations of neutron test radiation. Particular attention was paid to the published thermal neutron RBE dataset that is highly variable, with values ranging from 5.4–51.1.

Materials and methods: This involved a dual approach of 1) reaffirming dicentric chromosome assay (DCA) dose-response curve differences for ^{60}Co, ^{137}Cs, and 250 kVp X-rays, and 2) recalculating maximum RBE at minimal doses (RBE_M) for our previously reported neutron data, accompanied by an evaluation of reported studies that utilized two or more reference radiations.

Results and conclusions: The linear slope coefficient of the linear-quadratic dose-response curve, used to evaluate RBE_M, was found to be significantly different for ^{60}Co (0.0268 ± 0.0075 Gy^{-1}) compared to ^{137}Cs (0.0730 ± 0.0135, $P < 0.01$) and 250 kVp X-ray (0.1063 ± 0.0248, $P < 0.01$). Applying this finding to our previous thermal and fast neutron DCA evaluations, the RBE_M varied by a factor of 2.7 for ^{60}Co versus ^{137}Cs, and by a factor of four for ^{60}Co versus 250 kVp X-ray. A review of prior reported neutron RBE_M literature affirmed the finding that reference radiation selection can influence RBE_M magnitude. The selection of the reference radiation has implications for RBE evaluations of neutrons and other radiation qualities, as these RBE values underpin the radiation weighting factor, w_R, which informs radiation protection measures both terrestrially and in space. These experiments and reanalysis reconfirm and strongly demonstrate that reference radiation selection is a significant determinant of RBE variability, especially as applied to neutrons.

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Relative biological effectiveness; RBE; reference radiation; dicentric chromosome; lymphocytes; biodosimetry

Introduction

Relative biological effectiveness (RBE) is a measure of the ability of a test radiation to produce a specific biological effect, compared to that of an assigned reference radiation. RBE can be expressed as $RBE = D_{REF}/D_{TEST}$. Here, the dose of the reference radiation (D_{REF}) is divided by the dose of the test radiation (D_{TEST}) needed to produce the same effect. RBE can also be evaluated as the maximum RBE at minimal doses (RBE_M) and expressed as $RBE_M = \alpha_{TEST}/\alpha_{REF}$, where α is the linear slope coefficient of the dose-response curve. Experimental RBE and RBE_M values factor heavily in the current International Commission of Radiological Protection (ICRP) radiation protection guidelines, as RBE underpins the radiation weighting factor (w_R), a dimensionless quantity used to convert absorbed dose (in Gy) into equivalent dose (in Sv) (ICRP 2003), which forms the basis of many radiation protection programs globally.

Originally, ^{226}Ra gamma-rays filtered by 0.5 mm of platinum were prescribed as the reference radiation for RBE calculations (ICRP 1951). Later, X-rays were preferred, and the most recent ICRP guideline specifies that hard gamma rays with a dose-average linear energy transfer (LET) of 0.4 keV μm^{-1} or less should be used as a reference radiation (ICRP 2003). However, not all laboratories have access to a photon source with a dose-average LET of 0.4 keV μm^{-1} or less, such as ^{60}Co. As a result, the literature is plentiful with RBE studies utilizing a variety of photon sources for dicentric chromosome assay (DCA) RBE evaluations, the most common of which are ^{60}Co, ^{137}Cs, and orthovoltage X-rays in the 220–250 kVp range. These photon sources have very different physical characteristics as summarized in Figure 1. ^{60}Co and ^{137}Cs both emit discrete photons, with highest probability energies of 1.173 MeV and 1.332 MeV for ^{60}Co, and 0.662 MeV for ^{137}Cs (ICRP 2003). In contrast, X-ray

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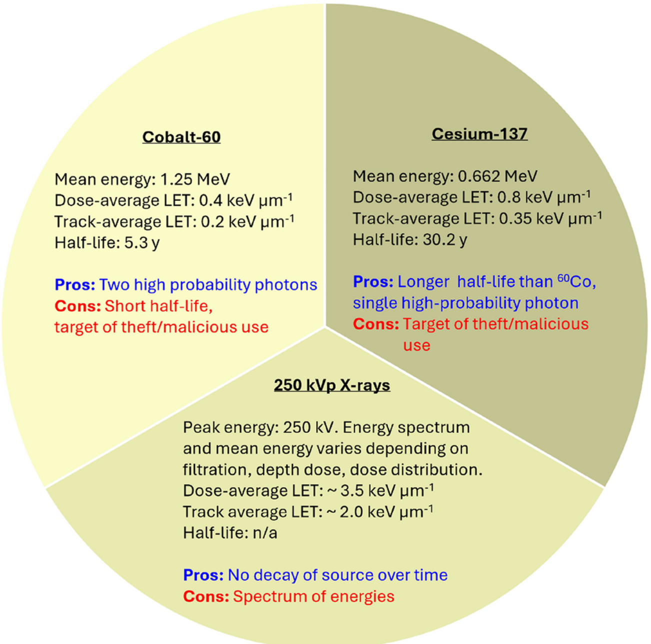

Figure 1. Overview of parameters of interest for radiobiology experiments using ^{60}Co, ^{137}Cs, and 250 kVp X-rays. Data from ICRP (2003); Cabrera-Santiago and Massillon-Jl (2016); Hall and Giaccia (2018).

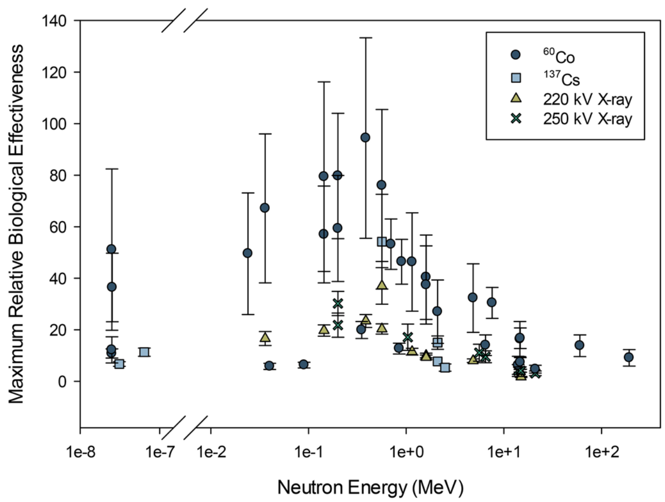

Figure 2. Overview of prior reported neutron DCA RBE_M values in lymphocytes delineated by reference radiation selection. Overall, RBE_M calculations utilizing ^{60}Co as a reference radiation often produced higher RBE_M values than ^{137}Cs or 220 kVp to 250 kVp X-rays (Bauchinger et al. 1975; Lloyd et al. 1976, 1978; Sevan'kaev et al. 1979; Bauchinger et al. 1984; Lloyd et al. 1984; Fabry et al. 1985; Lloyd et al. 1988; Dobson et al. 1991; Cebulska-Wasilewska et al. 1997; Schmid et al. 1998, 2000, 2002, 2003; Nolte et al. 2005, 2006; Sasaki et al. 2006; Tanaka et al. 2009; Wojcik et al. 2012; Schmid et al. 2013; Paterson et al. 2021, 2022, 2025; Zhang et al. 2025).

irradiators utilized for radiobiology studies produce polyenergetic spectra that can vary with peak operation voltage, filtration, and irradiation environment. The LET of photons is dependent on the energy of the secondary electrons liberated in the medium. Higher incident photon energies result in higher secondary electron energies that are less densely ionizing, hence the lower LET of higher incident photons. Of the three common reference radiations, ^{60}Co has a dose-average LET of ~0.4 keV μm^{-1}, which should not be confused with the oft-reported ^{60}Co track-average LET of ~0.2 keV μm^{-1} (Hall and Giaccia 2018). ^{137}Cs has a dose-average LET of ~0.8 keV μm^{-1} (ICRP 2003), and a track-average LET of ~0.35 keV μm^{-1} (Cabrera-Santiago and Massillon-Jl 2016). The 200 kVp and 250 kVp X-rays have higher LET values than ^{60}Co and ^{137}Cs. ICRP Publication 92 gives a dose-average LET value of ~3.5 keV μm^{-1} for 200 kVp X-rays (ICRP 2003). The track-average LET for 250 kVp X-rays is reported to be ~2.0 keV μm^{-1} (Hall and Giaccia 2018).

The DCA is widely used for RBE studies and biological dosimetry programs (IAEA 2011). This chromosome aberration assay evaluates DNA double-strand break (DSB) misrepair manifested as dicentric and ring chromosomes. It is one of the most robust and well-studied radiobiology assays (Edwards 1997; IAEA 2011). Decades of research have demonstrated that dicentric and ring chromosome aberrations strongly correlate with absorbed radiation dose. There is a very low frequency of dicentric and ring chromosome aberrations in unirradiated cells, with a typical background aberration incidence rate of 0.5–1.0 aberrations per ~1,000 lymphocytes (IAEA 2011).

An evaluation of neutron DCA RBE_M and neutron dose-response publications revealed that there are many instances of disagreement between laboratories regarding the RBE_M of neutrons of similar energies, as compiled in Figure 2. Prior studies identified possible reasons for this inter-laboratory dose-response curve (and thus RBE) variation, including the conflation of different neutron spectra (Hall et al. 1975), as well as the effects of protocol differences (Oestreicher et al. 2017). Reference radiation selection has also been identified as a source of divergent RBE_M evaluations, particularly between ^{60}Co and orthovoltage X-rays (Schmid et al. 2000). Figure 2 demonstrates that using ^{60}Co as a reference radiation often produced higher RBE_M evaluations compared to both ^{137}Cs and 220–250 kVp X-rays. To further explore the influence of reference radiation selection on neutron RBE_M evaluations, our research group evaluated whether ^{60}Co, ^{137}Cs, and 250 kVp X-ray irradiation produced differing rates of dicentric and ring chromosome induction, where experimental procedures, including cell culturing, harvesting, slide making, and microscopy, were kept consistent. Part 1 of this manuscript presents comparative DCA dose-response curve data following ^{60}Co, ^{137}Cs, and 250 kVp X-ray irradiations of human peripheral blood lymphocytes. Part 2 evaluates the influence of reference radiation on neutron RBE values and discusses our results within the context of prior reported literature.

Methods

Blood collection

All procedures related to the collection and handling of blood samples were conducted according to a protocols approved by the Research Ethics Board of Atomic Energy of Canada Limited (AECL) (RIHS-09-001; for the ^{137}Cs arm), by the Health Canada Research Ethics Board (2002-0012; for the 250 kVp X-ray arm), and by Veritas Independent Review Board (2701; Montreal, Canada, for the ^{60}Co arm). Blood was collected with informed consent by venipuncture into vacuum-evacuated sodium heparinized (^{137}Cs) or lithium heparinized (^{60}Co and 250 kVp X-ray) Vacutainer tubes (BD, Franklin Lakes, USA). All blood donors indicated feeling healthy on the day of the blood draw, were nonsmokers, and had no known underlying health conditions, nor a history of radiotherapy or chemotherapy treatment.

Irradiations

Cobalt-60

Blood samples from two donors (one male aged 41 years, one female aged 40 years) were irradiated at room temperature to achieve nine dose points of 0, 0.1, 0.25, 0.5, 0.75, 1.0, 2.0, 3.0, and 4.0 Gy. The lowest dose point of 0.1 Gy was irradiated using a Gammacell 200 (AECL, Ottawa, Canada) at a dose rate of 0.2 Gy min^{-1}, whereas all other dose points were irradiated using a Gammacell 220 (AECL, Ottawa, Canada) at a dose rate of 1.1 Gy min^{-1}. Both Gammacell irradiators were calibrated using a Keithley model 35040 therapy dosimeter. Immediately after irradiation, blood was incubated at 37 °C for 2 h, followed by a 22 h room temperature incubation. Culture set-up began 24 h post-irradiation. This timing was necessary to match the timeline of the previously published ^{137}Cs study (Flegal et al. 2012), which needed to accommodate shipment of samples post-irradiation.

Cesium-137

The details of the ^{137}Cs irradiation have been published previously (Flegal et al. 2012). Briefly, blood samples from two male donors (within age ranges: 25–30 years and 55–60 years) were irradiated at room temperature using a ^{137}Cs Gammacell 40 (AECL, Ottawa, Canada). The Gammacell 40 calibration was completed by Fricke dosimetry (MDS Nordion, Ottawa, Canada). Nine dose points of 0, 0.1, 0.25, 0.5, 0.75, 1.0, 2.0, 3.0, and 4.0 Gy were conducted at a dose rate of 0.801 Gy min^{-1}. Following irradiation, blood was incubated at 37 °C for 2 h, then for 22 h at room temperature, prior to culture set-up. The current study involved re-analysis of data from the AECL arm of the previously published ^{137}Cs study (Flegal et al. 2012).

250 kVp X-ray

Blood samples from two donors (one male aged 30 years; one female aged 38 years) were irradiated at room temperature with 250 kVp X-rays (15 mA; 0.75 mm Sn and 0.25 mm Cu and 1.5 mm Al filter; half value layer ~3.7 mm Cu; build-up 4.5 cm water; mean energy 133 keV) using a X-Rad 320 cabinet biological irradiator (Precision X-ray Irradiation, Madison, USA). Nine dose points of 0, 0.1, 0.25, 0.5, 0.75, 1.0, 2.0, 3.0, and 4.0 Gy were irradiated at a dose rate of 0.37 Gy min^{-1}. All doses were measured using a PTW TW30010–10 ion chamber and a PTW UNIDOS T10002 electrometer (PTW Dosimetry, Freiburg, Germany) with Nk = 48.3 mGy nC^{-1} at 250 kV (calibrated by the National Research Council, Ottawa, Canada, 2012). Immediately following the irradiation, blood was incubated at 37 °C for 2 h, followed by a 22 h room temperature incubation prior to culture set-up.

Dicentric chromosome assay

To ensure the utmost accuracy and sensitivity, identical cell culture, harvesting, slide making, and microscopy protocols were used. Duplicate whole blood cell cultures were established in Nunc T-25 flasks (Thermo Fisher Scientific Inc., Waltham, USA) according to the International Atomic Energy Agency (IAEA) cytogenetic dosimetry guidelines (IAEA 2011) and following ISO standard 19238:2023 (ISO 2023). Briefly, blood was diluted 1:9 with RPMI 1640 medium (Thermo Fisher Scientific™ Inc., Waltham, USA) supplemented with 15% fetal bovine serum, 100 units ml^{-1} penicillin and 100 μg ml^{-1} streptomycin (Millipore Sigma, Burlington, USA), 20 μM of bromodeoxyuridine (BD Biosciences, San Jose, USA), and 1% phytohemagglutinin (Millipore Sigma, Burlington, USA). Cell cultures were incubated for 48 h at 37 °C and 5% CO_2 in air. Colcemid (0.1 μg ml^{-1}, Thermo Fisher Scientific Inc., Waltham, USA) was present for the final 4 h. Samples were then harvested, placed on slides, and stained for microscopy using the fluorescent-plus-Giemsa method, which allowed for discernment between first- and second-division metaphase spreads. Slides were blinded and imaged under 630× magnification using the Metafer automated microscopy platform (Metasystems Group Inc., Newton, USA). Images of complete metaphase spreads containing 46 centromeres arrested during the first cell division were scored manually according to criteria described by Paterson et al. (2021). Differentially stained second-division metaphase spreads were not analyzed. Dicentric and ring chromosomes were both included in the total aberration tally. Acentric fragment count was recorded but not included in the total aberration tally. Microscopy was completed by one individual with extensive experience with this assay and who is a longtime member of the Canadian Biodosimetry Network (Wilkinson et al. 2007).

Statistics

The DCA assay aberration distributions were tested for agreement with the Poisson distribution. The dispersion index was calculated as the quotient of variance (σ^2) and mean (y). Variance is a measure of the spread of data points from their average value, or mean. A dispersion index of unity indicated compliance with the Poisson distribution. Dispersion indices outside of unity were further examined using the u-test, the normalized unit of the dispersion index. Here, a u value above 1.96 indicated non-Poisson over-dispersion and a u value below −1.96 indicated non-Poisson under-dispersion, both at the 5% significance level (Szluinska et al. 2007; IAEA 2011).

Dose-response curve fitting was achieved using the Dose Estimate software (version 5.2) (Ainsbury and Lloyd 2010).

Linear-quadratic regression is presented in the form $A = c + \alpha D + \beta D^2$, where A is the frequency of aberrations at a given dose point, c is the background frequency of aberrations, α is the linear slope coefficient, β is the dose-squared slope coefficient, and D is the dose in Gy. Dose-response curve goodness of fit was tested using the chi-squared test (χ^2). The z-test was used to evaluate the significance of the derived equation coefficients and compare α coefficients and RBE_M values. The P-values less than 0.05 were considered statistically significant. Error values were reported as either standard deviation (SD) or standard error of the mean (SE).

RBE_M calculation

RBE_M was calculated as the ratio of the neutron dose-response curve regression equation α coefficient (α_{TEST}) and the reference radiation dose-response curve regression equation α coefficient (α_{REF}) (IAEA 2011). RBE was calculated as the ratio of doses required to produce an equivalent effect.

Results

Part 1: Reference radiation dose-response curves

Cobalt-60

The distribution of dicentric and ring chromosome aberrations in lymphocytes following whole blood exposure to ^{60}Co is presented in Table 1. A total of 7,900 cells from two donors were scored across nine dose points between 0 Gy and 4 Gy. The background level of aberrations was 0.003 aberrations per cell, and the maximum aberration yield was 0.910 aberrations per cell for the highest dose of 4 Gy. Approximately 67% of cells at the highest dose point contained between one and five aberrations. Six of the eight irradiated dose points demonstrated Poisson dispersion, as demonstrated by u values between −1.96 and +1.96.

Cesium-137

The distribution of dicentric and ring chromosome aberrations in lymphocytes following whole blood exposure to ^{137}Cs is presented in Table 2. A total of 5,969 cells from two donors were scored across nine dose points between 0 Gy and 4 Gy. The background level of aberrations was zero aberrations per cell, and the maximum aberration yield was 1.395 aberrations per cell for the highest dose of 4 Gy. Approximately 82% of cells at the highest dose point contained between one and five aberrations. Four of the eight irradiated dose points demonstrated Poisson dispersion, as demonstrated by u values between −1.96 and +1.96.

250 kVp X-ray

The distribution of dicentric and ring chromosome aberrations in lymphocytes following whole blood exposure to 250 kVp X-rays is presented in Table 3. A total of 3,662 cells from two donors were scored across nine dose points between 0 Gy and 4 Gy. The background level of aberrations was 0.002 aberrations per cell, and the maximum aberration yield was 1.331 aberrations per cell for the highest dose of

Table 1. Our DCA aberration distribution in human blood lymphocytes from two donors following exposure to ^{60}Co.

^{60}Co

Total Dose (Gy)	Cells Scored	Dicentrics	Rings	Acentrics	Total Aberr.	Distribution of dicentric and ring chromosome aberrations: 0	1	2	3	4	5	Aberr. per Cell	Dispersion Index (σ^2/y)	u Statistic
0	1,000	2	1	10	3	997	3	0	0	0	0	0.003	1.00	−0.05
0.1	1,000	6	0	16	6	994	6	0	0	0	0	0.006	0.99	−0.12
0.25	1,000	11	0	26	11	989	11	0	0	0	0	0.011	0.99	−0.23
0.5	1,000	22	4	42	26	974	26	0	0	0	0	0.026	0.97	−0.57
0.75	1,000	58	5	89	63	938	61	1	0	0	0	0.063	0.97	−0.68
1	900	68	2	112	70	832	66	2	0	0	0	0.078	0.98	−0.40
2	1,000	205	16	322	221	803	173	24	0	0	0	0.221	0.95	−1.20
3	600	298	26	487	324	331	218	47	4	0	0	0.540	0.83	−3.02
4	400	331	33	587	364	132	191	60	15	2	0	0.910	0.73	−3.75

Aberr: Aberrations, sum of dicentrics and ring chromosomes.

Table 2. Our DCA aberration distribution in human blood lymphocytes from two donors following exposure to ^{137}Cs.

^{137}Cs

Total Dose (Gy)	Cells scored	Dicentrics	Rings	Acentrics	Total Aberr.	Distribution of dicentric and ring chromosome aberrations: 0	1	2	3	4	5	Aberr. per Cell	Dispersion Index (σ^2/y)	u Statistic
0	600	0	0	6	0	600	0	0	0	0	0	0	–	–
0.1	400	0	0	8	0	400	0	0	0	0	0	0	–	–
0.25	1,074	20	3	50	23	1,054	19	0	0	1	0	0.021	0.81	−4.43
0.5	400	18	0	32	18	382	18	0	0	0	0	0.045	0.96	−0.62
0.75	1,400	122	7	227	129	1,277	117	6	0	0	0	0.092	1.00	0.04
1	700	100	9	181	109	594	103	3	0	0	0	0.156	0.90	−1.87
2	245	120	14	229	134	137	84	22	2	0	0	0.547	0.87	−1.39
3	550	409	51	812	460	209	243	79	17	2	0	0.836	0.78	−3.61
4	600	762	75	1,422	837	109	255	155	55	23	3	1.395	0.77	−3.94

Aberr: Aberrations, sum of dicentrics and ring chromosomes.

Table 3. Our DCA aberration distribution in human blood lymphocytes from two donors following exposure to 250 kVp X-rays.

250 kVp X-ray														
						Distribution of dicentric and ring chromosome aberrations								
Total Dose (Gy)	Cells scored	Dicentrics	Rings	Acentrics	Total Aberr	0	1	2	3	4	5	Aberr. per Cell	Dispersion Index (σ^2/y)	u Statistic
0	500	1	0	7	1	499	1	0	0	0	0	0.002	1.00	–
0.1	500	6	1	19	7	493	7	0	0	0	0	0.014	0.99	−0.21
0.25	500	11	2	23	13	487	13	0	0	0	0	0.026	0.98	−0.40
0.5	500	19	2	44	21	479	21	0	0	0	0	0.042	0.96	−0.65
0.75	500	60	6	111	66	437	60	3	0	0	0	0.132	0.96	−0.62
1	500	93	11	167	104	402	92	6	0	0	0	0.208	0.91	−1.44
2	378	146	12	244	158	241	117	19	1	0	0	0.418	0.86	−1.89
3	163	151	12	232	163	51	68	39	3	2	0	1.000	0.74	−2.34
4	121	149	12	293	161	18	64	25	9	5	0	1.331	0.69	−2.38

Aberr: Aberrations, sum of dicentrics and ring chromosomes.

Table 4. Our DCA dose-response regression values and statistical testing results for reference radiation dose-response curves. Linear-quadratic regression is given by the equation $a = c + \alpha D + \beta D^2$.

Radiation source	α [±SE] (Gy^{-1})	β [±SE] (Gy^{-2})	c [±SE]	χ^2-test Sig.	α z-test Sig.	β z-test Sig.
^{60}Co	0.0268 ± 0.0075	0.0492 ± 0.0034	0.0029 ± 0.0014	0.83	0.0116	<0.0001
^{137}Cs	0.0730 ± 0.0135	0.0706 ± 0.0058	0	0.68	0.0017	<0.0001
250 kVp X-ray	0.1063 ± 0.0248	0.0624 ± 0.0117	0.0017 ± 0.0031	0.67	0.0051	0.0017

SE: standard error; Sig.: significance.

4 Gy. Approximately 85% of cells at the highest dose point contained between one and five aberrations. Six of the eight irradiated dose points demonstrated Poisson dispersion, as demonstrated by u values between −1.96 and +1.96.

Regression

Data from the three photon exposures were fit by linear-quadratic regression, as given in Table 4. In all cases, the α linear slope coefficients (column 2, Table 4) and the quadratic β dose-squared coefficient (column 3, Table 4) tested as significant (columns 6 and 7, Table 4), indicating a clear preference for the linear-quadratic regression fit, typical of low-LET irradiations. The χ^2-test P-values given in column 5 of Table 4 indicate that the regression fit is not statistically different from the observed DCA data points, further confirming a good fit.

Variation of our three reference radiation dose-response curves

The α coefficient of the ^{60}Co dose-response curve (0.0268 ± 0.0075 Gy^{-1}), was found to be significantly less than both the ^{137}Cs α coefficient (0.0730 ± 0.0135 Gy^{-1}, $z = 2.99$, $P < 0.01$) and the X-ray α coefficient (0.1063 ± 0.0248 Gy^{-1}, $z = 3.07$, $P < 0.01$). However, no significant difference was found between the α coefficients of the ^{137}Cs and X-ray dose-response curves ($z = 1.18$, $P = 0.24$). A visual comparison of the three reference radiation dose-response curves with the full range of doses is presented in Figure 3A, and the low-dose range, which factors heavily in the α coefficient used in the RBE$_M$ calculation, is highlighted in Figure 3B.

Part 2: Relative biological effectiveness of reference radiations and neutron exposures

Our reference radiation RBE$_M$ variation

To evaluate the effect of the differing reference radiation dose-response curves, ^{60}Co was assumed to have an RBE$_M$ of 1.0. Applying this assumption, RBE$_M$ values for ^{137}Cs and 250 kVp X-rays, relative to ^{60}Co, were calculated using a ratio of the α coefficients of the linear-quadratic dose-response

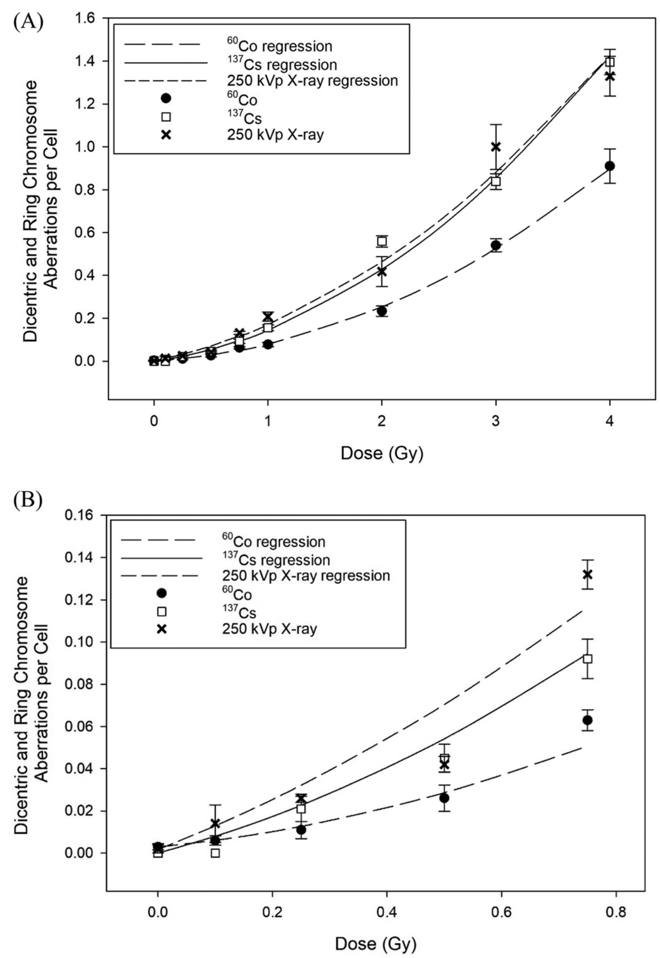

Figure 3. Comparison of our ^{60}Co, ^{137}Cs, and 250 kVp X-ray dose-response curves: (A) full dose range; (B) lower dose range only.

Table 5. Overview of high doses required to achieve a defined biological effect, here as aberrations per cell, calculated from linear-quadratic dose-response curves, and the resulting RBE values for these effect levels. Aberrations per cell were chosen on the basis of the ^{60}Co experimental findings for 1, 2, 3, and 4 Gy.

	Dose to achieve effect (Gy)			RBE		
Aberrations per cell	^{60}Co	^{137}Cs	250 kV X-ray	^{137}Cs relative to ^{60}Co	250 kV X-ray relative to ^{60}Co	250 kVp X-ray relative to ^{137}Cs
0.078	1.0	0.7	0.5	1.4	2.0	1.4
0.221	1.9	1.3	1.2	1.5	1.6	1.1
0.540	3.0	2.3	2.2	1.3	1.4	1.1
0.910	4.0	3.1	3.1	1.3	1.3	1.0

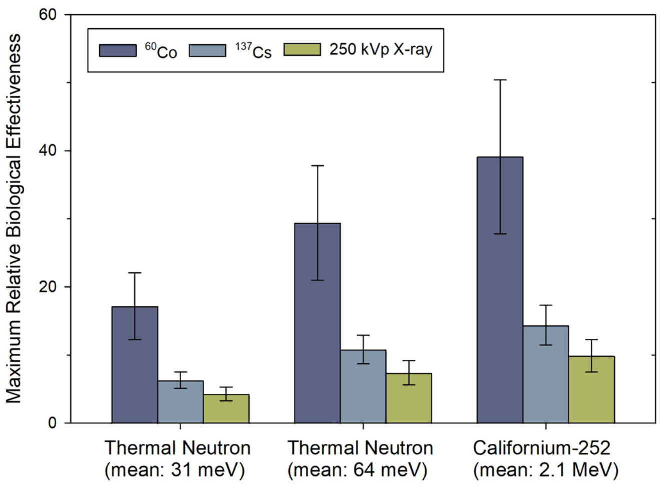

Figure 4. Our RBE_M values for thermal and fast neutron exposures were greatest when using ^{60}Co reference radiation. Significantly lower RBE_M values result when ^{137}Cs or 250 kVp X-rays are used as the reference radiation. Raw data are provided in Table S1.

regression. The RBE_M for ^{137}Cs relative to ^{60}Co was 2.7 ± 0.9, and the RBE_M for 250 kVp X-rays relative to ^{60}Co was 4.0 ± 1.5.

Our RBE estimates at high doses

The ^{60}Co irradiation resulted in the lowest number of aberrations per cell for all three radiation types at all dose points beyond 0.1 Gy. To estimate RBE at high doses, four aberration frequencies of 0.078, 0.221, 0.540, and 0.910 aberrations per cell were selected based on the ^{60}Co results at 1, 2, 3, and 4 Gy, respectively. At these aberration frequencies, the RBE for ^{137}Cs relative to ^{60}Co ranged from 1.5 to 1.3, and the RBE for 250 kVp X-rays relative to ^{60}Co ranged from 2.0 to 1.3. The RBE for 250 kVp X-rays relative to ^{137}Cs achieved unity at the highest aberration frequency of 0.910 (Table 5).

Prior reported neutron RBE_M variation

Neutron DCA regression data were extracted from our prior publications that evaluated thermal and fast neutrons (Paterson et al. 2021, 2022, 2025) to compare the effect of reference radiation selection on neutron RBE_M ($nRBE_M$). As illustrated in Figure 4, the largest $nRBE_M$ values were achieved when ^{60}Co was used as the reference radiation ($nRBE_{M(60Co)}$). In contrast, significantly lower neutron RBE_M values were attained when ^{137}Cs ($z = 2.16$, $P = 0.03$) and 250 kVp X-ray ($z = 2.58$, $P < 0.01$) were used as reference radiations (Table S1). The $nRBE_M$ values using ^{137}Cs ($nRBE_{M(137Cs)}$) and 250 kVp X-ray ($nRBE_{M(X\text{-}ray)}$) as reference radiations were not significantly different ($z = 1.28$, $P = 0.20$). Overall, $nRBE_{M(60Co)}$ was nearly 2.7-fold higher than $nRBE_{M(137Cs)}$, and nearly four-fold higher than $nRBE_{M(X\text{-}ray)}$.

Discussion

Part 1: Reference radiation dose-response curves

How do our DCA dose-response curves compare to the literature?

Photon DCA dose-response curves are typically best fit by linear-quadratic regression and expressed as $A = c + \alpha D + \beta D^2$. To reduce the statistical uncertainty of the α coefficient that is used in the RBE_M calculation, five dose points were irradiated in the lower dose range, namely at 0.1, 0.25, 0.5, 0.75, and 1.0 Gy (IAEA 2011). As the α coefficient is utilized for the calculation of RBE_M (where $RBE_M = \alpha_{TEST}/\alpha_{REF}$), only the α coefficients for α_{TEST} and α_{REF} will be discussed in this section.

Endesfelder et al. (2023) compiled DCA photon dose-response curve coefficients from the laboratories that participated in the 2021 Running the European Network of Biological and Physical Retrospective Dosimetry (RENEB) inter-comparison. The participating biological dosimetry laboratories were expected to take into consideration the IAEA cytogenetic dosimetry guidelines (IAEA 2011), and therefore, samples would have been handled in a similar manner to the protocol described in this manuscript, making this an ideal cohort for comparison. Using data entries with defined photon sources that were scored by manual microscopy, it was found that the ^{60}Co α coefficient of the linear-quadratic dose-response curve presented here (0.0268 ± 0.0075 Gy^{-1}) was not significantly different from the mean of the ^{60}Co α coefficients calculated from the RENEB comparison data (0.0201 ± 0.0027 Gy^{-1}, $n = 17$, $SD = 0.0111$, $z = 0.84$, $P = 0.40$). Similar results were also found for ^{137}Cs and for 250 kVp X-ray, whereby the α coefficient of the linear-quadratic dose-response equations presented here were not significantly different from the mean of the RENEB α coefficients (^{137}Cs: this manuscript 0.0730 ± 0.0135 Gy^{-1}, RENEB mean 0.0532 ± 0.0219 Gy^{-1}, $n = 3$, $SD = 0.0377$, $z = 0.77$, $P = 0.44$; 250 kVp X-ray: this manuscript 0.1063 ± 0.0248 Gy^{-1}, RENEB mean 0.0637 ± 0.0177 Gy^{-1}, $n = 2$, $SD = 0.0250$, $z = 1.40$, $P = 0.16$). Therefore, the ^{60}Co, ^{137}Cs, and 250 kVp X-ray dose-response curve α coefficients presented in the manuscript are comparable to many reported dose-response curve α coefficients utilized by recognized biological dosimetry laboratories. This comparison affirms the accuracy of our dose-response curves.

What are the implications for biological dosimetry?

Emergency biological dosimetry estimations require the *ex vivo* generation of a DCA dose-response curve (also referred to as a calibration curve) (IAEA 2011). The findings presented here demonstrate that ^{60}Co, ^{137}Cs, and 250 kVp X-rays produce significantly different frequencies of dicentric and ring chromosome aberrations, and hence different dose-response curve slopes. As such, our data reaffirms that caution should be taken in situations where the source of an accidental radiation over-exposure is mismatched with the calibration curve utilized to derive a dose estimate. For example, if a dicentric and ring aberration frequency of 0.1 aberrations per cell were found following an accidental photon radiation over-exposure, based on the data presented in this manuscript the estimated dose would be evaluated at approximately 1.15, 0.78, and 0.67 Gy using the ^{60}Co, ^{137}Cs, and 250 kVp X-ray calibration curves presented here, respectively.

The RENEB association recently noted this phenomenon during an inter-comparison, as the median α and β coefficients for manually scored linear-quadratic photon dose-response curves were significantly lower for ^{60}Co curves than for X-ray curves generated using voltages between 200 kVp and 250 kVp, making it possible to "…reveal a systematic shift of the dose estimates which could partly be attributed to differences in the biological effectiveness between X-rays and γ rays." (Endesfelder et al. 2023). Although the RENEB conclusions pertained only to ^{60}Co and X-rays, our findings, and those of Silva et al. (1997), suggest that ^{137}Cs dose-response curves also should not be used to evaluate the dose resulting from a ^{60}Co inadvertent exposure. However, this is not a unanimous finding as the data put forward by Schmid et al. (1995) revealed no significant difference between the α coefficients of the ^{60}Co and ^{137}Cs linear-quadratic dose-response curves. Overall, our work provides further evidence that biological dosimetry laboratories require multiple calibration curves to ensure accurate emergency biodosimetry dose evaluations and to avoid a situation where the reference radiation is mismatched with the accidental radiation exposure.

Part 2: Relative biological effectiveness of reference radiations and neutron exposures

How do our reference radiation findings compare to the literature?

DNA DSB modeling studies offer conflicting results regarding the differences we observed for the DCA when employing ^{60}Co, ^{137}Cs, or 250 kVp X-rays. Hsiao and Stewart (2008) found no significant difference between the DSB yields of ^{60}Co and ^{137}Cs using the PENELOPE Monte Carlo radiation transport code and Monte Carlo damage simulation; however, a difference was noted between filtered and unfiltered 220 kVp X-rays and both ^{60}Co or ^{137}Cs (X-ray RBE relative to ^{60}Co ranging from 1.08 to 1.20). In addition, Friedland et al. (1999) found no significant difference between the DNA DSB yield for ^{60}Co and 220 kVp X-rays using the Monte Carlo PARTRAC track structure code. For brevity, the Monte Carlo analysis details of their study are not given here, but it should be noted that these simulations can show a large variation in DNA DSB estimates depending on the simulation parameters utilized (Thompson et al. 2024).

Only a handful of other laboratories have published two or more DCA dose-response curves for human lymphocytes utilizing ^{60}Co, ^{137}Cs, and/or 220–250 kVp X-rays, as summarized in Table 6. The implicit assumption of this tabulated comparison of dose-response curve α coefficients is that the DCA protocols and handling were similar for all irradiations performed within the same laboratory. To compare within the data, ^{60}Co was assumed to have an RBE_M of 1.0. Using this dataset, the RBE_M of ^{137}Cs relative to ^{60}Co was found to range from 1.4 to 2.0 (mean = 1.7, n = 2), and 220–250 kV X-ray RBE_M values relative to ^{60}Co were found to range from 1.7 to 3.7 (mean = 2.8; n = 6). The literature-derived RBE_M values presented in Table 6 are not significantly different than the RBE_M value of 2.7 for ^{137}Cs and 4.0 for 250 kVp X-rays presented in this manuscript, except for the data put forward by Prassana et al. (2002). This is perhaps unsurprising, as the irradiation conditions and the experimental procedures, although similar, were not identical across all laboratories identified in Table 6. Regardless, the trend toward elevated RBE_M values for ^{137}Cs and 250 kVp X-rays relative to ^{60}Co is confirmed.

Sasaki et al. (2016) reported an in vitro DCA LET dependence (range 0.2 keV μm^{-1} to ~180 keV μm^{-1}) for DCA RBE_M in human G_0 lymphocytes following charged particle irradiation. For track-average LETs of 0.2 keV μm^{-1} (^{60}Co)

Table 6. Comparison of prior reported α linear slope coefficients from laboratories with two or more photon dose-response curves for human lymphocytes. RBE values are in reference to ^{60}Co.

α Linear slope coefficients (Gy^{-1})			RBE_M (± SE)		
^{60}Co	^{137}Cs	220–250 kV X-ray	^{137}Cs relative to ^{60}Co	220–250 kV X-ray relative to ^{60}Co	Literature references
0.0268 ± 0.0075	0.0730 ± 0.0135	0.1063 ± 0.0248[c]	2.7 ± 0.9	4.0 ± 1.5	This paper
0.0107 ± 0.0041	0.015 ± 0.005	0.04 ± 0.003[b]; 0.022 ± 0.004[b]	1.4 ± 0.7	3.7 ± 1.5; 2.1 ± 0.9	Bauchinger et al. (1983), Schmid et al. (1984), Schmid et al. (1995)
0.0526 ± 0.0148[a]	0.1035 ± 0.0146[a]		2.0 ± 0.6		Silva et al. (1997)
0.0157 ± 0.0029		0.0476 ± 0.0054[c]		3.0 ± 0.7	Edwards et al. (1982)
0.014 ± 0.004		0.046 ± 0.005[c]		3.3 ± 1.0	Lloyd et al. (1986)
0.059 ± 0.0136		0.098 ± 0.0209[c]		1.7 ± 0.5	Prasanna et al. (2002)

[a]recalculated using Dose Estimate software package (Ainsbury and Lloyd 2010); [b]220 kV; [c]250 kV.

and 0.35 keV μm^{-1} (^{137}Cs), the regression derived from Figure 4 of Sasaki et al. (2016) demonstrated an approximately 1.2-fold difference in DCA RBE_M. Similarly, theoretical modeling of dicentric chromosome induction found differing dose-response curves for ^{60}Co and ^{137}Cs, resulting in an RBE_M of ^{137}Cs relative to ^{60}Co to be approximately 1.6 (Mirrezaei et al. 2022). For the track-average LETs of 0.2 keV μm^{-1} (^{60}Co) and 2.0 keV μm^{-1} (250 kVp X-ray), Sasaki et al. demonstrated an approximately 6-fold difference for DCA RBE_M.

The DCA RBE variation for reference radiation is further supported by micronucleus studies in human lymphocytes that evaluated the mal-segregation of chromosomes. Hubner et al. (1994) found an elevated micronucleus α coefficient following 220 kV X-ray irradiation, compared to ^{60}Co irradiation, that resulted in an RBE_M of 2.6 ± 1.5 for 220 kV X-ray relative to ^{60}Co. Similarly, Sreedevi and Rao (1994) noted an elevated micronucleus α coefficient following 250 kVp X-ray exposure, compared to ^{60}Co exposure, that resulted in an RBE_M of 3.3 ± 2.1.

When comparing the biological effects of photons, prior microdosimetry utilizing proximity functions calculated by the Monte Carlo technique by Chen (2004), found little difference between the RBE_M of ^{60}Co and ^{137}Cs, but confirmed that the RBE_M of ^{60}Co and 250 kVp X-rays can vary by a factor of 2 as a result of energy deposition differences (albeit with different filtration than the 250 kVp X-rays than utilized here). ICRP publication 92 also acknowledges a RBE_M difference between gamma-rays and 200 kV X-rays, stating, "For dicentrics, it is seen that the RBE_M of moderately filtered 200 kV x rays is about 2–3 relative to γ rays…" (ICRP 2003).

The DCA data presented in this manuscript demonstrate a ~four-fold difference in the RBE_M of ^{60}Co and 250 kVp X-rays, higher than the ~two-fold estimate by microdosimetry that was based on energy deposition alone (Chen 2004; Lloyd et al. 1986), and elevated beyond the two- to three-fold metric for dicentrics put forward by the ICRP (2003). These data suggest that there may be physical and biological components to the elevated RBE_M observed for X-rays with peak energies in the 200 kVp to 250 kVp range compared to ^{60}Co photons, and possibly a largely biological component responsible for the differences between ^{137}Cs and ^{60}Co photons. Furthermore, the reported and current data suggest that much of the biological component influencing the differing levels of DCA aberrations following exposure to ^{60}Co, ^{137}Cs, and orthovoltage X-rays may occur after DNA DSB induction. This suggests the biological component may result from the influence of DNA repair, cellular respiration, mitosis, and/or other post-DNA damage factors. More research, via experiment or Monte Carlo simulation, would be beneficial to identify the exact nature of the RBE_M differences for reference radiation exposures. It should be noted that the DCA RBE of X-rays has been shown to be filtration-dependent (Schmid et al. 1984), so the conclusions presented here for 250 kVp X-rays with the set-up described in the methods section may not hold for all other X-ray configurations (Barnard et al. 2020).

Studies with other cell types and endpoints have also called into question the notion that all photon sources should be considered equal. For example, a study by Li et al. (2024) evaluated cell survival in three human cancer cell lines exposed to high-dose exposures of 2, 4, 6, and 8 Gy. The RBEs for a survival fraction of 0.1 for the HCT116 cell type for 6 MV X-rays, ^{192}Ir, and 50 kVp X-rays, relative to 225 kVp X-rays, were 0.89 ± 0.03, 0.95 ± 0.03, and 1.24 ± 0.04, respectively; for HeLa cells the RBEs were 0.95 ± 0.04, 0.97 ± 0.05, and 1.09 ± 0.03, respectively, and for PC3 cells the RBEs were 0.84 ± 0.01, 0.84 ± 0.01, and 1.13 ± 0.02, respectively. Similarly, Upton et al. (1956) found an RBE of 1.4 for a dose lethal within 30 days to one-half of the exposed experimental mice following a single dose of 250 kVp X-rays as compared to ^{60}Co. Bell et al. (2022) also observed that murine whole-body irradiation using either filtered X-rays or ^{137}Cs produced differential experimental responses depending on the radiation type for several endpoints, including reduction in bone marrow cellularity, hematopoietic stem and progenitor populations, intestinal crypts, and intestinal stem cells.

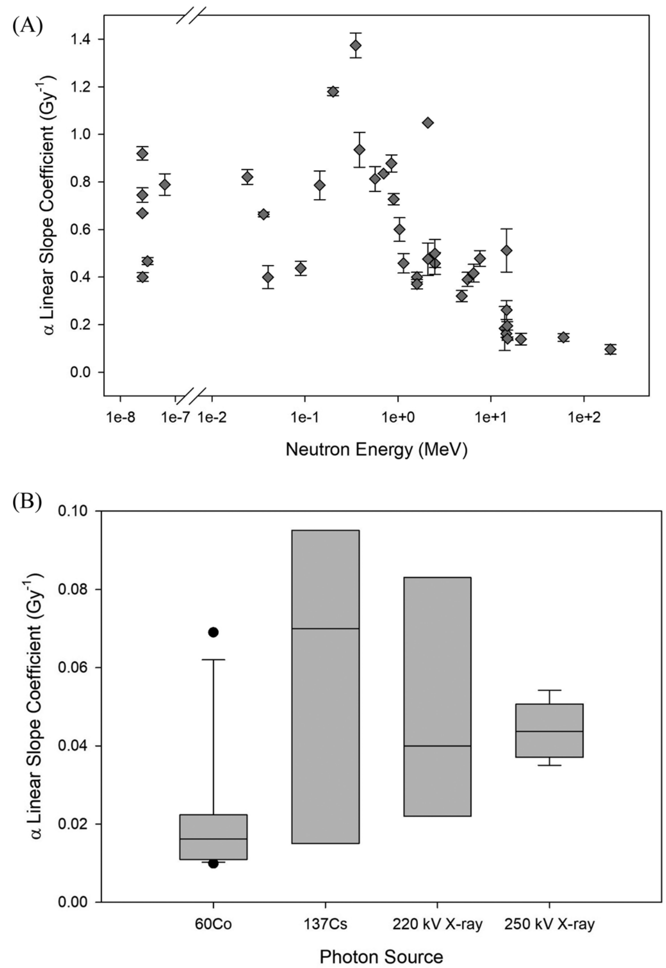

Figure 5. (A) Variation of prior reported α coefficient with neutron energy. (B) Box plot illustrating α coefficient by reference radiation. Solid circles represent outliers that fall beyond 1.5 times the interquartile range. For both (A) and (B), the data was extracted from the publications included in Figure 2.

Table 7. Prior reported α linear slope coefficient variation for neutron and the corresponding reference radiation, including ^{60}Co, ^{137}Cs, and 220–250 kV X-ray, across multiple neutron energy bins. The fold difference, or the ratio of the low and high α coefficients, is larger for reference radiation than for the neutron data.

	Neutron				Reference radiation			
Energy bin	Low α ± SE	High α ± SE	n	Fold difference	Low α ± SE	High α ± SE	n	Fold difference
Thermal	0.400 ± 0.018	0.92 ± 0.028	6	2.3	0.011 ± 0.004	0.070 ± 0.0088	5	6.4
0.001– 0.9 MeV	0.3995 ± 0.0483	1.374 ± 0.0522	12	3.4	0.0099 ± 0.004	0.069 ± 0.011	13	7.0
1–10 MeV	0.32 ± 0.024	1.049 ± 0.001	11	3.2	0.0099 ± 0.004	0.0951 ± 0.023	9	9.6
>10 MeV	0.096 ± 0.02	0.5117 ± 0.0909	9	5.3	0.0099 ± 0.004	0.069 ± 0.011	9	7.0

How does reference radiation selection affect neutron RBE_M values?

Using the dataset that was employed to generate the Figure 2 RBE_M plot by neutron energy, additional plots were generated to illustrate the α coefficients for the neutron (Figure 5A) and photon (Figure 5B) inputs. When the data is presented in this manner, this provides additional confirmation that reference radiation selection introduces much variability into the neutron RBE_M dataset. For example, the thermal neutron dataset in Figure 2 demonstrates a nearly five-fold difference between the lowest and highest RBE_M values (range: 10.8–51.1, $n = 6$). The neutron α coefficients evaluated from the same dataset demonstrate a 2.3-fold difference (range: 0.467–0.92, $n = 6$), while the reference radiation α coefficients demonstrate a 6.4-fold difference (range: 0.011–0.070, $n = 5$). This trend continues for all energy bins as described in Table 7, whereby greater variation in the α coefficient is found for the reference radiation, than across a range of neutron energies within each bin that are already known to produce different biological effects.

For RBE at a defined aberration frequency typical of high doses (1–4 Gy), much less variation is seen between the three reference radiations than was found using the RBE_M metric, as outlined in Table 5. For example, at 0.910 aberrations per cell, and when doses are extrapolated from the dose-response curves, the RBE was 1.3 for both ^{137}Cs and 250 kVp X-ray relative to ^{60}Co. At these high aberration levels, the variation of RBE for the three reference radiations is smaller than the $RBE_{M,}$ as RBE_M is only influenced by the linear component of the linear-quadratic dose-response curve that is representative of the low dose range.

The result that ^{60}Co, ^{137}Cs, and 250 kVp X-rays can produce significantly different frequencies of dicentric chromosomes at identical doses highlights the importance of defining the reference radiation when presenting RBE evaluations. Chen proposed that only hard gamma rays (the most common of which are from ^{60}Co or ^{137}Cs) should be used for RBE evaluations (ICRP 2003; Chen 2004). However, using the DCA, we have demonstrated that the α coefficients for dicentric and ring chromosome induction for gamma-emitters ^{60}Co and ^{137}Cs are also significantly different and can result in incongruent RBE evaluations. Tighter guidelines around reference radiation selection and irradiation conditions may remedy some of the variation seen in the human lymphocyte neutron RBE_M dataset; however, given the amount of variation within the three reference radiation datasets, a move toward common protocols could also prove advantageous.

Limitations

Two limitations arose for the current experimental study. First, it was not possible to obtain blood from the same donors for each radiation treatment group. This had to be accepted due to blood donor availability. Second, anticoagulant status between the treatment groups differed. The ^{137}Cs samples were treated with sodium heparin, while the ^{60}Co and 250 kVp samples were treated with lithium heparin. It is currently not known whether the use of sodium versus lithium heparin affects the yield of dicentric chromosomes.

Conclusion

DCA dose-response curves in human lymphocytes were generated following irradiation with ^{60}Co, ^{137}Cs, or 250 kVp X-rays. A significant difference was found for the linear component of the linear-quadratic dose-response curve between ^{60}Co and both ^{137}Cs and 250 kVp X-rays. The implications of this are far-reaching, including: i) re-confirmation of significant variation in comparative RBE_M assessments of all types of test ionizing radiation sources, ii) the possibility of incorrect biological dosimetry dose estimates following accidental or unintended radiation over-exposures, if there is a calibration curve mismatch, and iii) the possible introduction of uncertainty in the RBE_M values that underpin w_R determinations, which feed into radiation protection guidelines and affect dosimetry and risk estimates. The accuracy of the results presented here, which include a robust low-dose range, indicates that DCA RBE values of a test radiation, such as neutron exposures, can be substantially and significantly modified by reference radiation selection. These results reaffirm the stance of the ICRP whereby "it is essential that any statement of RBE must be accompanied by a specification of the reference radiation".

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Institutional review board statement

The ^{60}Co arm of this study was approved by Veritas Independent Review Board (Montreal, QC, Canada). The X-ray and ^{137}Cs arms of the study conducted at CNL were approved by the AECL Committee on Research

Involving Human Subjects (Chalk River, ON, Canada). The X-ray arm of the study, involving blood draws and irradiations at Health Canada, was approved by the Health Canada Research Ethics Board.

Informed consent statement

Informed consent was obtained from all subjects involved in the study.

Disclosure statement

The authors report there are no competing interests to declare.

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