

RBE of Radiations in Space and the Implications for Space Travel

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Abstract

Space travellers are irradiated with cosmic rays to a dose rate considerably higher than that received on earth. In order to make sensible judgements about space exploration, the risks to health of such radiation need to be assessed. Part of the assessment of risk is to allow for the enhanced biological effectiveness of high LET radiations with respect to others. In space the high LET radiations of concern are high energy neutrons and charged particles. At the doses and dose rates encountered in space, the important risk is the induction of cancer in the astronauts.

For this biological end-point there is no direct human evidence for the relative effectiveness of these radiations. There are some data for neutrons for cancer and life-shortening in laboratory animals but these are for fission spectra neutrons, which are of lower energy than those encountered in space. There is a small amount of data for protons and high energy heavier charged particles. The remaining evidence comes from cellular experiments observing chromosome aberrations and gene mutations. From this sparse information, pragmatic choices need to be made for application to protection in space. The data are reviewed and the bases for the pragmatic choices discussed.

KEYWORDS: Space travel, cancer, risk, RBE.

1. Introduction

Travelling in space is nowadays an everyday occurrence albeit limited to a few hundred individuals. It is the responsibility of individual governments to judge whether the benefits of space travel outweigh the disadvantages. One disadvantage is that space travellers are exposed to higher radiation doses than persons remaining on earth. The measurement and calculation of these extra doses requires assumptions about the precise definition of the dose in Sv. In the radiation protection community there are definitions of equivalent dose, dose equivalent, effective dose, ambient dose equivalent and several others, all of which are measured or calculated in Sv but which use different conversions from Gy to Sv. All these conversions are judgements which are ultimately based on experimental values of relative biological effectiveness, RBE.

In this paper, the experimental basis for the judgements of the conversions of Gy to Sv, concentrating on those that are applicable to space radiation, is reviewed. This is followed by a discussion of the principles that have been used or might be used to make such judgements.

2. Radiations in space

The space radiation environment is very complex [1, 2]. The three major sources of this radiation are galactic cosmic rays, the sun and particles trapped in the radiation belts. Galactic cosmic rays come from outside our solar system and consist of charged particles, mainly hydrogen and helium but there are heavier ions of which the more dominant are carbon, oxygen, neon, silicon and iron. Their energies lie mostly in the range from 50 to 5000 MeV per atomic

mass unit although their spectrum varies with solar activity. The solar produced particles have spectra similar to that of galactic cosmic rays. Particles that are trapped in the earth's magnetic field to form radiation belts consist of protons and electrons of energies up to about 500 MeV.

The relative contributions of these components vary with altitude, latitude and solar activity. With such highly energetic particles other radiations are produced by atomic collisions with the material of space craft and the astronauts themselves, to form photons and electrons (that is low LET), and neutrons (high LET). The result is a complex mixture of radiations. In order to assess risk from space radiation a judgement of relative biological effectiveness (RBE) is required. Several exist already [3] and ICRP have used radiation weighting factor w_R , quality factor, Q , and other un-named approximations.

For space radiation there are basically four radiation components to assess. They are γ -rays and electrons, high energy protons, high energy heavy ions and neutrons.

3. Radiobiological Review

When attempting to derive values of RBE from radiobiological data, the intention is to specify the RBE at low doses. This is necessary because the shape of dose response relationships for high and low LET are generally different and so RBE varies as a function of level of effect or dose. Strictly RBE is defined as the ratio of doses for the reference compared with the tested radiations to produce the same biological effect. At low doses where most dose response relationships are linear, or at least are assumed linear, RBE is the ratio of the initial slopes,

designated RBE_m . On the basis that responses are linear with dose at low doses, it is assumed that RBE_m also represents the maximum value of RBE at low dose rates.

3.1. Neutrons

RBE values for neutrons have been reviewed recently [4, 5]. In brief, estimates of RBE_m for fission spectrum neutrons were based on life-shortening and cancer induction experiments in laboratory animals. Variations of RBE_m with neutron energy are demonstrated by cellular data, mainly from chromosomal aberrations and mutation assays. The analysis of laboratory animal data showed clearly that for low LET, cancer yields and life-shortening are reduced at lower dose rates. Moreover, the higher neutron RBE_m values correlated with the reduction due to low dose rate of the reference radiation. The higher the reduction due to low dose rate at low LET, the higher the observed RBE_m for fission neutrons. On average an RBE_m of 20 for fission neutrons corresponded to a reduction factor due to dose rate of about 4. The cellular data indicated that RBE_m reduces by a factor of about 4 for 15 MeV neutrons compared with fission spectrum neutrons.

3.2. Protons

For the purposes of space travel it is the RBE_m of high energy protons which is of concern. As with neutrons there are no human data. The next most relevant end-point is cancer and life-shortening in laboratory animals and here data are limited. Clapp et al [6] irradiated RF/Un mice with 60 MeV protons and with 300 kVp x-rays to compare their life-shortening effects. The lowest energy proton emerging from the mouse was about 20 MeV so the irradiations were approximately of the track segment type with average proton energy 40 MeV and LET 1.5 keV/ μ m. The authors reported that for doses of 0.5 to 4 Gy, protons were less effective than the x-rays by a factor 1.5. Further inspection of the data suggests a ratio of between 1 and 2 depending upon which doses are included in linear fits to the data. This range suggests the magnitude of uncertainty in the RBE_m .

The same study also assessed the RBE_m for the incidence of specific tumours. The crude incidence of reticulum cell sarcoma and lung cancer decreased with increasing dose of both x-rays and protons. The incidence of non-thymic lymphoma did not change with dose and it was only for thymic lymphoma, myeloid leukaemia and ovarian tumours that dose response relationships were seen. RBE_m values for the three cancers ranged from 0.5 to 1.0. The conclusion from this experiment is that for life-shortening and tumorigenic end-points, 40 MeV protons are not more effective than 300 kVp x-rays and

indeed may be up to a factor 2 less effective.

A series of papers by staff from the USAF in Texas, describe the irradiation of rhesus monkeys by protons of various energies and the ensuing effects. Wood [7] reported life-shortening and tumorigenic end-points but the numbers of animals exposed were small. About 360 animals were distributed amongst 6 proton energies, x-rays, two electron energies and controls and the data are insufficient for making even an approximate estimate of RBE_m for the proton energies used.

Cellular studies are more numerous. Two major end-points have been used. One is the observation of structural chromosomal changes at metaphase following irradiation in the G_1 or G_0 phases of the cell cycle and the other is gene mutations in cultured cells. Table I shows the results of fitting the yield equation (1)

$$Y = c + \alpha D + \beta D^2 \quad (1)$$

to dicentric yields in G_0 irradiated human lymphocytes, measured by several authors. Here, Y is the dicentric yield, D the absorbed dose and c , α and β are fitted coefficients.

Takatsuji et al. [8] used protons of 4.9 MeV to irradiate separated lymphocytes in an approximate monolayer. Rimpl et al. [9] used 20 MeV protons to irradiate a 2 mm thick blood sample with a mean proton energy of 16.5 MeV. Schmid et al. [10] used three blood samples each of 1.2 mm thickness to form a sandwich 3.6mm thick. The incident proton energy was 16.5 MeV and the energies entering the second and third samples were 12 and 5 MeV respectively. Since the range of a 5 MeV proton is only 0.4 mm, only 30% of the third sample was irradiated and so the results from the third element have not been included here. In the first two samples the mean energies were 14 and 8.5 MeV respectively. Edwards et al. [11] irradiated a blood sample 100 μ m thick with a mean energy of 8.7 MeV. Results for γ -rays, x-rays and tritium are also shown in Table I for comparison [12, 13, 14].

For proton energies above 8 MeV, the linear coefficients α agree very well with those obtained for x-rays and tritium. They are approximately 3 times higher than the values obtained for ^{60}Co γ -rays although uncertainties are large. The slightly higher result at 8.5 MeV [10] could be because the sample is thick and therefore some of the blood is irradiated by 5 MeV protons which have a higher RBE.

Studies with the gene mutation endpoint provide data at lower proton energies. Belli et al. [15] have investigated the effectiveness of protons of energy below 4 MeV in producing *HPRT* gene mutations in V79 CHO cells. Irradiating monolayers of cells, all proton energies produced a linear dose response relationship whereas for x-rays the dose-response was linear-quadratic. After extrapolation to low doses, RBE_m values of about 5 were obtained for 3.2, 1.4 and 0.76 MeV protons. Their respective LET values were 11, 20 and 31 keV/ μ m.

Table I – Yield coefficients for dicentric induction by protons and other low LET radiations.

Author	Proton energy MeV	LET KeV mm ⁻¹	α Gy ⁻¹	β Gy ⁻²
Takatsuji et al ⁽⁸⁾	4.9	8	$\phi.28 \pm .05$	$\phi.14 \pm \phi.03$
Schmid et al ⁽⁹⁾	8.5	5.3	$\phi.065 \pm .010$	$\phi.014 \pm \phi.003$
Edwards et al ⁽¹¹⁾	8.7	5.1	$\phi.044 \pm .008$	$\phi.058 \pm \phi.006$
Schmid et al ⁽¹⁰⁾	14	3.5	$\phi.044 \pm .010$	$\phi.020 \pm \phi.005$
Rimpl et al ⁽⁹⁾	16.5	3.2	$\phi.044 \pm .007$	$\phi.020 \pm \phi.003$
Schmid et al ⁽¹⁰⁾	x-rays	-	$\phi.040 \pm .005$	$\phi.059 \pm \phi.003$
Lloyd et al ⁽¹²⁾	x-rays	-	$\phi.036 \pm .005$	$\phi.067 \pm \phi.003$
Lloyd et al ⁽¹²⁾	⁶⁰ Co γ -rays	-	$\phi.014 \pm .004$	$\phi.076$
Bauchinger et al ⁽¹³⁾	⁶⁰ Co γ -rays	-	$\phi.011 \pm .004$	$\phi.056 \pm \phi.003$
Prosser et al ⁽¹⁴⁾	tritium	-	$\phi.054 \pm .006$	$\phi.022 \pm \phi.003$

Table II – Estimates of RBE for Harderian gland tumour for ions of very high energy from Fry et al.⁽¹⁶⁾. Results for fission neutrons are presented for comparison

Ions	Energy range	LET range keV/mm	RBE wrt ⁶⁰ Co γ -rays
⁴ He	0-200 MeV	5 – 250	5
¹² C	0 – 1 GeV	30 – 800	12
²⁰ Ne	0 – 2 GeV	70 – 1500	18
⁴⁰ Ar	0 – 3 GeV	350 – 2800	27
Fission neutrons			27

Table III – Results of fitting the cobalt-60 data of Alpen et al⁽¹⁷⁾. Fitting is by iteratively reweighted least squares except for *, where equal weighting has been given to each point. In this case errors are based on the scatter of data about the fitted curve.

Dose range	α % per Gy	β % per Gy ²	χ^2	DF
0 – 0.8	7.8 ± 3.0	-	0.3	1
0 – 1.6	7.3 ± 1.9	-	0.4	2
0 – 3.2	8.7 ± 1.2	-	1.2	3
0 – 3.2	6.3 ± 3.2	1.0 ± 1.1	0.5	2
* 0 – 3.2	5.5 ± 1.8	1.1 ± 0.5	N/A	
Alpen et al 0 – 3.2	5.4 ± 1.8	1.1	not given	

The overall judgement is that protons of energy greater than about 8 MeV have similar RBE_m values to x-rays. There is some evidence from the animal experiments that RBE_m may decrease further as proton energy increases. Below 8 MeV, the proton RBE_m increases and should reach values observed for fission neutrons because those neutrons deposit most of their energy by recoil protons of a few MeV and less.

3.3. Heavy ions

Data which give information on the RBE for heavy ions are sparse. The only study using laboratory animals appears to be that measuring the induction

of Harderian gland tumours in mice [16, 17]. Table II shows RBE values taken from Fry et al. [16]. The range of LET values should be noted because the mice were irradiated with particles where the Bragg peak was spread over the whole width of the mouse. Raw data were not given so that it was not possible to make a more detailed examination. A data point for ⁵⁶Fe is not included because that experiment was performed under track segment conditions and extended data are given later [17]. The graphs [16] indicated that ⁵⁶Fe ions of 600 MeV/u were about as effective as fission neutrons.

Raw data, obtained using track segment irradiation of mice (i.e. irradiation at nearly constant LET) have been reported [17]. It was therefore possible

to refit these data using different assumptions from those made by the authors. In the light of experience obtained when examining neutron data, Table III gives the results of fitting the data for ^{60}Co using several different assumptions. Various linear fits have been made in addition to several different fits of a linear quadratic equation to dose points up to 3.2 Gy. It is interesting to note that the uncertainties on the coefficients are larger when fitting is performed by iteratively reweighted least squares with binomial distribution assumptions than when a standard regression analysis is used. From the similarity of the last 2 fits it appears that Alpen et al. [17] performed a least squares regression giving each point an identical weight.

The difficulty in choosing an initial slope from the data in Table III is immediately apparent. Fitting a straight line to the low dose data gives a value of α similar to that obtained by fitting a linear-quadratic equation to data up to 3.2 Gy. The 1 standard error uncertainty on the β coefficient is greater than the estimated coefficient. The errors quoted on the fit marked with an asterisk are too low because they ignore the binomial errors which must exist on each data point. The consistent observation that χ^2 is less than the degrees of freedom confirms that binomial based uncertainties are larger. The conclusion is that from the experiment there is no evidence for significant positive curvature in the dose response relationship up to 3.2 Gy. One possible solution is to believe the linear quadratic fit and choose $\alpha = 6.3 \pm 3.2\%$ per Gy but note the very large uncertainty. Another is to argue that the judged RBE is to be applied to a human risk that includes a judged DDREF of 2. Thus a value of α based on the linear fit up to 3.2 Gy divided by 2, might be a more appropriate value upon which to calculate RBE_m . This produces a value for α of $4.4 \pm 0.6\%/Gy$. The authors in fact chose $5.5 \pm 1.8\%/Gy$ based on their equally weighted regression.

With high LET exposure a linear component to the curve is more readily identified and this leads to a somewhat more accurate estimate of initial slope. Table IV shows values of α for the various ions used with estimates of RBE_m using both of the values derived from ^{60}Co data. RBE_m values for fission neutrons would be about 40 based on graphs given in Fry et al.⁽¹⁶⁾ because they show that fission

neutrons and 600 MeV/u ^{56}Fe ions have similar yields. The conclusion is that none of the ions investigated have values for RBE_m greater than that for fission neutrons. Many that are important in space application have lower values.

Studies on cell killing are numerous but the end-point has little relevance to radiation protection since a cell that cannot proliferate cannot produce a cancer. Mutation and chromosome aberration end-points bear a closer relationship to cancer and so this review will be restricted to those end-points.

The induction of *HPRT* mutations has been studied by Thacker et al. [18] using V79 Chinese hamster cells and by Cox et al. [19] using human fibroblasts. Both used ions of helium, boron and nitrogen of energies less than 10 MeV/amu. All the particles used had ranges in tissue less than 1.5 mm and are not of concern in the space environment except for energetic ions that stop within the human body. Both groups showed RBE values for mutation yields which peaked between 100 and 200 keV/ μm . The maximum observed RBE_m was about 20 by Thacker et al. [18] and about 7 by Cox et al. [19]. However Thacker et al. used ^{60}Co as the reference radiation whereas Cox et al. used x-rays.

Kiefer [20] reports measurements of RBE_m for the induction of *HPRT* mutations in V79 cells using more than 40 different ions. The LET range was from 10-10000 keV/ μm and values of RBE_m vary from about 20 to less than 1. The most efficient particles are those with LET between 200 and 500 keV/ μm . However the low LET reference radiation is not stated. The data indicate that the ICRP relationship between Q and LET is generally conservative when compared with these RBE_m values.

Chromosome aberrations in human lymphocytes have similarly been studied using a few heavy ions. Edwards [21] reported results for 60 and 90 MeV/a oxygen ions and for 40 MeV/a carbon ions. While not very energetic in terms of space radiations the LET values reported ranged from 50 to 70 keV/ μm and their values of RBE_m were about 10-20 with respect to x-rays and 20-40 with respect to ^{60}Co γ -rays. For comparison fission neutrons give values of RBE_m of about 40-50 with respect to the γ -rays.

It should be noted that for cellular end-points with relatively precise dose-response relationships the method of extrapolation to low doses for all radia-

Table IV – Values of α for energetic ions for Harderian gland tumours in mice (Alpen et al. [17]).

Ion	Energy MeV/u	LET	α	SE	RBE 4.4 \pm .6	RBE 6.3 \pm 3.2
^4He	228	1.6	.13	0.01	3.0 \pm 0.5	2 \pm 1
^{56}Fe	600	193	2.0	0.4	45 \pm 11	32 \pm 17
^{56}Fe	350	253	1.0	0.3	23 \pm 8	16 \pm 9
^{20}Ne	670	25	0.3	–	7	5
^{93}Nb	600	464	1.0	–	23	16
^1H	250	0.4	0.1	–	2	1.6

tions is more certain than for experiments of cancer or life-shortening in animals.

4. Judgements of RBE

From the foregoing but rather sparse data it is necessary to make some pragmatic choices for space radiations. Unfortunately judgements on which RBE factor to apply cannot be made in isolation because it will be used to estimate a risk at high LET and the type of estimate depends on its intended use. ICRP is the body that has traditionally made this judgement and the most recent recommendation involves the adoption of radiation weighting factors, w_R , and the definition of equivalent dose and effective dose [3]. It is pertinent to consider what ICRP states about the use of that judgement. Paragraph (32) states: "Both equivalent dose and effective dose are quantities intended for use in radiological protection, including the assessment of risk in general terms. They provide a basis for estimating the probability of stochastic effects only for absorbed doses well below the threshold for deterministic effects. For the estimation of the likely consequences of an exposure of a known population, it will sometimes be better to use absorbed dose and specific data relating to relative biological effectiveness of the radiations concerned and probability coefficients relating to the exposed population".

The exact meaning of this paragraph is somewhat open to debate but one interpretation is that in certain circumstances different risk estimates may be used for different purposes in radiological protection. In my view the first sentence refers to control applications in radiological protection. They are to be used to set dose limits in situations where doses can be reasonably controlled and tend to be prospective. The limits themselves are social judgements on what level of risk is tolerable or acceptable. The third sentence above, again in my view, refers to applications concerned with settling compensation claims or the provision of reassurance and will normally be retrospective.

So in respect of this statement and the views given the question arises, "where does space radiation fit in?" It could be argued that doses to astronauts are not easily controlled and therefore it is the reassurance application that is of most importance. For the remainder of this discussion I would like to examine the consequences of such thinking.

For the purposes of exercising control of radiation exposure, ICRP have judged that photons and electrons of all energies should have the same radiation weighting factor even though cellular experiments indicate RBE_m values of 2 or more for x-rays and lower energy electrons with respect to ^{60}Co γ -rays. They have judged that a DDREF of 2 should be applied to the linear fit to risks derived from the Hiroshima and Nagasaki data. In that linear fit, ICRP has extrapolated to include future radiation induced cancers which might occur particularly for

the younger age groups. They have further judged radiation weighting factors for neutrons and other heavy ions. It is important to note that all these judgements took place independently and took no account of any interdependence. Because of this and because uncertainties in these judgements are recognised, there is a tendency to err on the side of caution. In particular ICRP [3] accept that a DDREF of 2 may be conservative.

For reassurance, a more realistic rather than conservative approach might be considered and the interdependence of RBE_m , the reduction factor due to dose rate and the choice of low LET radiation quality taken into account. The first point to note is that the judgement of the quality parameter for fission neutrons is based predominantly on animal data. The message is that a judgement of 20 for fission neutrons is based upon a comparison with low dose rate γ -ray exposure which, in turn, is associated with a dose rate reduction factor of 4. If the reduction due to low dose rates were only 2 for cobalt-60, then the appropriate quality adjustment factor for fission neutrons would be 10. Applying this to the 4%/Gy low LET risk derived by ICRP [3] gives 40%/Gy for fission neutrons. Now all of the radiobiological data reviewed in this paper has shown that high LET accelerated particles have approximately the same or lower effectiveness compared with fission neutrons. This implies an effectiveness for the high LET component in space of 40%/Gy or less. Note that this estimate of high LET risk does not depend on any judgement made for DDREF at low LET values. A judgement of DDREF affects only the estimate of risk at low LET. Perhaps one would choose a risk of 2%/Gy for high energy gamma-rays and electrons and 4%/Gy for the energetic proton component because some of the energy is deposited by protons below 10 MeV where RBE increases. In essence the approach suggested for discussion is to apply different risk factors to each of the radiation components and combine them by simple additivity in proportion to their respective abundance. In this way the notion of Sv would disappear for space applications.

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