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REVIEW ARTICLE

In vitro RBE-LET dependence for multiple particle types

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Abstract

Background. In vitro RBE values for various high LET radiation types have been determined for many different cell types. Occasionally it is criticized that RBE for a given endpoint cannot be single-value dependent on LET alone, but also on particle species, due to the different dose deposition profiles on microscopic scale. Hence LET is not sufficient as a predictor of RBE, and this is one of the motivations for development of radiobiological models which explicitly depend on the detailed particle energy spectrum of the applied radiation field. The aim of the present study is to summarize the available data in the literature regarding the dependency of RBE on LET for different particles. *Method.* As RBE is highly dependent on cell type and endpoint, we discriminated the RBE-LET relationship for the three investigated cell lines and at the same endpoint (10% survival in colony formation). Data points were collected from 20, four and four publications for V79, CHO and T1, respectively, in total covering 228 RBE values from a broad range of particle species. *Results and discussion.* All RBE-LET data points demonstrate surprising agreement within the general error band formed by the numerous data points, and display the expected RBE peak at around 100–200 keV/μm. For all three cell lines, the influence of varying the particle type on the RBE was far from obvious, compared to the general experimental noise. Therefore, a dependence of particle type cannot be concluded, and LET alone in fact does seem to be an adequate parameter for describing RBE at 10% survival.

High linear energy transfer (LET) radiation is characterized by a higher biological effectiveness compared to photons of low LET. Because high LET radiation is densely ionizing, the correlated damages of the DNA structure within one cell occur more often so that it becomes more difficult for the cell to repair the damage, leading to a markedly increased efficiency of cell killing [1]. The concept of relative biological effectiveness (RBE) has been introduced to account for this increased efficiency. RBE is defined as the ratio of a dose of photons to a dose of any other particle to produce the same biological effect. High LET beams may have RBEs ranging from 1.5 to 3 [2].

RBE values for various high LET radiation types have been determined for many different cell types, both in vitro and in vivo. It has been demonstrated in in vitro studies that RBE is highly dependent on both cell type and the studied endpoint [3], but also on particle species, due to the different dose deposition profiles on microscopic scale [4,5].

Hence LET is not sufficient as a predictor of RBE. This is one of the motivations for the development of radiobiological models which explicitly depend on the detailed particle energy spectrum of the applied radiation field. Several models exist which aim to predict the biological response of cells irradiated with high-LET radiation. The most prominent models in radiotherapy context are based on the amorphous track formalism established by Butts and Katz [6]. These models explicitly point out that the response of a biological system cannot be characterized with LET as a single valued parameter. The aim of the present study is to review the available data in the literature regarding the dependency of RBE on LET for different particles for three different cell lines at the same endpoint (survival fraction at 10%).

Method

By means of a MEDLINE search (September 2010), 52 papers were found that investigated the relationship

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between LET and RBE. The MEDLINE search was based on the keywords: LET and RBE. Additional publications were located using citations within the identified papers. All together 838 RBE data point were found reported. From these, data points from studies with the endpoint clonogenic survival (survival fraction at 10%), for the three cell lines V79 (Chinese hamster lung fibroblasts), CHO (Chinese hamster ovarian cells) and T1 (human kidney cells) were included. With these criteria, 26 papers were selected, studying various particle species in the LET range between 7 keV/μm and 2000 keV/μm.

The data is both from publications using monoenergetic beams, quasi-monoenergetic degraded beams, and Spread Out Bragg Peaks. There are two methods to calculate average LET: dose-averaged LET and track-averaged LET. These two methods yields identical results for monoenergetic charged particles [7,8], but large differences between the two methods appear for fragmented beams [9,10]. Not all publications have stated which way they have calculated their LET values, but amongst the ones that have, all track-averaged LET values came from monoenergetic beams. A few studies have stated their LET differently, e.g. Todd (1967) [11] where the given LET is stopping power in tissue, and Folkard (1996) [12] where LET is volume averaged. In some papers, a dose response curve was shown, but the RBE values were not reported. In that case, where it was possible, we calculated the RBE by reading of the dose values at the isoeffect dose of the ions and the reference radiation using WinDIG2.5 (www.unige.ch/sciences/chifi/cpb/windig.html). Thirteen papers used x-rays while three papers used ^{60}Co as reference beams. All obtained data points are from experiments using normoxic conditions. As the compiled data is from different studies, some experimental conditions varied. For publications on V79 cells, there were different V79 sublines used (V79-4, V79-379A and V79-753B).

We found 228 published RBE in vitro data points from 26 publications on inactivation of V79, CHO and T1 cells irradiated with various particle types. For V79, data points were collected from 20 publications with 139 RBE values from 11 different particle types. For CHO there were four publications with 37 RBE values from four different particle types. For the T1 cells there were four publications with 54 RBE values for eight different particle types. More papers reported several cell types and particle types.

Regression analysis where performed on the RBE-LET plots (LET $\leq$ 100 keV/μm) using the statistical package SPSS (SPSS Inc., Chicago, IL). Furthermore slopes and intercepts were for each cell line compared between plots of carbon ions and plots of all particles following [13].

All extracted data are shown in a supplementary table available at http//www.informahealthcare.com/doi/abs/10.3109/0284186X.2011.582518.

Results

RBE against LET curves has been studied in a comparative approach with respect to the different ion types. As RBE is highly dependent on cell type and on endpoint, we discriminated the RBE-LET relationship for the three investigated cell lines and same endpoint. The three cell lines V79, CHO and T1 were chosen based on the level of comparable published data.

For V79 cells, 49 RBE values for carbon ions from eight different publications [3,5,14–19] were plotted as a function of the reported LET value (Figure 1A). As the different publications have calculated their RBE values differently in regards to whether it is a mean value from more experiments, and how a standard deviation is derived (if any is reported), we did not include standard errors. RBE was plotted on a logarithmic axis, as the relative standard deviation appeared to be constant at both high and low RBE values (Figure 1A). To compare to the RBE-LET relationship from various particles, 139 RBE values from 11 different particle types [12,20–30], in the range 7.7 to 2106 keV/μm, were plotted similar to the carbon data (Figure 1C). There is a high variation in the number of data points for each particle type, for some particles, only one or two data points have been reported (as argon, boron, lithium or nitrogen), whereas other particle types were much better represented. Also, particles as protons are restricted to a maximum LET of 37.8 keV/μm and iron ions have only been reported in the range from 200 to 2106 keV/μm. The general trend for the particles was that all the RBE values increased with an increase of LET, and reached a peak at ~100–200 keV/μm. When plotted together, all RBE-LET data points demonstrate surprising agreement within the general error band formed by the numerous data points. RBE data points against LET $\leq$ 100 keV/μm was plotted (Figure 1B and D), to be able to analyze the RBE data on the ascending part of the curve. Regression analysis were significant for both plots ($p < 0.0001$ for both plots, correlation coefficients 0.96 and 0.85). The two slopes and y-intercepts were tested against each other, and were found not to be different.

For CHO cells 17 RBE values from carbon ions from four different publications [3,31–33] were plotted (Figure 2A). The RBE values increase with increasing LET, with a peak at ~100–200 keV/μm. When plotted together with data points from other particle types (argon: two RBE values, iron: three RBE values and neon: 15 RBE values) (Figure 2C), there is no difference in the course of the curve. Regression analysis on the ascending part of the curve were significant for both plots ($p < 0.005$ for both plots, correlation coefficients 0.96 and 0.94) (Figure 2B and D). The slopes and intercept of the regression lines are tested not to be different from each other.

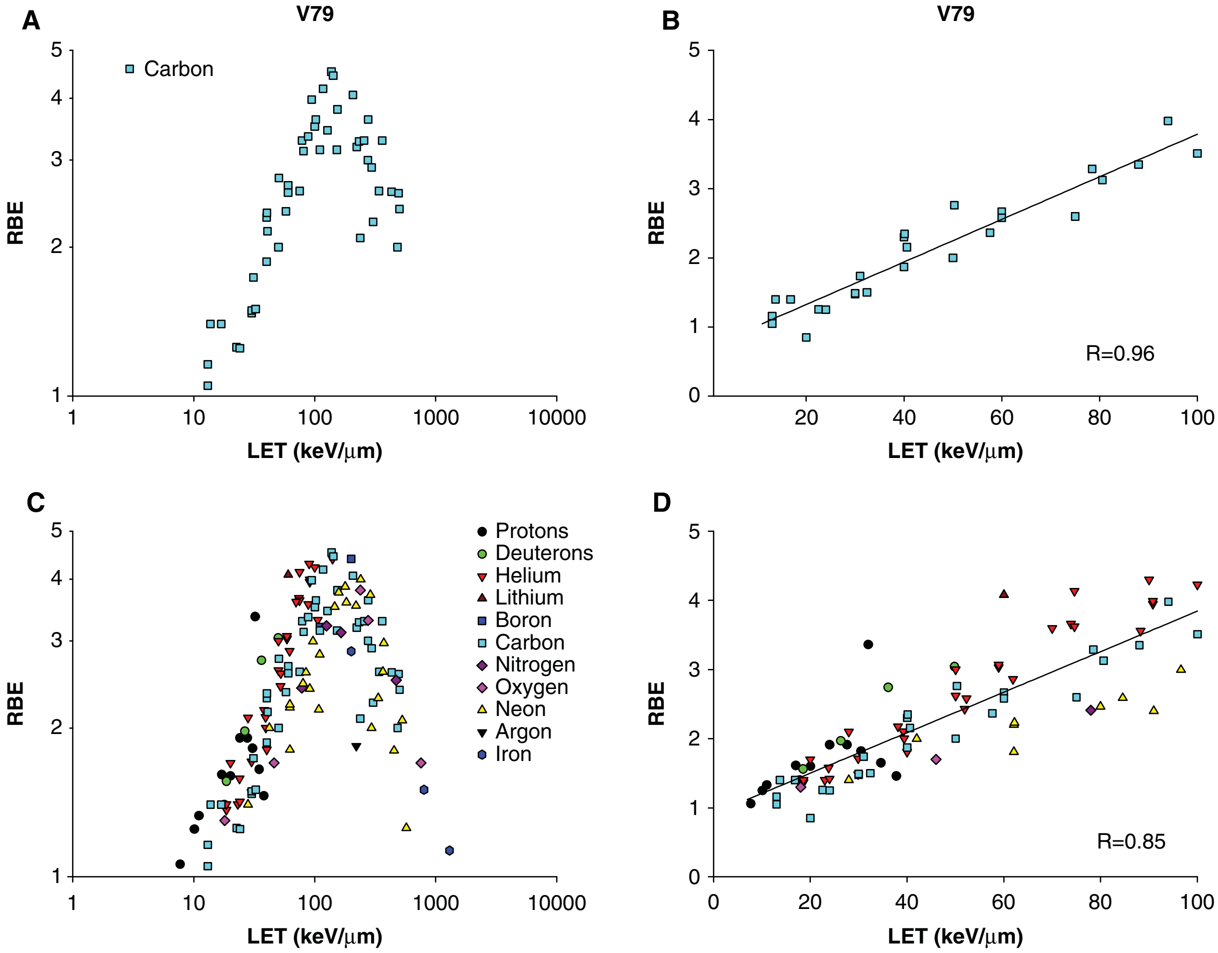

Figure 1. RBE-LET plot for V79 cells A) For carbon ions. B) For carbon ions, LET below 100 keV/μm. The solid line represents the regression line (RBE = 0.709 + (0.0308 *LET)). C) For additional particle types. D) For additional particle types, LET below 100 keV/μm. The solid line represents the regression line (RBE = 0.915 + (0.0293 *LET)).

The reported data points for T1 cells include 53 RBE values from four publications [5,11,34,35]. The LET for the carbon ions range from 10–252 keV/μm. Within this range the RBE-LET curve do not reach a peak or start to decline (Figure 3A). The variance in the data when more particle types are included is again very limited (Figure 3C). Regression analysis on the ascending part of the curve were significant for both plots ($p < 0.005$ for both plots, correlation coefficients 0.96 and 0.89) (Figure 3B and D). The slopes and intercept of the regression lines are not significantly different from each other.

Discussion

It has previously been shown that RBE, besides LET, depends on particle type. In this study, we have compared a large range of already published RBE-LET data from three different cell lines. The aim was to compare the RBE-LET relationship from different particle types, in order to visualize the magnitude of the effect of different ion-types.

As RBE is highly dependent on cell type and endpoint, we discriminated the RBE-LET relationship for the three investigated cell lines for a single endpoint (10% survival in colony formation). Data points were collected from 20, four and four publications for V79, CHO and T1, respectively, in total covering 228 RBE values from a broad range of particle species.

This review is on data from in vitro studies, and not in vivo or clinically based, due to the level of comparable data. This off course presents limitation to the study, and to the conclusions drawn thereof. The in vitro situation is very simplified compare to the much more complicated in vivo situation, which is characterized by high heterogeneity and influence of microenvironmental factors, such as hypoxia and low pH.

Previous meta-analyses have also addressed the LET dependence of RBE. Ando et al. (2009) [36], have analyzed a wide range of RBE data, and demonstrated a correlation between the LET of carbon ions and RBE values from more studies. In Belloni

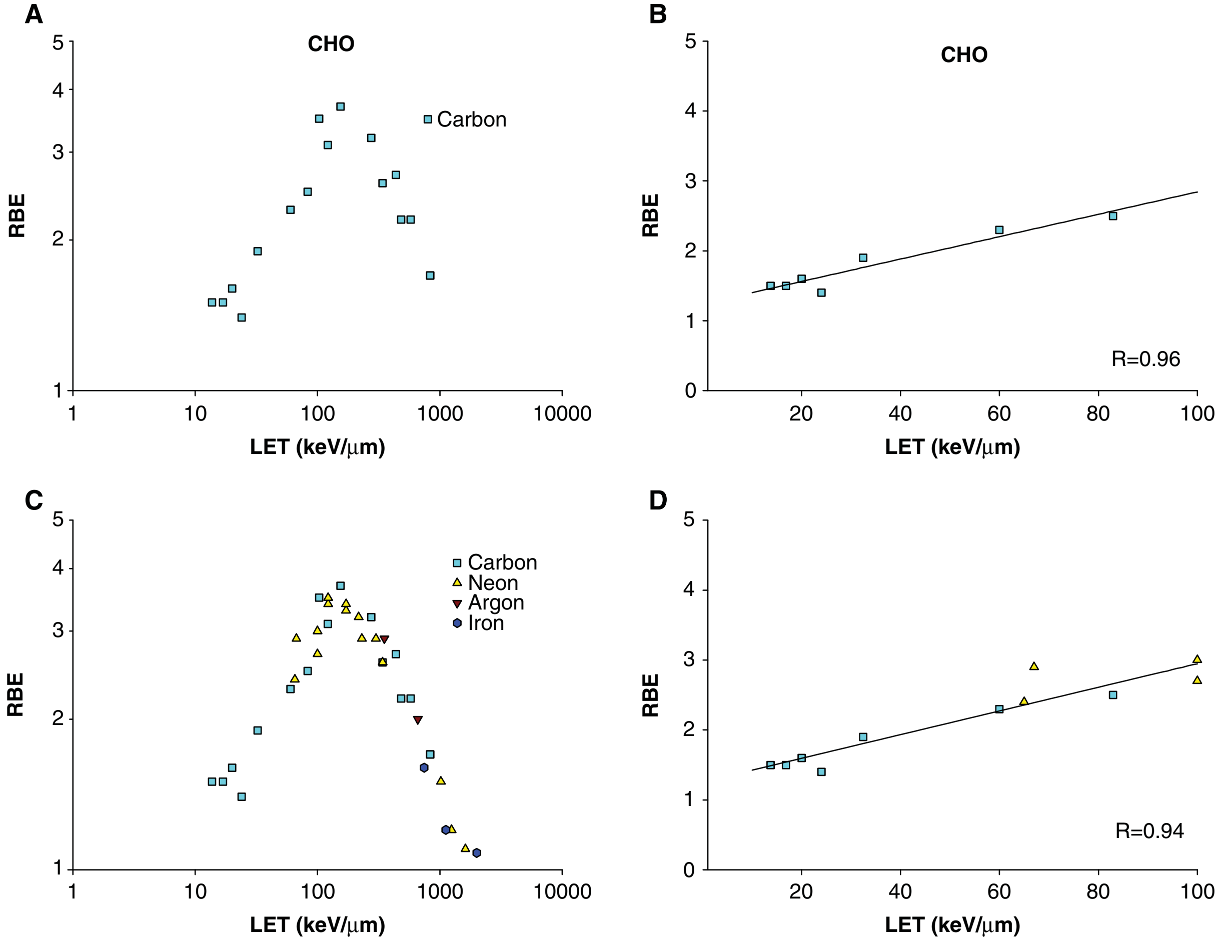

Figure 2: RBE-LET plot for CHO cells A) For carbon ions. B) For carbon ions, LET below 100 keV/μm. The solid line represents the regression line (RBE = 1.258 + (0.0169 *LET)). C) For additional particle types. D) For additional particle types, LET below 100 keV/μm. The solid line represents the regression line (RBE = 1.243 + (0.0160 *LET)).

2002 it is concluded that the RBE against LET curves for V79 depends strongly on the type of ion [37]. However, only limited data is included in this study, where it looks like a very apparent effect of the different ion types. When more data points are included to the same types of plots, it becomes quite obvious that this difference is rather small and hidden by the general errors arising from the biology.

In our study we show that when we plot data from a range of studies for a large number of different particles, all RBE-LET data points demonstrate surprising agreement within the general error band formed by the numerous data points, and display the expected RBE peak at around 100–200 keV/μm. For all three cell lines, the influence of varying the particle type on the RBE was far from obvious, compared to the general experimental noise. Therefore this supports the widespread assumption that the RBE for the same cell line and the same biologic endpoint may be assumed to be dependent on LET alone.

Yet, we will not object to the fact that there is a particle difference, which is well established. Instead, we call for a possibility of addressing it in a more quantitative way. In other words: can a single-valued LET approximately be adopted without introducing a significant error to the subsequently calculated RBE?

The motivation for this view arises from multiple contradictions: 1) When investigating the RBE as a function of LET, it is clear that even for the same particle there are two LET values which give the same RBE. However, given the energy spectrum of high-LET ions applied in radiotherapy, the one of the two LET values are found at the distal edge of the Bragg-peak, where particle suddenly come to rest. In practice in such a point a wide range of LET values will be found, which will dilute the average (either dose or track average) in this point; and 2) Different ions at different energy may have equal LET but different RBE. Again these iso-LET situations may occur either in the low or high energy regime. One could assume from premise 1) that the low-LET radiation is unimportant. The question remains then, how large is the resulting uncertainty from an iso-LET = iso-RBE assumption? The nature of the answer to this question

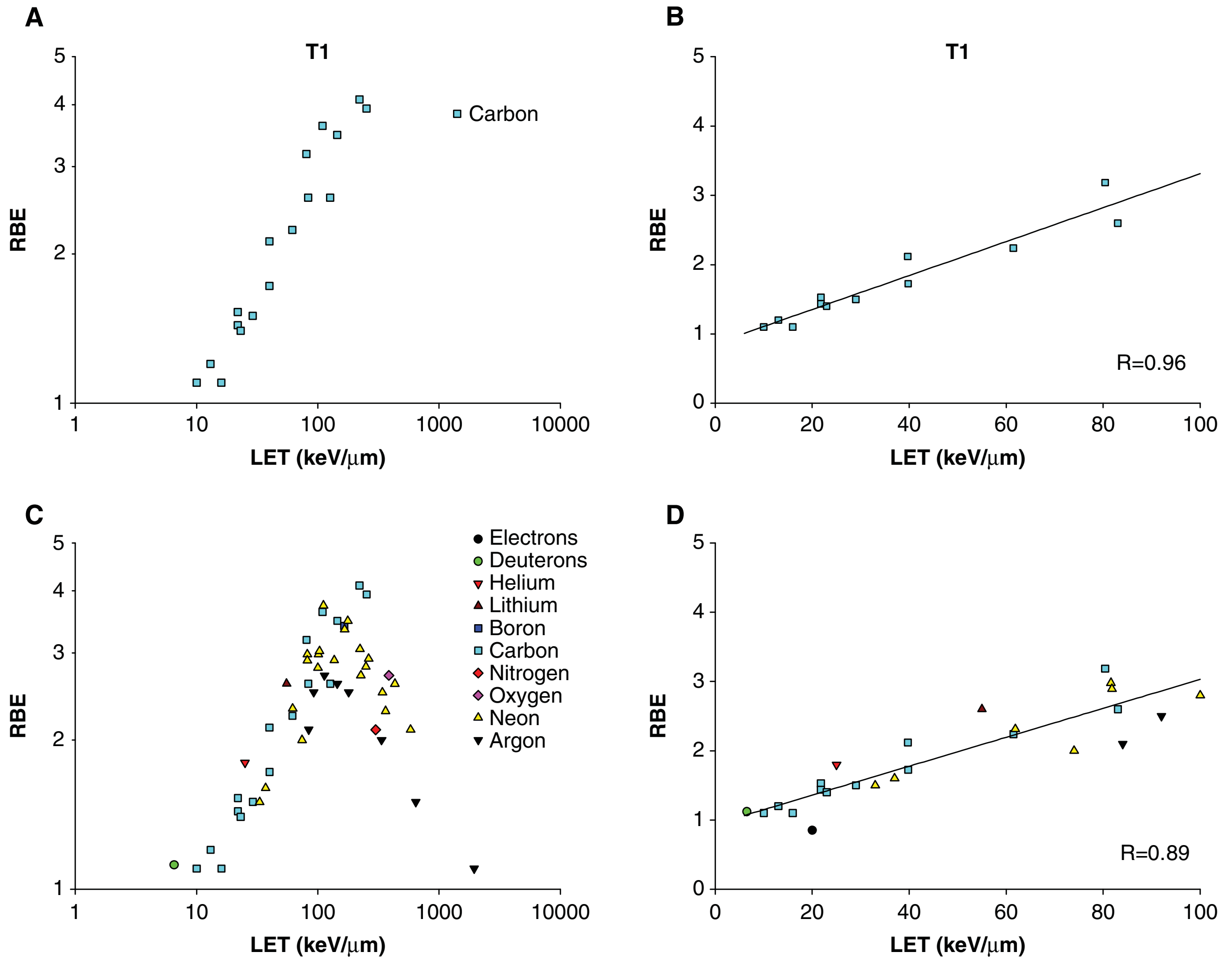

Figure 3: RBE-LET plot for T1 cells A) For carbon ions. B) For carbon ions, LET below 100 keV/µm. The solid line represents the regression line (RBE = 0.863 + (0.0245* LET)). C) For additional particle types. D) For additional particle types, LET below 100 keV/µm. The solid line represents the regression line (RBE = 0.941 + (0.0209 * LET)).

is depending on the context wherein the assumption is applied, and remains to be investigated. Such a formalism will possibly also be very relevant for detector response models, and could enable new ways of measuring LET, which will become relevant if new treatment strategies such as LET-painting is realized [38].

Here, the present data demonstrates that the particle dependence of LET is very small, and suggests that a general model for the RBE-LET relationship may be formulated.

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Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Supplementary material available online

Supplementary table available at http//www.informahealthcare.com/doi/abs/10.3109/0284186X.2011.582518.

Supplementary Material for Sørensen BS, Overgaard J & Bassler N. In vitro RBE-LET dependence for multiple particle types. Acta Oncologica, 2011;50:757–762.

Supplementary Table. Physical and radiobiological parameters for various kind of ions in experiments on V79, CHO and T1 cell lines.

Particle type	Cell type	RBE10%	LET (keV/μm)	MeV/u	Beam type[1]	Dose av /Track av	Reference
Protons	V79 753B	1.06	7.7	6	ME	–	Belli et al 1998
Protons	V79 379A	1.25	10.1	3.66	ME	–	Folkard et al, 1996
Protons	V79 753B	1.33	11	4.5	ME	–	Belli et al 1998
Protons	V79 379A	1.61	17	4	ME	Track av	Folkard et al, 1989
Protons	V79 379A	1.4	17.8	1.83	ME	–	Folkard et al, 1996
Protons	V79 753B	1.6	20	3.3	ME	–	Belli et al 1998
Protons	V79 379A	1.91	24	4	ME	Track av	Folkard et al, 1989
Protons	V79 379A	1.91	27.6	1.07	ME	–	Folkard et al, 1996
Protons	V79 753B	1.82	30.5	3	ME	–	Belli et al 1998
Protons	V79 379A	3.36	32	4	ME	Track av	Folkard et al, 1989
Protons	V79 753B	1.65	34.6	2.96	ME	–	Belli et al 1998
Protons	V79 753B	1.46	37.8	2.93	ME	–	Belli et al 1998
Deuterons	V79 379A	1.56	18.5	3.4	ME	–	Folkard et al, 1996
Deuterons	V79 379A	1.97	26.3	2.14	ME	–	Folkard et al, 1996
Deuterons	V79 379A	2.74	36.1	1.4	ME	–	Folkard et al, 1996
Deuterons	V79 379A	3.04	49.8	0.93	ME	–	Folkard et al, 1996
He	V79	1.37	18.6	12	ME, degraded	Dose av	Furasawa et al, 2000
He	V79	1.40	18.6	12	ME, degraded	Dose av	Furasawa et al, 2000
He	V79 4	1.7	20	–	–	–	Cox et al, 1977
He	V79	1.40	23	12	ME, degraded	Dose av	Furasawa et al, 2000
He	V79	1.58	23.8	12	ME, degraded	Dose av	Furasawa et al, 2000
He	V79	1.42	24	12	ME, degraded	Dose av	Furasawa et al, 2000
He	V79 4	2.1	28	–	–	–	Cox et al, 1977
He	V79	1.49	29.9	12	ME, degraded	Dose av	Furasawa et al, 2000
He	V79	1.71	29.9	12	ME, degraded	Dose av	Furasawa et al, 2000
He	V79	2.18	38.1	12	ME, degraded	Dose av	Furasawa et al, 2000
He	V79	2.10	39.2	12	ME, degraded	Dose av	Furasawa et al, 2000
He	V79	2.00	39.4	12	ME, degraded	Dose av	Furasawa et al, 2000
C	V79	1.74	31	135	ME, degraded	Dose av	Furasawa et al, 2000
C	V79	1.5	32.4	85	ME	Dose av	Weyrather et al , 1999
C	V79	1.87	40	290	SOBP (6cm)	Dose av	Belli et al 2008
C	V79	2.3	40	400	SOBP, 4cm	–	Chapman et al, 1979
C	V79	2.35	40.1	135	ME, degraded	Dose av	Furasawa et al, 2000
C	V79	2.16	40.6	135	ME, degraded	Dose av	Furasawa et al, 2000
C	V79	2	50	290	SOBP (6cm)	Dose av	Belli et al 2008
C	V79	2.76	50.3	135	ME, degraded	Dose av	Furasawa et al, 2000
C	V79	2.36	57.6	135	ME, degraded	Dose av	Furasawa et al, 2000
C	V79	2.58	60	290	ME, degraded	Dose av	Aoki et al, 2000
C	V79	2.67	60	135	ME, degraded	Dose av	Furasawa et al, 2000
C	V79	2.6	75	290	SOBP (6cm)	Dose av	Belli et al 2008
C	V79	3.29	78.5	135	ME, degraded	Dose av	Furasawa et al, 2000
C	V79	3.13	80.6	135	ME, degraded	Dose av	Furasawa et al, 2000
C	V79	3.35	88	135	ME, degraded	Dose av	Furasawa et al, 2000
C	V79	3.98	94	19	ME	Dose av	Belli et al 2008
C	V79	3.51	100	290	ME	–	Zhou et al, 2006
C	V79	3.63	102	135	ME, degraded	Dose av	Furasawa et al, 2000
C	V79	3.15	110	290	ME, degraded	Dose av	Aoki et al, 2000
C	V79	4.18	117	135	ME, degraded	Dose av	Furasawa et al, 2000
C	V79	3.45	127	135	ME, degraded	Dose av	Furasawa et al, 2000

(Continued)

Supplementary Table. (*Continued*)

Particle type	Cell type	RBE10%	LET (keV/μm)	MeV/u	Beam type[1]	Dose av /Track av	Reference
C	V79	4.53	137	135	ME, degraded	Dose av	Furasawa et al, 2000
C	V79	4.45	142	135	ME, degraded	Dose av	Furasawa et al, 2000
C	V79	3.15	152	135	ME, degraded	Dose av	Aoki et al, 2000
C	V79	3.8	153.5	11.4	ME	Dose av	Weyrather et al , 1999
C	V79	4.06	206	12	ME, degraded	Dose av	Furasawa et al, 2000
C	V79	3.19	222	6.7	ME	Dose av	Belli et al 2008
C	V79	3.27	232	12	ME, degraded	Dose av	Furasawa et al, 2000
C	V79	2.09	237	135	ME, degraded	Dose av	Aoki et al, 2000
C	V79	3.29	255	12	ME, degraded	Dose av	Furasawa et al, 2000
C	V79	3	275	6.12	ME	Dose av	Weyrather et al , 1999
C	V79	3.63	276	12	ME, degraded	Dose av	Furasawa et al, 2000
C	V79	2.9	295	–	ME	–	Pathak et al, 2007
C	V79	2.25	303	4.5	ME	Dose av	Belli et al 2008
C	V79	2.6	339.1	5	ME	Dose av	Weyrather et al , 1999
C	V79	3.29	360	12	ME, degraded	Dose av	Furasawa et al, 2000
C	V79	2.59	432	12	ME, degraded	Dose av	Furasawa et al, 2000
C	V79	2	482	3.5	ME	Dose av	Weyrather et al , 1999
C	V79	2.57	493	12	ME, degraded	Dose av	Furasawa et al, 2000
C	V79	2.39	502	12	ME, degraded	Dose av	Furasawa et al, 2000
N	V79	2.41	78	45	ME, degraded	–	Tilly, 1998
N	V79	3.22	125	21	ME	–	Stenerlöv, 1995
N	V79	3.12	165	45	ME, degraded	–	Tilly, 1998
N	V79 4	2.5	470	–	–	–	Cox et al, 1977
O	V79	1.3	18	–	–	–	Stoll et al, 1995
O	V79	1.7	46	–	–	–	Stoll et al, 1995
O	V79	3.8	238	–	–	–	Stoll et al, 1995
O	V79	3.3	276	–	–	–	Stoll et al, 1995
O	V79	1.7	754	–	–	–	Stoll et al, 1995
Ne	V79	1.4	28	–	–	–	Stoll et al, 1995
Ne	V79	2	42	–	–	–	Stoll et al, 1995
Ne	V79	2.20	62.1	135	ME, degraded	Dose av	Furasawa et al, 2000
Ne	V79	1.81	62.1	135	ME, degraded	Dose av	Furasawa et al, 2000
Ne	V79	2.23	62.2	135	ME, degraded	Dose av	Furasawa et al, 2000
Ne	V79	2.46	80	135	ME, degraded	Dose av	Furasawa et al, 2000
Ne	V79	2.59	84.6	135	ME, degraded	Dose av	Furasawa et al, 2000
Ne	V79	2.4	91	–	–	–	Stoll et al, 1995
Ne	V79	3.00	96.6	135	ME, degraded	Dose av	Furasawa et al, 2000
Ne	V79	2.18	108	400	SOBP, 4cm	–	Chapman et al, 1979
Ne	V79	2.82	110	135	ME, degraded	Dose av	Furasawa et al, 2000
Ne	V79	3.52	146	135	ME, degraded	Dose av	Furasawa et al, 2000
Ne	V79	3.76	158	135	ME, degraded	Dose av	Furasawa et al, 2000
Ne	V79	3.86	178	135	ME, degraded	Dose av	Furasawa et al, 2000
Ne	V79	3.54	219	135	ME, degraded	Dose av	Furasawa et al, 2000
Ne	V79	3.99	239	135	ME, degraded	Dose av	Furasawa et al, 2000
Ne	V79	3.72	287	135	ME, degraded	Dose av	Furasawa et al, 2000
Ne	V79	2	294	–	–	–	Stoll et al, 1995
Ne	V79	2.3	335	–	–	–	Stoll et al, 1995
Ne	V79	2.6	366	–	–	–	Stoll et al, 1995
Ne	V79	2.97	373	135	ME, degraded	Dose av	Furasawa et al, 2000
Ne	V79	1.8	452	–	–	–	Stoll et al, 1995
Ne	V79	2.07	528	135	ME, degraded	Dose av	Furasawa et al, 2000

(Continued)

Supplementary Table. (*Continued*)

Particle type	Cell type	RBE10%	LET (keV/μm)	MeV/u	Beam type[1]	Dose av /Track av	Reference
Ne	V79	1.26	569	135	ME, degraded	Dose av	Furasawa et al, 2000
Ar	V79	1.84	220	500	SOBP, 4cm	–	Chapman et al, 1979
Fe	V79	2.86	200	500	ME, degraded	–	Hirayma et al, 2009
Fe	V79	1.5	797	90	ME, degraded	–	Hirayma et al, 2009
Fe	V79	1.13	1298	90	ME, degraded	–	Hirayma et al, 2009
Fe	V79	0.9	2106	90	ME, degraded	–	Hirayma et al, 2009
C	CHO K1	1.5	13.7	270	ME	Dose av	Weyrather et al, 1999
C	CHO K1	1.5	16.8	195	ME	Dose av	Weyrather et al, 1999
C	CHO K1	1.6	20	135/290	ME, degraded	Dose av	Saski et al, 1997
C	CHO K1	1.4	24	135/290	ME, degraded	Dose av	Saski et al, 1997
C	CHO K1	1.9	32.4	85	ME	Dose av	Weyrather et al, 1999
C	CHO K1	2.3	60	135/290	ME, degraded	Dose av	Saski et al, 1997
C	CHO K1	2.5	83	135/290	ME, degraded	Dose av	Saski et al, 1997
C	CHO K1	3.5	103	18.4	ME	Dose av	Weyrather et al, 1999
C	CHO K1	3.1	121	135/290	ME, degraded	Dose av	Saski et al, 1997
C	CHO K1	3.7	153.5	11.4	ME	Dose av	Weyrather et al, 1999
C	CHO K1	3.2	275	6.12	ME	Dose av	Weyrather et al, 1999
C	CHO K1	2.6	339.1	5	ME	Dose av	Weyrather et al, 1999
C	CHO K1	2.7	438	33.2	–	–	Czub et al, 2008
C	CHO K1	2.2	482	3.5	ME	Dose av	Weyrather et al, 1999
C	CHO K1	2.2	576	9.1	–	–	Czub et al, 2008
C	CHO K1	1.7	830	48.5	–	–	Czub et al, 2009
C	CHO K1	1.7	832	20.3	–	–	Czub et al, 2008
Ne	V79	3.54	219	135	ME, degraded	Dose av	Furasawa et al, 2000
Ne	V79	3.99	239	135	ME, degraded	Dose av	Furasawa et al, 2000
Ne	V79	3.72	287	135	ME, degraded	Dose av	Furasawa et al, 2000
Ne	V79	2	294	–	–	–	Stoll et al, 1995
Ne	V79	2.3	335	–	–	–	Stoll et al, 1995
Ne	V79	2.6	366	–	–	–	Stoll et al, 1995
Ne	V79	2.97	373	135	ME, degraded	Dose av	Furasawa et al, 2000
Ne	V79	1.8	452	–	–	–	Stoll et al, 1995
Ne	V79	2.07	528	135	ME, degraded	Dose av	Furasawa et al, 2000
Ne	V79	1.26	569	135	ME, degraded	Dose av	Furasawa et al, 2000
Ar	V79	1.84	220	500	SOBP, 4cm	–	Chapman et al, 1979
Fe	V79	2.86	200	500	ME, degraded	–	Hirayma et al, 2009
Ne	CHO K1	2.4	65	135	ME, degraded	Dose av	Saski et al, 1997
Ne	CHO K1	2.9	67	135	ME, degraded	Dose av	Saski et al, 1997
Ne	CHO K1	2.7	100	135	ME, degraded	Dose av	Saski et al, 1997
Ne	CHO K1	3	100	135	ME, degraded	Dose av	Saski et al, 1997
Ne	CHO K1	3.4	122	135	ME, degraded	Dose av	Saski et al, 1997
Ne	CHO K1	3.5	122	135	ME, degraded	Dose av	Saski et al, 1997
Ne	CHO K1	3.3	171	135	ME, degraded	Dose av	Saski et al, 1997
Ne	CHO K1	3.4	171	135	ME, degraded	Dose av	Saski et al, 1997
Ne	CHO K1	3.2	217	135	ME, degraded	Dose av	Saski et al, 1997
Ne	CHO K1	2.9	230	135	ME, degraded	Dose av	Saski et al, 1997
Ne	CHO K1	2.9	300	135	ME, degraded	Dose av	Saski et al, 1997
Ne	CHO K1	2.6	340	135	ME, degraded	Dose av	Saski et al, 1997
Ne	CHO K1	1.5	1017	56.1	–	–	Czub et al, 2008
Ne	CHO K1	1.2	1245	34.7	–	–	Czub et al, 2008
Ne	CHO K1	1.1	1616	15	–	–	Czub et al, 2008
Ar	CHO K1	2.9	352	328	ME, degraded	Dose av	Saski et al, 1997
Ar	CHO K1	2	660	328	ME, degraded	Dose av	Saski et al, 1997

(*Continued*)

Supplementary Table. (*Continued*)

Particle type	Cell type	RBE10%	LET (keV/μm)	MeV/u	Beam type[1]	Dose av /Track av	Reference
Fe	CHO K1	1.6	743	90	ME, degraded	Dose av	Saski et al, 1997
Fe	CHO K1	1.2	1120	90	ME, degraded	Dose av	Saski et al, 1997
Fe	CHO K1	1.08	2000	90	ME, degraded	Dose av	Saski et al, 1997
β–particles	T1 cells	0.85	20	–	–	–	Barendsen et al, 1960
Deuterons	T1 cells	1.12	6.5	6.58	–	–	Todd, 1967
He	T1 cells	1.8	25	6.58	–	–	Todd, 1967
Li	T1 cells	2.6	55	6.58	–	–	Todd, 1967
B	T1 cells	3.4	165	6.58	–	–	Todd, 1967
C	T1 cells	1.1	10	400	ME	Track av	Blakely et al, 1979
C	T1 cells	1.2	13	400	ME	Track av	Blakely et al, 1979
C	T1 cells	1.1	16	400	ME	Track av	Blakely et al, 1979
C	T1 cells	1.53	21.8	135	ME, degraded	Dose av	Furasawa et al, 2000
C	T1 cells	1.44	21.8	135	ME, degraded	Dose av	Furasawa et al, 2000
C	T1 cells	1.4	23	400	ME	Track av	Blakely et al, 1979
C	T1 cells	1.5	29	400	ME	Track av	Blakely et al, 1979
C	T1 cells	2.12	39.7	135	ME, degraded	Dose av	Furasawa et al, 2000
C	T1 cells	1.72	39.8	135	ME, degraded	Dose av	Furasawa et al, 2000
C	T1 cells	2.24	61.5	135	ME, degraded	Dose av	Furasawa et al, 2000
C	T1 cells	3.19	80.4	135	ME, degraded	Dose av	Furasawa et al, 2000
C	T1 cells	2.6	83	400	ME	Track av	Blakely et al, 1979
C	T1 cells	3.63	109	135	ME, degraded	Dose av	Furasawa et al, 2000
C	T1 cells	2.6	126	400	ME	Track av	Blakely et al, 1979
C	T1 cells	3.48	144	135	ME, degraded	Dose av	Furasawa et al, 2000
C	T1 cells	4.1	220	6.57	–	–	Todd, 1967
C	T1 cells	3.93	252	12	ME, degraded	Dose av	Furasawa et al, 2000
N	T1 cells	3	300	6.5	–	–	Todd, 1967
O	T1 cells	2.7	385	6.58	–	–	Todd, 1967
Ne	T1 cells	1.5	33	425	ME	Track av	Blakely et al, 1979
Ne	T1 cells	1.6	37	425	ME	Track av	Blakely et al, 1979
Ne	T1 cells	2.32	61.9	135	ME, degraded	Dose av	Furasawa et al, 2000
Ne	T1 cells	2	74	425	ME	Track av	Blakely et al, 1979
Ne	T1 cells	2.98	81.6	135	ME, degraded	Dose av	Furasawa et al, 2000
Ne	T1 cells	2.89	81.8	135	ME, degraded	Dose av	Furasawa et al, 2000
Ne	T1 cells	2.8	100	425	ME	Track av	Blakely et al, 1979
Ne	T1 cells	2.98	101	135	ME, degraded	Dose av	Furasawa et al, 2000
Ne	T1 cells	3.03	103	135	ME, degraded	Dose av	Furasawa et al, 2000
Ne	T1 cells	3.74	111	135	ME, degraded	Dose av	Furasawa et al, 2000
Ne	T1 cells	2.9	136	425	ME	Track av	Blakely et al, 1979
Ne	T1 cells	3.34	166	135	ME, degraded	Dose av	Furasawa et al, 2000
Ne	T1 cells	3.48	176	135	ME, degraded	Dose av	Furasawa et al, 2000
Ne	T1 cells	3.06	222	135	ME, degraded	Dose av	Furasawa et al, 2000
Ne	T1 cells	2.7	226	425	ME	Track av	Blakely et al, 1979
Ne	T1 cells	2.81	249	135	ME, degraded	Dose av	Furasawa et al, 2000
Ne	T1 cells	2.92	262	135	ME, degraded	Dose av	Furasawa et al, 2000
Ne	T1 cells	2.50	340	135	ME, degraded	Dose av	Furasawa et al, 2000
Ne	T1 cells	2.29	361	135	ME, degraded	Dose av	Furasawa et al, 2000
Ne	T1 cells	2.6	432	425	ME	Track av	Blakely et al, 1979
Ne	T1 cells	2.1	580	6.58	–	–	Todd, 1967
Ar	T1 cells	2.1	84	570	ME	Track av	Blakely et al, 1979
Ar	T1 cells	2.5	92	570	ME	Track av	Blakely et al, 1979
Ar	T1 cells	2.7	113	570	ME	Track av	Blakely et al, 1979
Ar	T1 cells	2.6	144	570	ME	Track av	Blakely et al, 1979

(Continued)

Supplementary Table. (*Continued*)

Particle type	Cell type	RBE10%	LET (keV/µm)	MeV/u	Beam type[1]	Dose av /Track av	Reference
Ar	T1 cells	2.5	179	570	ME	Track av	Blakely et al, 1979
Ar	T1 cells	2	335	570	ME	Track av	Blakely et al, 1979
Ar	T1 cells	1.5	641	570	ME	Track av	Blakely et al, 1979
Ar	T1 cells	1.1	1940	5.7	–	–	Todd, 1967