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The unified approach of radiation action on biological matter: The induction of oncogenic transformation by heavy charged particles in C3H10T1/2 cells

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Abstract

The induction of oncogenic transformation to C3H10T1/2 cells by different types of ionizing radiation has been widely studied in various radiological laboratories. Based on the information available in literature, a database is structured to include radiological parameters, which manifest oncogenic effects as well as cellular inactivation of C3H10T1/2 cells, resulted from exposure to different types of heavy charged ions including neutrons. We find that oncogenic transformation effective cross-section is best correlated with mean free path for linear primary ionization. A simple radiobiological model is proposed merely to quantize cross-sections against mean free path. The model reveals saturations of; cellular inactivation cross-section of about 75 μm^2, and oncogenic transformation cross-section of about 3.98 x 10^{-2} μm^2, both started at mean free path of 1.8 nm (inflection points) and lower values. Since the interspacing distance between the DNA strands is about 1.8 nm, the model explains the crucial roles of DNA lesions (caused by heavy charged particles) to play as the starting point leading to cell death or oncogenic transformation. The effective cross -sections in the sloping regions are primarily due to repairable DNA single strand breaks while saturation regions are essentially due to unrepaired or incorrectly repaired DNA double strand breaks.

Keywords: Effect cross-section; Oncogenic transformation; C3H10T1/2 cells; Heavy charged particles; Mean free path for primary ionization; Biophysical modeling.

1. Introduction

Studying the biological effects induced by ionizing radiation (IR), is of special interest in many applied radiation fields; i.e., radiobiology, radiation therapy and radiation protection. IR can induce deleterious effects leading to cellular damage or cell death including cancer.

The current systems of measuring the effects of IR on living matter are based on what is known as the relative biological effectiveness (RBE). The RBE is defined as the ratio of a dose of a (low ionization density) reference radiation (usually of ^{137}Cs or ^{60}Co γ-rays or 250 kVp x-rays) to a dose of the (high ionization density) test radiation considered that gives the identical level of a biological effect. For a given radiation quality, RBE values vary with the dose, dose fractionation, dose rate, and species, strains and biological endpoint considered [1]. Although many scientists debate against this concept, RBE for a particular endpoint is still expressed in terms of linear energy transfer (LET) as a radiation quality parameter to define effectiveness of heavy ions including neutrons. LET is defined as the mean energy deposited in a biological entity per track length and is measured in (keV/μm) [2]. The basic idea of RBE is to compare the degree by which different heavy charged particles (HCP's) have maximum effects against LET. The RBE-LET relationship for all endpoints seems to fall apart where it departs for each type of HCP's having a unique curve of its own [3-5].

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Watt's group introduce a meaningful radiation quality parameter which is known as mean free path for linear primary ionization (MFP; λ). MFP is simply representing the mean spacing distance between two consecutive ionizations along the primary track measured in (nm) [6].

HCP's interact with biological matter primarily through collisions with electrons. Unlike sparsely ionizing radiations (SIR's), i.e., x-rays, γ-rays and fast electrons, HCP's, i.e., protons, a-particles produce dense tracks while they lose energy through biological matter. Both MFP and LET are characterized by ionisation density. For this, HCP's have higher LET values, compared to that of SIR's. LET of HCP's have values ranged between ~ 0.2 keV/μm for protons of energy 1000 MeV to much higher values, up to 2000 keV/μm for U-238 of 2.3 x 10^5 MeV, depending on their energy and their intrinsic properties (mass and charge).

Since neutrons are uncharged particles, they interact with living cells indirectly. Within the biological material, neutrons with energies of 1 – 14 MeV, interact with the main constituent elements; H, C, N and O, producing secondary charged particles i.e., protons, deuterons, α-particle [7]. The contribution of recoil protons is predominant, thus their track quality parameters (LET and MFP) averaged over the equilibrium H-recoil Spectra. For this reason, neutrons classified as a close competent with charged particles.

Radiobiological laboratory studies provided extensive amount of data, measuring the effects of IR toward different biological endpoints. Among those, cellular transformation, is of particular interest to study the early development of cancer. They are related to genetic processes caused by mutations of genes (oncogenes) involved in normal cell growth. Oncogenic transformations induced by IR, could provide answers to fundamental questions; i.e., whether the deoxyribonucleic acid (DNA) damage is responsible for such end-point [8]. Unrepaired or incorrectly repaired DNA damage can lead to serious genome aberrations or mutations, potentially affecting cell survival. However, some mutations change cell proliferation due to defects of certain genes, e.g., oncogene, a tumor-suppressor gene, or a gene that controls the cell cycle [9, 10].

The dose-effect curves for the induction of oncogenic transformations by IR are usually reported by radiological laboratories in terms of the number transformations per surviving cells per Gy; $T(D)$ against absorbed dose; D (Gy). The frequency of transformation-dose response curve is generally linear-quadratic for HCP's and the mathematical trend expressed as [11]:

$$T(D) \cong T_o + \alpha_T D + \beta_T D^2$$

where T_o is the spontaneous frequency (~ 10^{-6} transformations/cell-Gy) [12].

Cellular inactivation or what is also known as cell survival fraction, SF; is commonly considered as a reference endpoint, to characterize the action of IR in different subcellular targets toward different biological endpoints. In radiological experimentation, the SF (D) as a function of dose (D) is measured using the same transformation assay system. Mathematically, the survival-dose response curve fits with the following semi-logarithmic relation:

$$SF(D) = ln(S(D)/S_o) = -\alpha_I D - \beta_I D^2$$

The above relations for both oncogenic transformation and survival cells fit the data reasonably well. Here $\alpha_T(Gy^{-1})$, $\beta_T(Gy^{-2})$, $\alpha_I(Gy^{-1})$, and $\beta_I(Gy^{-2})$ are used as fitting parameters with proper units to maintain consistency of the terms in both equations. Hence, the parameters $\alpha_T(Gy^{-1})$ and $\alpha_I(Gy^{-1})$ represent, respectively, the slopes of the transformation and survival curves at zero dose. For HCP's with high LET, cellular inactivation curves mostly have linear response; hence $\beta_I = 0$, and the survival equation would simply become; $SF(D) = \ln(S/S_o) = -\alpha_I D$. On the other hand, results of the cellular transformation-dose response curves are quite complex in shape, but they generally tend to have linear quadratic terms at low dose regions.

Unlike other mammalian cells including human, C3H10T1/2 cell lines, cultured from mouse embryonic cells, are the most often used in radiation transformation studies. They are easy to culture and give good quantitative dose-response curves particularly for low dose [13]. The current study will focus on physical parameterization of the biological damage caused by different HCP's including neutrons. Hence presenting a model that unifies the action of HCP's on C3H10T1/2 cells to induce oncogenic transformation and cell death.

2. Method of Approach

The cellular inactivation and transformation effects induced by HCP's can be quantified clearly in terms of the probability to produce damage in units of area; inactivation cross-section, $\sigma_I(\mu m^2)$ and transformation cross-section $\sigma_T(\mu m^2)$. The effective cross-section; σ_x (μm^2) for either endpoint *x* (inactivation or transformation), of C3H10T1/2 cells can be calculated using the relation:

$$\sigma_x = \frac{L}{6.25\rho D_{xo}}$$

where L is the track average LET (in keV/μm) for the equilibrium spectrum of charged particles involved, D_{xo} (in Gy) is the initial dose for specific endpoint *x* and ρ (in gm/cm^3) is the density of biological matter. The initial slope for response curve is simply the slope of the radiobiological dose-effect curve at zero dose. For both dose-effect curves whether shouldered or linear types, the initial slope is equivalent to α_x. Hence the effective cross-sections for both endpoints are evaluated at $D_{xo} = 1/\alpha_x$. For wet cells, the density of medium is assumed of water.

The radiobiological parameters α_I (Gy^{-1}) and α_T (Gy^{-1}) for cellular inactivation and transformation of C3H10T1/2 cells by the various HCP's (including neutrons) were extracted from published data [14 - 22]. The present study includes radiological parameters of both inactivation and oncogenic transformations data induced by HCP's of different radiation qualities. The physical data related to HCP's; energy (MeV), the track average LET (keV/μm) and λ (nm) are estimated using Watt's group foundations [23] and are tabulated in Table-1. The corresponding inactivation and transformation cross-sections σ_I (μm^2) and $\sigma_T(\mu m^2)$ were estimated using the above formula and the results are included in the same table.

The search for a model implies several trials of various functions to find a unique semi-empirical formula F= F(λ), that fits both curves observed by the σ_x - λ relations, in terms of justifiable physical parameters, λ and possibly geometrical structure parameters. The relation should assure radiobiological data observed earlier by the response curves for both cellular inactivation and oncogenic transformation by HCP's. The goodness of the model relies on its prediction power to foresee other HCP's to induce certain damage in the cellular and subcellular scales.

Table 1 HCP's track structure data; E(MeV), LET(keV/μm), and **λ**(nm) along with cell inactivation $\alpha_I(Gy^{-1})$ and transformation $\alpha_T(Gy^{-1})$ radiobiological parameters of C3H10T1/2 Cells**.** (n: neutron; p: proton; H-2: deuteron; He-3, He-4: helium ions; C-12: carbon; O-16: oxygen; F-19: fluorine; Ne-20: neon; Si-28: silicon; Ar-40: argon; Fe-56: Iron U-238: uranium).

Ions	E(MeV)	$\alpha_I(Gy^{-1})$	$\alpha_T(Gy^{-1})$	LET (keV/μm)	λ(nm)	$\sigma_I(\mu m^2)$	$\sigma_T(\mu m^2)$	References
n	0.23	1.600	6.80E-04	62.41	1.29	15.98	6.79E-03	Miller, 1989
n	0.35	2.000	1.61E-03	63.38	1.44	20.28	1.63E-02	Miller, 1989
n	0.45	1.400	8.20E-04	61.82	1.59	13.85	8.11E-03	Miller, 1989
n	0.50	3.260	2.40E-03	60.74	1.67	31.75	2.33E-02	Barrendsen, 1985
n	0.70	1.200	1.00E-03	55.60	2.00	10.68	8.90E-03	Miller, 1989
n	0.96	1.300	6.00E-04	49.37	2.45	10.27	4.74E-03	Miller, 1989
n	1.96	1.200	9.60E-04	34.19	4.25	6.56	5.25E-03	Miller, 1989
n	4.20	1.550	1.30E-03	20.79	8.37	5.16	4.32E-03	Barrendsen, 1985
n	5.90	1.400	7.60E-04	16.29	11.55	3.65	1.98E-03	Miller, 1989
n	9.70	0.500	8.34E-04	11.18	18.69	0.89	1.49E-03	Blacer-Kubiczek, 1991
n	13.70	1.200	8.60E-04	8.70	26.35	1.67	1.20E-03	Miller, 1989
n	15.00	0.820	9.00E-04	7.91	28.84	1.04	1.14E-03	Barrendsen, 1985
P	2.25	0.753	7.83E-04	15.13	23.51	1.82	1.90E-03	Miller, 1995

P	4.00	0.310	2.20E-05	9.48	42.08	0.47	3.34E-05	Hei, 1988
P	31.00	0.050	1.30E-05	1.80	335.99	0.01	3.73E-06	Bettega, 1990
D	0.55	1.718	9.85E-04	57.79	3.33	15.89	9.10E-03	Miller, 1995
D	1.10	0.741	1.09E-03	39.42	6.04	4.67	6.90E-03	Miller, 1990
D	25.80	0.202	2.92E-04	3.83	136.57	0.12	1.79E-04	Miller, 1995
He-3	0.10	1.300	5.10E-04	128.96	0.51	26.82	1.05E-02	Hei, 1988
He-3	4.40	1.140	3.00E-04	79.59	3.98	14.52	3.82E-03	Hei, 1988
He-3	5.00	1.703	2.35E-03	73.37	4.45	19.99	2.76E-02	Miller, 1995
He-4	1.44	1.446	1.67E-03	195.37	1.10	45.21	5.23E-02	Miller, 1995
He-4	2.37	2.181	1.94E-03	151.19	1.62	52.75	4.70E-02	Miller, 1995
He-4	2.70	1.650	2.90E-04	136.85	1.88	36.13	6.35E-03	Hieber, 1987
He-4	3.33	1.906	2.50E-03	118.65	2.29	36.19	4.74E-02	Miller, 1995
He-4	4.15	1.650	6.20E-04	102.03	2.84	26.94	1.01E-02	Bettega, 1990
He-4	5.12	1.439	2.56E-03	90.18	3.43	20.76	3.70E-02	Miller, 1995
C-12	64.30	1.793	7.98E-04	265.65	1.63	76.23	3.39E-02	Miller, 1995
C-12	5688.00	0.271	7.45E-05	10.51	87.38	0.45	1.25E-04	Yang,1985
O-16	96.60	1.006	5.05E-04	419.82	1.05	67.60	3.39E-02	Miller, 1995
F-19	91.60	1.495	6.18E-04	599.95	0.70	143.53	5.93E-02	Miller, 1995
Ne-20	8500.00	0.428	7.40E-05	30.98	29.15	2.12	3.67E-04	Yang,1985
Si-28	8960.00	0.659	4.48E-04	68.80	12.63	7.25	4.93E-03	Yang,1985
Si-28	18760.00	0.406	5.63E-05	50.22	19.20	3.26	4.52E-04	Yang,1985
Ar-40	13200.00	0.849	1.36E-04	112.56	7.79	15.29	2.46E-03	Yang,1985
Fe-56	5480.00	0.612	8.15E-05	500.00	1.46	48.98	6.52E-03	Yang,1985
Fe-56	12110.00	0.692	1.53E-04	300.00	2.77	33.20	7.34E-03	Yang, 1985
Fe-56	29400.00	0.902	6.26E-04	190.00	4.92	27.41	1.90E-02	Yang, 1985
U-238	228480.00	0.244	9.52E-05	1943.50	0.53	75.94	2.96E-02	Yang, 1985

3. Results and discussion

The physical and radiological components of Table-1 can be studied and analyzed to further understand the mechanism of inducing cellular transformations by HCP's. Effective cross-section for survival; σ_I (μm^2) of C3H10T1/2 cells as a function of λ(nm) for HCP's including neutrons, as depicted in the Table-1, are shown in Figure-1 in log-log scales.

On examining the σ_T-λ relationship in Figure-1; oncogenic transformation cross-section, σ_T(μm^2) seems to be well grouped and consistence against the mean free path, λ(nm) for most HCP's. An exception for this harmony is observed for helium ions radiological data (the 4.425 MeV for He-3 and He-4 of energies lies between of 1.44 – 5.12 MeV, and iron ions Fe-56) carried by their respective authors [17, 22], where the coefficients, α_T estimated from the original works, seems to be overestimated by factor of 10 or may be due to errors on scoring transformations at low dose. On the σ_T-λ plot, a trend toward an imminent inflection point is evident, at about λ_o = 1.8 nm. At lower MFP; λ < 1.8 nm, a maximum transformation is visualized, with effective cross-section of about $\sigma_T \sim 0.05$ μm^2. This saturated region is expected to be related to the unrepaired or wrongly repaired dsb's of the DNA. At higher MFP; λ > 1.8 nm, the transformation cross-section; σ_T decreases with increasing MFP, λ. Few neutrons of energies lower than 0.7 MeV seems to be capable of reaching saturation, while most of them fall below the projected saturation. The reason is related to the short ranged recoiled protons which are incapable to traverse the whole cell nucleus and thus fewer DNA segments will intact to

reduce the size of transformation damage. On the other hand, heavy ions like; ^{12}C, ^{16}O, ^{19}F, ^{238}U seems to align well in this region.

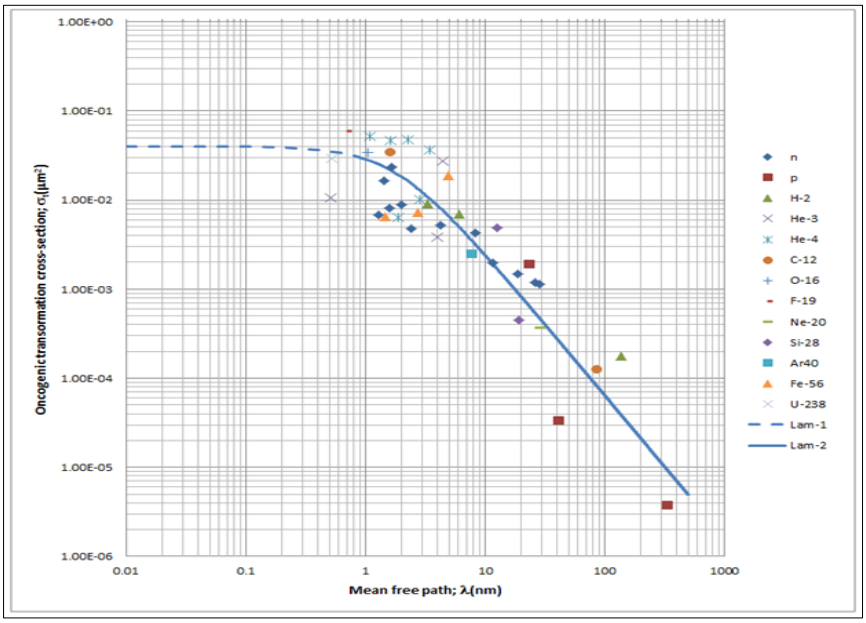

Figure 1 The transformation cross-section σ_T (μm^2) for C3H10T1/2 vs. mean free path for primary ionization λ(nm) by various heavy charged particles. The symbols in different colours referred to the HCP's already stated in Table-1, whereas the dashed and solid blue curves represent the model suggested in this paper.

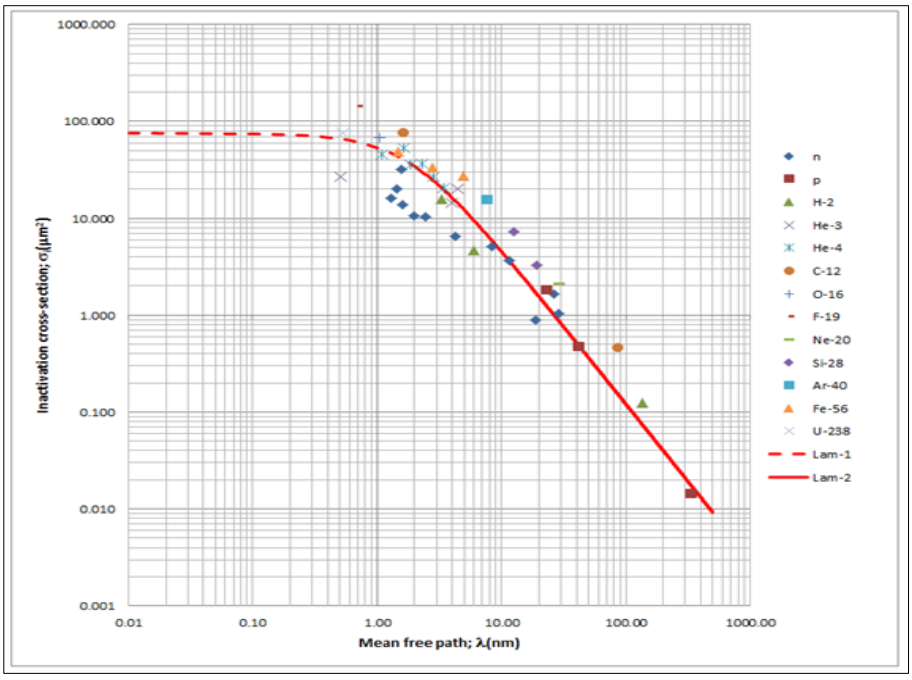

Figure 2 The inactivation cross-section σ_I (μm^2) for C3H10T1/2 vs. mean free path for primary ionization λ(nm) by various heavy charged particles. The symbols in different colours referred to the HCP's already stated in Table-1, whereas the dashed and solid blue curves represent the model suggested in this paper.

The effective cross-section for survival; $\sigma_I(\mu m^2)$ of C3H10T1/2 cells as a function of λ(nm) for neutrons and HCP's, as depicted in the Table-1, are shown in Figure-2 in log-log scales. The overall shape of (σ_I - λ) response seems to fall in agreement with earlier studies by the 1st author; on the effect of HCP's on mammalian cells [24].

On the (σ_I - λ) plot, again like cellular transformation response (σ_T - λ), is characterized by two regions separated by an inflection point, at about λ_o = 1.8 nm. At lower MFP; λ < 1.8 nm, a maximum saturated cross-section is projected at about $\sigma_o \sim 80\ \mu m^2$. The saturation region is expected to be related to the basic damage, particularly dsb's, caused by HCP's in the DNA. At higher MFP; λ > 1.8 nm, a linear declining cross-section, σ_I with MFP, λ again is apparent.

Based on the analysis of data in table-1 and the plots of $\sigma_T - \lambda$ and $\sigma_I - \lambda$ in figures 1-2, a simple model to fit both endpoints can be reached with the following mathematical relation:

$$\sigma_x(\lambda) = \frac{\sigma_{ox}}{1 + \left(\frac{\lambda}{\lambda_o}\right)^n}$$

Data generated by the above formula presented in blue and red curves for oncogenic transformation and survival of C3H10T1/2, respectively. For both endpoints, the inflection point is found at $\lambda_o = 1.8 \pm 0.4$ nm, and with n = 1.6. These values are associated to both types of damages at nanometric sites, presumably in the DNA intra spacing. For λ > 1.8, the (σ_x - λ) relations show linear correlations on the log-log scale plots, as presented by solid blue and red lines for transformations and inactivation of C3H10T1/2 respectively in figures 1 – 2, of different magnitudes, but with same gradient of -1.59 ± 0.06. They are both due to ssb's of the DNA caused by either IR or water radicals.

For λ < 1.8 nm, the saturation cross-section for transformations of C3H10T101/2 generated by $\sigma_T(\lambda) = \sigma_{oT}/[1+(\lambda/\lambda_o)^n]$ is at $\sigma_{oT} = (3.98 \pm 0.6) \times 10^{-2}\ \mu m^2$; projected by the dashed part of the blue curve in Figure-1. This value should be related to the geometrical cross-section for oncogenes responsible for transformation of C3H10T1/2. If assuming the targeted genomic material is contained in spherical compact form, the size of the oncogenes involved into transformation would be slightly about few mega base pairs (Mbp). This indicates that transformation of mammalian cells by IR could not simply resulted from small changes in one gene (proto-oncogene). It is a very complicated processes which cannot be described by only a single point mutation in specific gene but rather from large rearrangements or deletion of large segment of chromosomal material. There could be more than one chromosome involved in the formation of oncogenic transformations.

On the other hand, the saturation cross-section for cellular inactivation of C3H10T1/2 generated by the mathematical relation $\sigma_I(\lambda) = \sigma_{oI}/[1+(\lambda/\lambda_o)^n]$ where λ < 1.8 nm, is at $\sigma_{oI} = 75 \pm 5\ \mu m^2$; as projected by the dashed part of the red curve in Figure-2. Although the size of flatted cells of C3H10T1/2 measured under microscope, is averaged at about 250 μm^2 [21], the effective saturation cross-section is only about 0.3 of geometrical cross-section. This is an expected result, since the genomic target (DNA) occupies about 1/3 portion of the super flatted cells of C3H10T1/2. The maximum damaging effect is attributed to the mean chord of the strands in the DNA segment which can only identify that the double strand break (dsb) of the DNA are the critical lesions for inactivation for all HCP's.

When comparing the saturation cross-sections for oncogenic transformation and cell inactivation, we find that the ratio: $\sigma_{oT}/\sigma_{oI} = 3.89 \times 10^{-2}/75 = 5.31 \times 10^{-4}$. This means that; the probability of cell death that suffering oncogenic transformation effect is about 5.31×10^{-4}.

4. Conclusion

One of the most important late effects of ionizing radiation is the cellular oncogenic transformation which is a necessary early step in the process of cancer induction. The generalization for quantifying this endpoint for various mammalian cells is still facing experimental difficulties. This is due to the molecular nature of the event. Whereas the concept behind the interaction of IR radiation with specific genes remains unclear, we focused on the induction of oncogenic transformation for C3H10T1/2 cells by HCP's.

In this work, we modeled the biophysical effects of cellular inactivation and transformations of C3H10T1/2 cells using a nanometric quality parameter. The phenomenological model seems to show its unification feature among the different HCP's, independent of their types, to produce specific damage in terms of nanometric events characterized by MFPλ (nm). The model has significant advantage to describe the fundamental mechanisms in which HCP's produce oncogenic transformations in terms of DNA breaks. The model can also be used to estimate the risk by which the induced transformations leading to cell death. The response curve specified by ($\sigma_x - \lambda$) for specific endpoint x; cellular or oncogenic transformation, also can be used to predict the dose effect curves for HCP's with high LET. It can also redefine the dose dependent RBE on estimating maximum or minimum biological damages.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declared that no potential conflicts of interest concerning the research, authorship, and/or publication of this article.

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