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Araştırma Makalesi / Research Article

Charged Particle Interactions of Human Organs and Tissues in Heavy Ion Therapy; Effective Atomic Number and Electron Density

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Keywords
Hadron Therapy; Effective Atomic Number; Electron Density; Tissue Equivalence; Water Equivalence

Abstract

In this work, various organs of human and tissues were studied in terms of the effective atomic numbers (Z_{eff}) and electron densities (N_e) in the continuous kinetic energy region for different types of heavy ions. Variations of Z_{eff} and N_e with kinetic energy were investigated and significant variations were noted. In addition, water and tissue equivalences of the given materials with respect to their Z_{eff} and N_e were evaluated based on the results obtained. The best water equivalents were found to be Urinary Bladder_Urine for H, He and C ions and Skeleton Cartilage for Ne ion since differences in Z_{eff} relative to water for H (≤%3), He (≤%1), C (≤%1) and Ne (≤%6) ions were significantly low. Moreover, variations in water equivalences of the materials have been discussed in detail in the continuous energy region. The reported data should be useful when heavy ions are intended to be used in these materials for radiotherapy and dosimetry applications as they represent the interaction of ions with these materials in the continuous kinetic energy region.

Ağır İyon Terapide İnsan Organları ve Dokularının Yüklü Parçacık Etkileşimleri; Etkin Atom Numarası ve Elektron Yoğunluğu

Anahtar kelimeler
Hadron Terapi; Etkin Atom Numarası; Elektron Yoğunluğu; Doku Eşdeğeri; Su Eşdeğeri

Öz

Bu çalışmada, farklı iyon tipleri için sürekli kinetik enerji aralığında birçok insan organ ve dokuları için etkin atom numaraları (Z_{eff}) ve elektron yoğunlukları (N_e) çalışılmıştır. Z_{eff} ve N_e 'in kinetic enerji ile değişimi incelenmiş ve önemli değişimler not edilmiştir. Ayrıca elde edilen sonuçlara dayalı olarak Z_{eff} ve N_e için verilen malzemelerin su ve doku eşdeğerleri değerlendirilmiştir. En iyi su eşdeğerlikleri H, He ve C iyonları için idrar kesesi ve Ne iyonu için iskelet kıkırdağı olarak bulundu, çünkü suya nispeten Z_{eff}'deki farklılıklar H (≤%3), He (≤%1), C (≤%1) ve Ne (≤%6) iyonları için önemli ölçüde düşüktü. Ayrıca malzemelerin su eşdeğerliklerindeki değişimler sürekli enerji aralığında tartışılmıştır. Rapor edilen veriler, sürekli kinetik enerji aralığında bu malzemelerle iyonların etkileşimini gösterdiklerinden dolayı, ağır iyonlar radyoterapi ve dozimetri uygulamaları için bu materyallerde kullanılmak için hedeflendiğinde kullanışlı olmalıdırlar.

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1. Introduction

There are various cancer types in the world and some methods such as surgery, chemotherapy and radiotherapy are used to treat these cancers in terms of any cancerous cells or tissues. Differently from the others, the cancerous cells or tissues are exposed to uncharged and charged radiations for treatment in radiotherapy. For this aim, energetic photons, protons, electrons, heavy ions can be generally can be utilized for treatment. To use the hadrons such as proton or ion, they are accelerated by available systems such as synchrotrons, linacs and cyclotrons. Recently, hadron therapy has been of increasing interest because of its some superiorities over the conventional radiotherapy. For example, helium ion treatment is preferred on ion therapy due to their physical and biological advantages for some patients such as pediatric patients (Gallasa *et al.* 2017). Another example is carbon ion has some physical and biological advantages. It has less Coulomb interactions which

indicates a superior dose distribution, and it has 2-3 range or higher relative biological effectiveness (RBE), while for protons RBE is generally considered to be 1.1 (Mohamad *et al.* 2018). Neon ions used in cancer therapy are another type of ions that and are now showed as a good candidate for hypoxic problems of carcinogenicity (Banaś *et al.* 2018). In conventional X-ray radiotherapy, the radiation dose decreases in the body with the increasing penetration depth. In heavy ion therapy, however, the radiation dose increases with increasing penetration depth in the body and produces the Bragg peak in a specific depth, thus letting selectively irradiation of cancers with a maximum dose. In this regard, studies on ion interaction with different materials of interest become crucial for both therapy and equivalent materials design.

Effective atomic number is a well known term used to characterize composite materials respect to equivalence since a number cannot symbolize the composite material in the continuous energy region. For description of multi-element or composite materials on behalf of equivalent elements, effective atomic number and electron density have an important role in radiation interaction with matter or designing new equivalent materials. Studies on biological materials are interesting for researcher in terms of photon or ion interactions in literature. Z_{eff}s of some biological materials were investigated in the energy region 10-200 keV (Rao *et al*. 1985). Yang et al. studied Z_{eff}s of human tissues for low energy total photon interactions via introduced a new method and the results were compared with water and tissue (1987). Z_{eff}s of muscle, spleen and liver were investigated in 1, 5, 10, 20 and 50 MeV for photons, electrons and He ions, the results evaluated by Parthasaradhi *et al.* (1989). Some composite materials such as water, Perspex and nylon were studied in terms of effective atomic numbers for photon (1-50 MeV), electrons (1-50 MeV) and protons (1-200 MeV) (Prasad *et al.* 1997). And important data for particle interactions was reported by authors in the relevant energy regions. Shivaramu calculated effective atomic numbers of human organs and tissues such as ovary, testis, eye lens, adipose tissue, lung tissue etc. for photon energy absorption and photon interaction by direct method in the energy region of 1 keV to 20 MeV (2002). Z_{eff}s and its variation with photon energy have been also discussed in terms of effect of absorption edge in the study. Z_{eff}s of some molecules such as fatty acids and carbohydrates were studied for photon absorption and interaction from 1 keV to 20 MeV, and energy dependence of Z_{eff} for photon energy was discussed by Manohara *et al.* (2008). Also, Manohara *et al.* computed energy absorption buildup factors of human organs and tissues for photon energy range 0.015-15 MeV and penetration depths up to 40 mfp (mean free path) and they discussed chemical composition effect and energy dependences in Z_{eff}s of human organs and tissues (2011). Manjunatha *et al.* determined Z_{eff}s and N_es of cortical and compact bone for photon interactions in the energy region of 1 keV – 100 GeV and useful data were determined for choosing a suitable composite material in place of bone (2012). Mann *et al.* investigated the dosimetric materials to be used as tissue-substitutes in radiological diagnosis in terms of mass energy absorption coefficient, equivalent atomic number and KERMA (kinetic energy released per unit mass) in the energy range 0.015–15 MeV (2012). More recently, Singh *et al.* have used effective atomic numbers of some thermoluminescent materials to study photon buildup factors (2014). Kurudirek calculated effective atomic numbers of 107 different materials of dosimetric interest for electron interactions in the continuous energy region, the tissue equivalent materials were compared with the tissues and dosimetric materials in the study (2014a). In the light of the existing studies in literature, studies for photon radiation are widely available while studies for charged particle radiation are scarce. But literature is poor of studies regarding Z_{eff} and N_e of human organs and tissues for heavy ions which are often used in ion therapy. This motivated us to focus on this study. In the present work, effective atomic numbers (Z_{eff}) and electron densities (N_e) of human organs and tissues such as skin, skeletal muscle, skeleton red and yellow marrow, thyroid, pancreas, ovary,

spleen, prostate, testis, A-150 tissue-equivalent plastic (ICRU), B-100 Bone Eqiv. Plastic (ICRU), bone compact (ICRU and ICRP) etc. have been computed for light and hard ion i.e. in the kinetic energy region of 10 keV-10 (for He and Ne), 250 (for H) and 400 (for C) MeV for different types of heavy ions.

2. Materials and methods

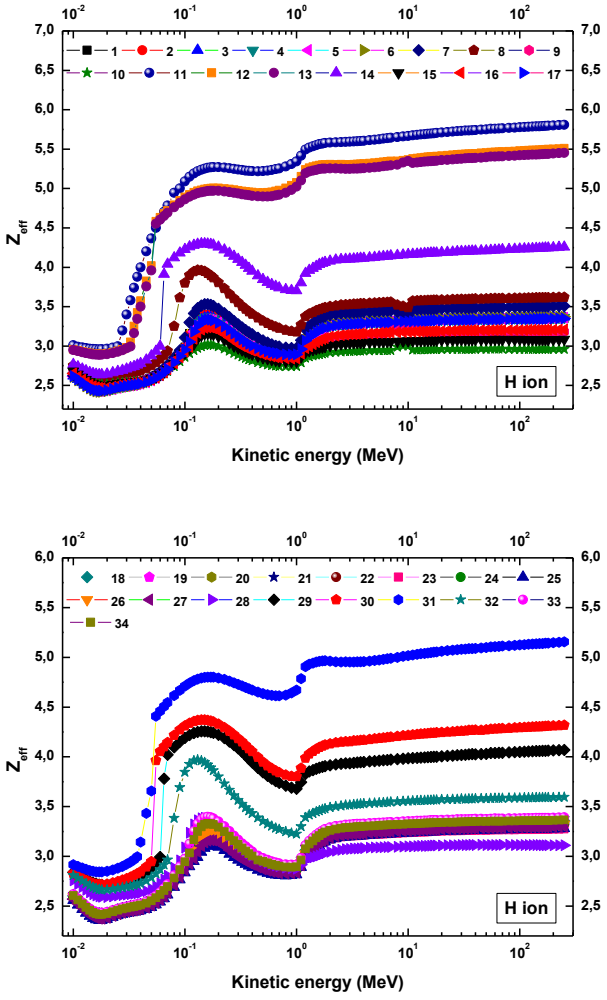
The human organs and tissues used in the present work include Skin 1,2,3, Skeletal muscle (Type 1,2,3), Skeleton Cartilage, Skeleton Spongiosa, Skeleton Red Marrow, Skeleton Yellow Marrow, Cortical Bone Adult, Cort. Bone Ages 6-13, Cort. Bone Ages 2-5, Perinatal Rhesus Monkey, Mammary Gland (Type 1,2,3), Spleen, Testis, Thyroid, Trachea, Ovary, Pancreas, Prostate, Urinary Bladder_Urine, Urinary Bladder_Empty, Urinary Bladder_Filled, A-150 Tissue-Eqiv. Plastic (ICRU), B_100 Bone Eqiv. Plastic (ICRU), Bone, Compact (ICRU), Bone, Compact (ICRP), MS_20 Tissue Substitute (ICRU), Muscle_Eqiv.Liquid w_sucrose (ICRU) and Muscle_Eqiv.Liquid wo_sucrose (ICRU). Also, water and some human tissues such as adipose tissue, muscle skeletal (ICRP) and muscle striated (ICRU) were used for comparison.

In the present work, a similar method described elsewhere was adopted for calculation of effective atomic numbers and electron densities for heavy ions (Kurudirek 2014b, Kurudirek and Onaran 2015, Kurudirek 2015, Büyükyıldız 2017a, 2017b). Briefly, a Z-wise interpolation procedure has been adopted to obtain Z_{eff} for heavy charged particles. First, the mass stopping powers of the given materials were obtained using the SRIM code (Zeigler *et al.* 2010). Z_{eff} then can be obtained by interpolation of Z values between the adjacent stopping cross section data in the kinetic energy region of 10 keV-10 (for He and Ne), 250 (for H) and 400 (for C) MeV for different types of heavy ions. The N_es of the materials were obtained using the well-known formula given elsewhere.

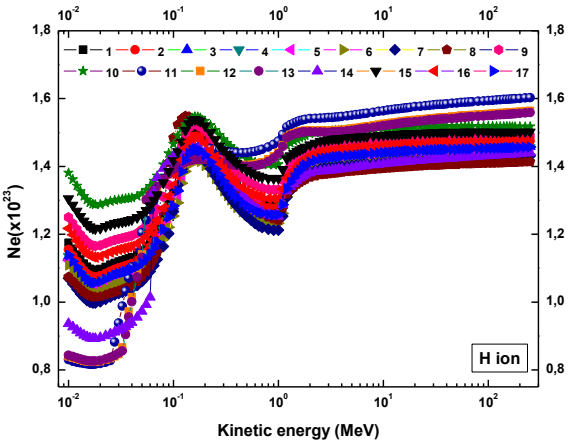
3. Results and discussion

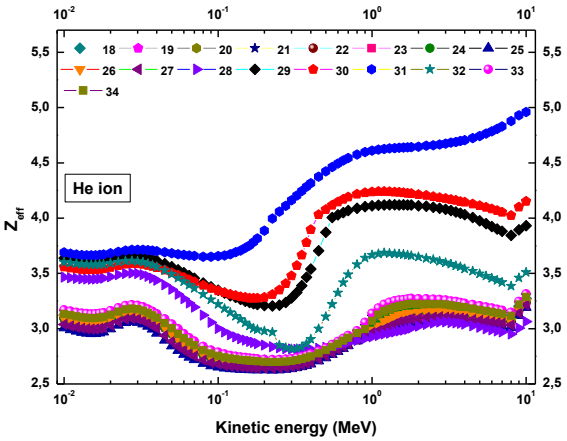
Z_{eff}s and N_es of the all biological materials are shown in Figs. 1 - 4 (a,b) for H, He, C and Ne ion interaction in continuous energy region.

a)

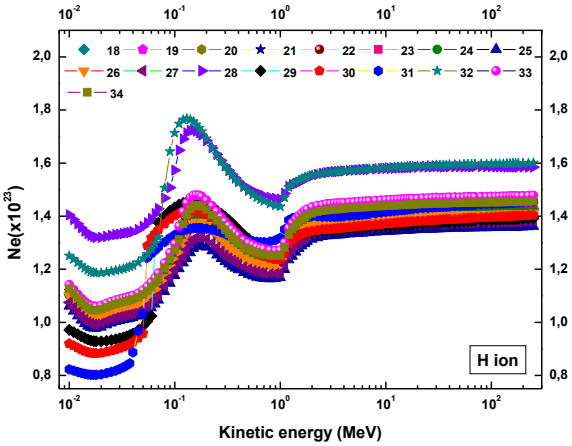


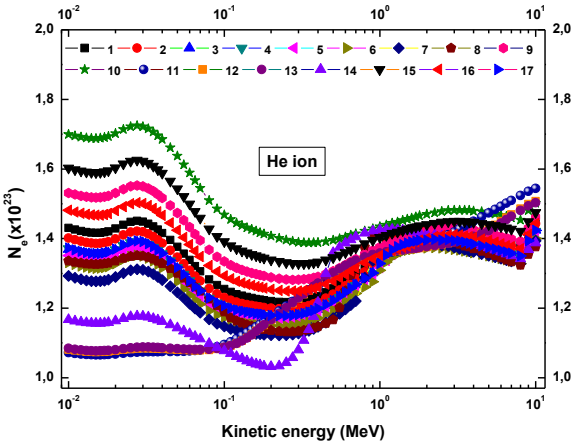
b)





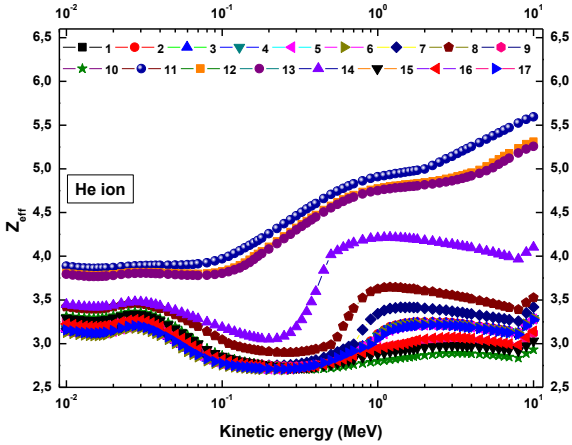
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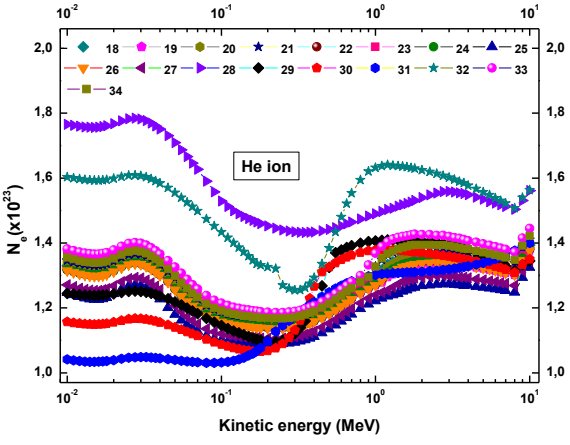




Figs. 1 (a) Z_{eff}s and (b) N_es of the all biological materials for H ion interaction.

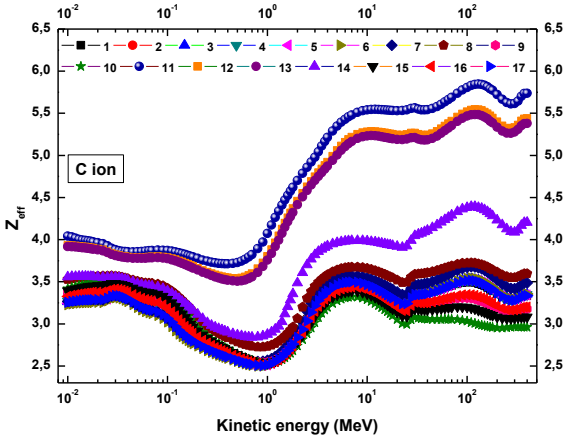
a)

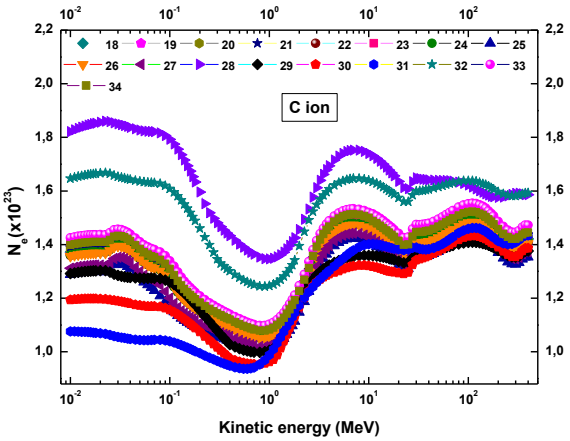




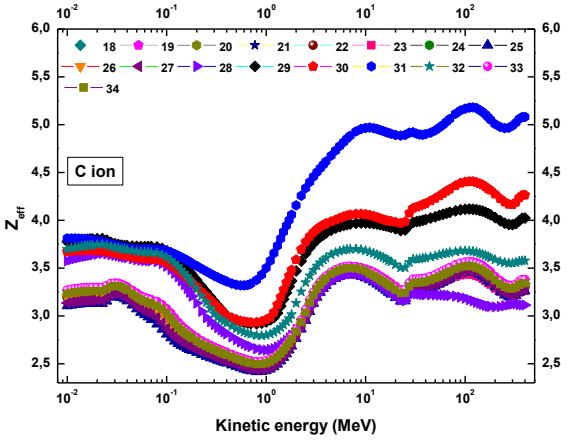
Figs. 2 (a) Z_{eff}s and (b) N_es of the all biological materials for He ion interaction.

a)

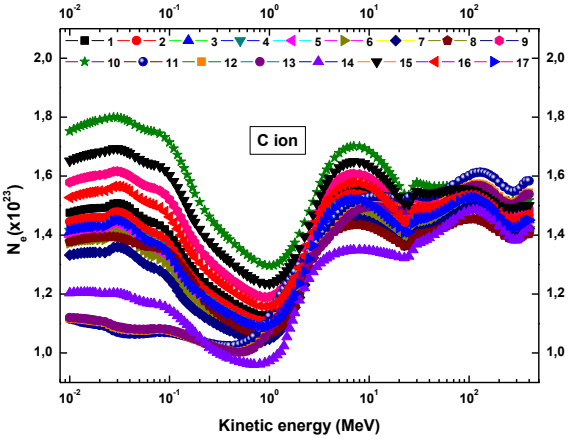




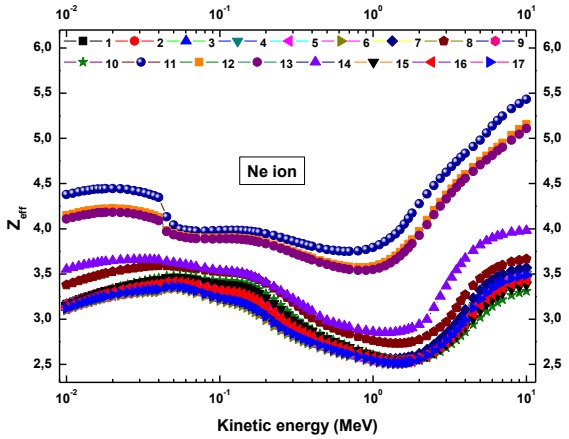
Figs. 3 (a) Z_{eff}s and (b) N_es of the all biological materials for C ion interaction.

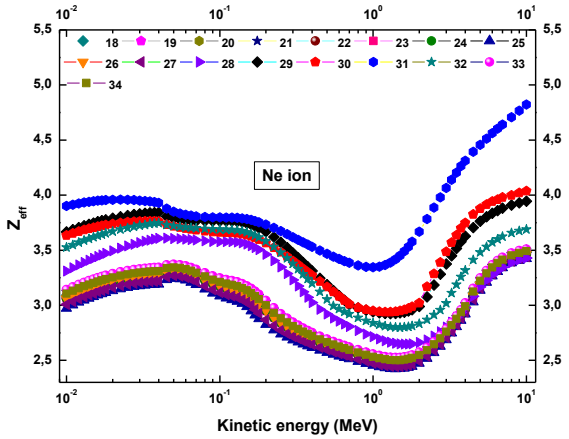


b)

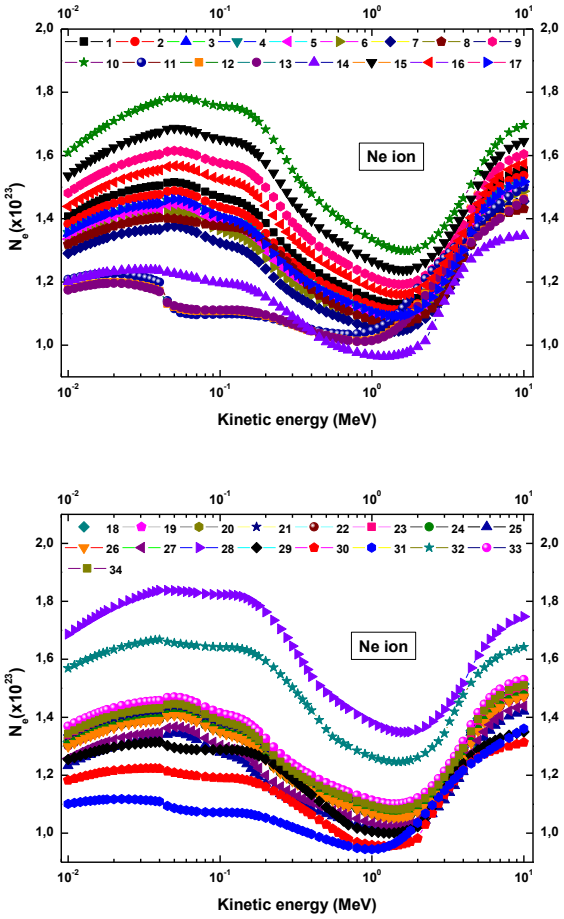


a)





b)



Figs. 4 (a) Z_{eff}s and (b) N_es of the all biological materials for Ne ion interaction.

As shown in Fig. 1a, generally Z_{eff} has lowest values at low energy values and the lowest values of Z_{eff} were observed for the Perinatal Rhesus Monkey around 0.017-0.018 MeV for H ion interaction. Z_{eff} has highest values at high energy values and the highest values of Z_{eff} were observed for the Cortical Bone Adult. It can be clearly seen from Fig. 2a and Fig. 3a for He and C ion interaction that Z_{eff} has lowest values at intermediate energy values and the lowest values of Z_{eff} were observed for the Urinary Bladder_Urine around 0.15 - 0.25 MeV (for He) and 0.80 - 0.90 MeV (for C), highest values of Z_{eff} were observed at highest energy values and the highest values of Z_{eff} were observed for the Cortical Bone Adult. One can see from Fig. 4a that Z_{eff} has lowest values at higher energy values and the lowest values of Z_{eff} were observed for the Skeleton Cartilage in 3.75 MeV and the highest values of Z_{eff} were observed for the Cortical Bone Adult at highest energies. On the other hand, when Figs. 1a – 4a are scrutinized, Z_{eff} shows minimum values at minimum energies, then takes a peak, but interestingly minimum values of Z_{eff} shift to the maximum energies as atomic number of heavy ions rises (H, He, C and Ne, respectively). Variation of N_es of the materials with energy has the same energy dependence approximately as Z_{eff}s, so the N_e is closely related to the Z_{eff} as shown Figs. 1b – 4b.

For biological materials, relative differences (%) in Z_{eff}RW (relative to water) less than 10% are shown in Table 1 for H, He, C and Ne ion interaction in different energy regions, respectively.

Table 1. Maximum relative differences (%) below 10% in Z_{eff} RW for H (10 keV-250 MeV), He (10 keV-10 MeV), C (10 keV-400 MeV) and Ne (10 keV-10 MeV) heavy ions

	Materials	H ion	He ion	C ion	Ne ion
1	Skin 1		1.08		0.92
2	Skin 2		1.07		0.92
3	Skin 3		1.06		0.91
4	Skeletal Musc.(Type1)		1.06		0.91
5	Skeletal Musc.(Type2)		1.06		0.91
6	Skeletal Musc.(Type3)		1.06	1.09	0.91
7	Skeleton Cartilage				0.94
8	Skeleton Spongiosa				
9	Skeleton Red Marrow	1.08			
10	Skeleton Yellow Marrow	0.91			
11	Cortical Bone Adult				
12	Cort. Bone Ages 6-13				
13	Cort. Bone Ages 2-5				
14	Perinatal Rhesus Monkey				
15	Mammary Gland (Type 1)	1.07			
16	Mammary Gland (Type2)	1.07	1.08		
17	Mammary Gland (Type3)		1.06		0.91
18	Spleen		1.05	1.08	0.91
19	Testis	1.06	1.03	1.07	
20	Thyroid	1.08	1.04	1.08	
21	Trachea		1.06		0.92
22	Ovary	1.07	1.04	1.07	
23	Pancreas	1.07	1.05	1.09	
24	Prostate	1.08	1.04	1.07	
25	Urinary Bladder_Urine	1.03	1.01	1.01	
26	Urinary Bladder_Empty	1.07	1.04	1.07	
27	Urinary Bladder_Filled	1.04	1.02	1.04	
28	A-150 Tissue-Eqiv. Plastic (ICRU)				
29	B_100 Bone Eqiv. Plastic (ICRU)				
30	Bone, Compact (ICRU)				
31	Bone, Compact (ICRP)				
32	MS_20 Tissue Substitute (ICRU)				
33	Muscle_Eqiv.Liquid with sucrose (ICRU)		1.07		0.92
34	Muscle_Eqiv.Liquid without sucrose (ICRU)		1.06	1.09	0.91

The relative differences (%) in Z_{eff}RW (relative to water) refer to the deviation from the value one. It can be seen from Table 2 that max difference (%) in Z_{eff}RW for H ion interaction was estimated as %8 for Thyroid, Prostate, Skeleton Red and Yellow Marrow in different energy regions and min difference (%) in Z_{eff}RW was estimated as <%1 for Mammary Gland (Type 1 and 2), Urinary Bladder_Urine, Skeleton Red and Yellow Marrow.

Table 2. Water equivalence based on Z_{eff} RW for some materials for H ion interaction

	Z_{eff} RW	Energy region (MeV)	Z_{eff} RW	Energy region (MeV)
Skeleton Red Marrow	1.08	1.30E-01/1.60E-01	< 1.01	1.20E+00/1.50E+00
Skeleton Yellow Marrow	0.91	1.00E+02/2.50E+02	< 1.01	1.40E-01/1.70E-01
Mammary Gland (Type 1)	1.07	1.40E-02/1.80E-02	< 1.01	1.00E+00 and 1.10E+00
Mammary Gland (Type2)	1.07	1.30E-02/1.70E-02	< 1.01	1.30E+00/1.80E+00
Testis	1.06	1.40E-01/1.80E-01	1.02	1.00E-02/5.50E-02 and 8.00E-1/2.50E+02
Thyroid	1.08	1.40E-01/1.80E-01	1.02	1.00E-02/3.75E-02
Ovary	1.07	1.40E-01/1.80E-01	1.02	1.00E-02/4.50E-02 and 2.00E+01/2.50E+02
Pancreas	1.07	1.50E-01	1.01	1.60E+00/2.50E+02
Prostate	1.08	1.50E-01	1.02	1.00E-02/4.50E-02
Urinary Bladder_Urine	1.03	1.60E-01/1.80E-01	< 1.01	1.00E-02/1.30E-02
Urinary Bladder_Empty	1.07	1.30E-01/1.80E-01	1.02	1.00E-02/4.50E-02 and 13.00E+00/2.50E+02
Urinary Bladder_Filled	1.04	1.40E-01/2.00E-01	1.01	1.00E-02/5.50E-02

Max dif. (%) in Z_{eff}RW for He ion interaction was obtained as %8 for Skin 1 and Mammary Gland (Type2) in different energy regions and min dif. (%) in Z_{eff} was ≤ %2 as seen Table 3.

Table 3. Water equivalence based on in Z_{eff} RW for some materials for He ion interaction

	Z_{eff} RW	Energy region (MeV)	Z_{eff} RW	Energy region (MeV)
Skin 1	1.08	4.50E-02/5.50E-02	1.02	5.00E-01/9.00E-01
Skin 2	1.07	4.50E-02/5.50E-02	1.02	4.50E-01/8.00E-01
Skin 3	1.06	1.20E+00/5.50E+00	1.02	2.75E-01/9.00E-01
Skeletal Musc.(Type1)	1.06	1.20E+00/5.00E+00	1.02	3.00E-01/9.00E-01
Skeletal Musc.(Type2)	1.06	2.25E+00/3.75E+00	1.01	6.50E-01/9.00E-01
Skeletal Musc.(Type3)	1.06	1.60E+00/4.50E+00	1.01	5.50E-01/7.00E-01
Mammary Gland (Type2)	1.08	4.50E-02/6.50E-02	<1.01	6.50E+00/9.00E+00
Mammary Gland (Type3)	1.06	5.00E-02/5.50E-02	1.01	6.00E-01/9.00E-01
Spleen	1.05	1.60E+00/6.00E+00	1.01	3.75E-01/9.00E-01
Testis	1.03	2.25E+00/6.50E+00	<1.01	4.00E-01/1.10E+00
Thyroid	1.04	1.80E+00/6.00E+00	1.01	2.50E-01/1.00E+00
Trachea	1.07	2.50E+00	1.02	2.75E-01/9.00E-01
Ovary	1.04	2.50E+00/5.00E+00	<1.01	5.50E-01/9.00E-01
Pancreas	1.05	5.00E-02	<1.01	4.50E-01/1.50E+00
Prostate	1.04	2.00E+00/6.00E+00	<1.01	5.50E-01/8.00E-01
Urinary Bladder_Urine	1.01	1.00E-02/1.00E+01	<1.01	1.70E+00/2.25E+00
Urinary Bladder_Empty	1.04	2.50E+00/5.00E+00	<1.01	5.50E-01/9.00E-01
Urinary Bladder_Filled	1.02	2.50E+00/1.00E+01	≤1.01	1.00E-02/2.00E+00
Muscle_Eqiv.Liquid with sucrose (ICRU)	1.07	1.10E+00/5.00E+00	1.02	3.50E-01/8.00E-01
Muscle_Eqiv.Liquid without sucrose (ICRU)	1.06	1.70E+00/4.50E+00	1.02	5.00E-01/8.00E-01

For C ion interaction, max and min dif. (%) in Z_{eff}RW were determined as %9 for Skeletal Musc.(Type3), Pancreas, Muscle_Eqiv.Liquid without_sucrose (ICRU) and ≤%1 for Urinary Bladder_Urine, respectively as shown in Table 4.

Table 4. Water equivalence based on in Z_{eff} RW for some materials for C ion interaction

	Z_{eff} RW	Energy region (MeV)	Z_{eff} RW	Energy region (MeV)
Skeletal Musc.(Type3)	1.09	1.00E-01	1.03	3.50E+00/1.70E+01 and 7.00E+01/1.60E+02
Spleen	1.08	9.00E-02/1.10E-01	1.02	5.50E+00/9.00E+00
Testis	1.07	9.00E-02/1.00E-01	1.01	11.00-12.00 and 9.00E+01/1.70E+02
Thyroid	1.08	9.00E-02/1.00E-01	1.02	3.50E+00/1.00E+01 and 5.50E+01/2.00E+02
Ovary	1.07	9.00E-02/1.00E-01	1.02	1.70E+00/1.00E+01 and 2.75E+01/4.00E+02
Pancreas	1.09	9.00E-02/1.20E-01	1.01	3.75E+00/1.00E+01 and 8.00E+01/2.00E+02
Prostate	1.07	9.00E-02/1.00E-01	1.02	3.25E+00/1.00E+01 and 5.50E+01/2.00E+02
Urinary Bladder_Urine	1.01	1.00E-02/5.00E-02	<1.01	5.50E-02/1.00E+01
Urinary Bladder_Empty	1.07	9.00E-02/1.10E-01	1.02	1.70E+00/1.00E+01 and 2.75E+01/4.00E+02
Urinary Bladder_Filled	1.04	8.00E-02	1.01	3.25E-01/1.00E+01 and 6.50E+01/1.60E+02
Muscle_Eqiv.Liquid without_sucrose (ICRU)	1.09	9.00E-02 and 1.00E-01	1.03	1.70E+00/1.20E+01

In addition, Urinary Bladder_Urine seems to be the best water equivalent as relative differences (%) in Z_{eff}RW are significantly low %3 for H, %1 for He and C ions in the energy regions 0.16 - 0.18 MeV for H, 10 keV - 10 MeV for He and 5.50 keV - 10 MeV for C. Therefore, it can be considered as a water equivalent in these energy regions when bombarded with H, He and C ions, respectively. For Ne ion interaction, generally max. dif. (%) in Z_{eff}RW was found to be %8-9 for all materials (except Skeleton Cartilage) in the energy region 3.75 - 4.00 MeV as shown in Table 5.

Table 5. Water equivalence based on in Z_{eff} RW for some materials for Ne ion interaction

	Z_{eff} RW	Energy region (MeV)	Z_{eff} RW	Energy region (MeV)
Skin 1	0.92	3.75E+00 and 4.00E+00	<1.01	5.50E-01/7.00E-01
Skin 2	0.92	3.75E+00 and 4.00E+00	<1.01	4.50E-01/5.50E-01
Skin 3	0.91	4.00E+00	<1.01	3.00E-01/3.75E-01
Skeletal Musc.(Type1)	0.91	4.00E+00	<1.01	3.25E-01/4.00E-01
Skeletal Musc.(Type2)	0.91	3.75E+00 and 4.00E+00	<1.01	2.50E-01/3.25E-01
Skeletal Musc.(Type3)	0.91	4.00E+00	<1.01	1.30E-01/2.50E-01
Skeleton Cartilage	0.94	3.75E+00	<1.01	3.50E-01/6.00E-01
Mammary Gland (Type3)	0.91	3.75E+00 and 4.00E+00	<1.01	2.75E-01/3.50E-01
Spleen	0.91	3.75E+00 and 4.00E+00	<1.01	5.00E-02/2.25E-01
Trachea	0.92	3.75E+00 and 4.00E+00	<1.01	2.75E-01/3.50E-01
Muscle_Eqiv.Liquid with sucrose (ICRU)	0.92	3.75E+00 and 4.00E+00	<1.01	2.25E-01/4.00E-01
Muscle_Eqiv.Liquid without sucrose (ICRU)	0.91	3.75E+00 and 4.00E+00	<1.01	1.70E-01/2.50E-01

Skeleton Cartilage has the lowest deviation (%6 for Ne ion) among the max dif. (%) in Z_{eff}RW in this energy region. Table 5 also presents the obtained min. dif. (%) in Z_{eff}RW as <1% in the relevant energy regions. Parthasaradhi *et al.* have calculated Z_{eff} for spleen at 1, 5 and 10 MeV and they found values 3.30, 3.40 ve 3.20 (±0.2) (1989). Values of Z_{eff} obtained in the present work (3.04, 3.15 and 3.27 at 1, 5 and 10 MeV, respectively) agree well with the findings of Parthasaradhi *et al.* as relative differences are significantly low (≤8% at 1 MeV, ≤7% at 5 MeV and ≤2% at 10 MeV).

4. Conclusions

This work presents data on water and tissue equivalence properties of some human organs and tissues in terms of effective atomic number and electron density in the relevant kinetic energy region for different types of heavy ions. Some of Z_{eff}s of the organs and tissues were compared with the other values available in the literature. Also relative differences (%) in Z_{eff}RW (relative to water) of the organs and tissues, and significant variations were determined in the relevant energies. In the light of the results obtained, the best water equivalents were found to be Urinary Bladder_Urine for H, He and C ions (differences in Z_{eff}RW are ≤3% for H, ≤1% for He, ≤1% for C) and Skeleton Cartilage for Ne ion (difference in Z_{eff}RW is ≤6%). The reported data should be useful when heavy ions are intended to be used in these materials for radiotherapy or hadron therapy and dosimetry applications as they represent the interaction of ions with these materials in the continuous kinetic energy region. The data should be also significant if a new material is designed for radiotherapy or hadron therapy due to definition of effective atomic number.

Conflict of interest

There is no conflict of interest to declare.

Ethical approval

This article does not contain any studies with human or animal subjects performed by any of the authors.

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