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Using terahertz irradiation to mitigate the effects of radiation exposure

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Experimental data are presented on the effect of broadband irradiation in the terahertz range, modulated in the gigahertz range, on the survival of mice that have received acute poisoning with depleted uranium compounds. For the first time, the results indicate a clinically significant increase in the life span of mice, the control terms for the development of end-stage renal disease and death, as well as an increase in the survival of mice by 50%. Long-term consequences that form in the period after therapy with antidotes / chelators of toxic metals can be prevented or significantly weakened by the proposed method of physiotherapy, which can solve many problems facing society, both in ensuring occupational health and the health of the population as a whole in case of accidents at nuclear power facilities.

Keywords: occupational health, broadband terahertz irradiation, GHz modulation, poisoning with depleted uranium compounds, mouse survival.

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Introduction

Human body exposure to radiation is one of the occupational health problems. This is a serious problem for nuclear industry personnel, NPP accident response personnel, medical personnel, aircraft crews, astronauts, sea vessel crews, mine personnel [1–3].

As a result of radiation exposure, excitation of separate atoms may lead to intramolecular and intermolecular energy transfer, activation of free radical processes, transmutation reactions, bond opening, etc. General biological changes in the body are characterized by biochemical, physiological and structural, as well as epigenetic changes [4]. Vital biopolymers and lipids required for normal cell activity may be damaged. Thus, radiation and nuclear fission products impact the body at microlevel causing damage which took many years to become visible. Damage of separate groups of proteins in a cell may cause cancer diseases and genetic mutations which can be passed down through several generations. Low irradiation dose expose (radiation exposure) is problematic for diagnostics, while this exposure causes serious harm to health both at an early stage and after a long time.

Hazard of radioactive substances when they enter the body is associated with spatial distribution of absorbed energy and chemical toxicity of radionuclides (radioactive isotope toxicity) [4]. However, the existing methods for radionuclide and heavy metal elimination from the body are not developed to a full extent [2].

In recent years, to ensure radiation safety, a special focus is paid on antiradiation drugs which shall have high protective effect without prominent side effects and ensure radiation protection in any occupational environment and for various types of expose (chronic, long-term, acute) and exposure doses not exceeding 10 Gy (1000 rad) [5]. However, currently, not all radioprotectors have sufficient therapeutic margin. Thus, a potential radioprotector for protection against radiation damage in case of nuclear power plant accidents—melatonin (N-acetil-5-metoxytryptamine)-has pronounced antioxidant and antiradical action, but it can facilitate hypotension development, cause heart beat rhythm disorder in some sensitive people [6,7].

The most efficient radioactive poisoning treatment agents are antidotes which is due to their ease of use and applicability in any conditions, including accidents [8]. These special pharmacological agents allow to stop body intoxication process, but do not prevent the pathological changes that have already occurred in organs and tissues. Therefore, the search for comprehensive pharmacological agents and methods and physiotherapeutic support of adaptation and regenerative capabilities of the body, and radiation damage effect prevention constitute an essential healthcare issue [4].

In recent 10–15 years, significant progress was achieved in the field of creating semiconductor sources and receivers of radiation in the terahertz (THz) wavelength range and this immediately attracted the attention of physicians, researchers and medical equipment designers, because opportunities have appeared to develop brand-new

physiotherapeutic equipment and treatment methods for wide range of diseases [9].

THz irradiation or „terahertz" covers a wide electromagnetic emission spectrum range from 100 GHz to 30 THz (emission wavelength is approx. from 3 mm to 10 μm). This range borders with microwave range and extends to far and middle infrared (IR) bands.

THz quanta do not impose ionization hazard for biological tissues because they have much lower energy than visible and X-ray wavelength band quanta. At a first glance, it can seem unreal that percutaneous THz band exposure can stimulate therapeutic effect because its intensity is attenuated at a depth of several hundreds micron from skin surface. Nevertheless, it has been shown that penetrating radiation with a strength of even dozens to hundreds nanowatt effectively impacts essential biochemical reactions [9]. Moreover, an important physiotherapeutic factor is that THz irradiation is resonant for protein molecules, excites their rotational and vibrational modes which belong to THz frequency range [10].

The current open scientific literature include very few publications devoted to THz frequency band effect on mammals. The study of THz frequency band effect on living organisms in stress and pathology has shown high efficiency of THz physiotherapy [11,12]. It has been shown [11] that THz frequency band exposure of intact animals is not accompanied by hemodynamic changes in major vessels and microcirculatory bloodstream, but leads to hemodynamic parameter normalization in stress conditions. Also, THz exposure in acute and long-term stress caused restoration of microcirculatory hemodynamics in rat brain, heart, liver, kidneys and stomach. One of possible THz action mechanisms includes activation of NO-syntase component of nitrogen oxide cycle and restriction of cascade hypothalmic-pituitary-adrenal axes activation of stress reaction in acute and long-term stress [13]. Stress correction efficiency using THz depends on the animal sex and estrous cycle phases in female rats: efficiency is maximum in estrus phase compared with diestrus phase or males [13]. Together with the explanation described above, alternative THz exposure efficiency explanations are described in literature.

The use of exogenous heat shock proteins or endogenous protein synthesis induction may be a promising approach to radiation damage therapy *in situ*. Study of uranium salt (alpha-emitting radionuclide) toxicity with multiple injections has shown that rats were resistant to repeated injection of 5 mg/kg uranyl acetate 1−2 weeks after the first injection of the same toxicant dose due to the increase in renal HSP73 up to 148 ± 12% of the initial level and tubule damage and increase in serum creatinine after the second poison dose were much lower than after the first dose [14].

Analysis of THz irradiation impact in acute and long-term stress on the pituitary thyroid axis is described in [12]. The author has shown that daily exposure to THz (5 days) during 15 min facilitates partial normalization of hormonogenesis function of thyroid and 5 min exposure is not efficient. Exposure to 129 GHz radiation during 30 min causes full normalization of corticosterone in blood in rats. The author emphasizes that exposures lower than 15 min (and in some experiments lower than 30 min) are not efficient, and operating frequencies are 129.0 GHz for oxygen and 150.1−150.7 GHz for nitrogen oxide. These ranges and 5-day scheme with 30 min exposures define stress limiting function of the test THz frequency band.

However, despite the good results, the disadvantages of [11–13] shall include the fact that the authors in both cases used narrow-band emitter with about 150 GHz what did not allow carry out comprehensive study of THz irradiation on living organisms. Partially this was associated with the absence of required THz equipment on the market.

Therefore, the purpose of the research was to carry out experimental study of the influence of broadband THz irradiation modulated in gigahertz band (physiotherapeutic equipment „IR-Dipole" produced by „Dipole Structures" LLC St. Petersburg) on survival rate of mice with acute depleted uranium intoxication.

Methods

The current research used THz irradiation modulated in GHz band generated by solid-state emitters made using silicone nanotechnology based on monocrystalline silicone. The emitters consist of controlled THz irradiation generators in the wavelength band from 1 to 650 μm with GHz modulation throughout the radiation spectrum[9]. Creation of such emitters was possible due to implementation of quantum-dimensional $p-n$-junction on silicon monocrystalline surface with a depth from 20 to 30 nm and 2 nm ultrathin insulating barriers. Simultaneously nanotechnology of such quantum-dimensional $p-n$-junctions using self-arrangement processes of nanostructures, makes it possible to form a fractal microcavity system integrated in the $p-n$-junction plane, the presence of which allows to enhance the THz irradiation intensity exponentially in a broad wavelength band. Nanotechnology of self-consistent systems similar to fractal microcavities combined with quantum-dimensional $p-n$-junctions allowed to get THz irradiation generation using silicone nanostructures for the first time in the world. GHz modulation throughout the spectrum in 40−1200 GHz band ensures enhanced photoexposure by several times sine GHz radiation is resonant for protein molecules [15].

First prototype modifications of „IR-Dipole" THz therapy equipment emerged in 1992 and have immediately shown high performance in multiple therapy applications. Design and operation principle of this instrument are based on modern nanotechnology achievements in nano- and opto-electronics and are unparalleled anywhere in the world.. In recent years, unique results have been obtained and efficient methods have been developed for demyelinating disease therapy of central nervous system [16], treatment of postsurgery pneumonia after cardiac operations [17], and

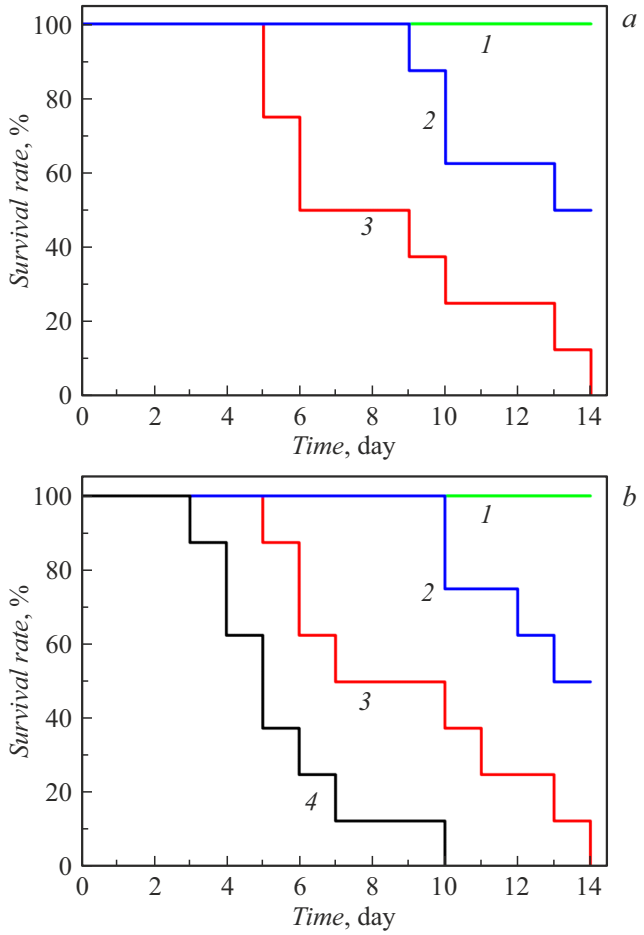

Figure 1. Kaplan-Meier survival curves: *a* — in the first experiment series, *b* — in the third experiment series. Group comparison by Mantel'Cox Log-rank test (exact significance level *p* for two groups). *a* — *1* — intact, *2* — THz + UAD, *3* — UAD, $p = 0.0124$. *b* — *1* — intact, *2* — THz + UAD, *3* — UAD, *4* — thermostat + UAD, $p = 0.0001$.

in addition a unique method was developed (together with standard medicamental method) for COVID-19 pneumonia treatment [18].

The study has shown [9] that stimulation with THz irradiation of metabolism reactions with enzyme deficiency may be of ambivalent nature. First, the cell uses light quantum energy rather than adenosine triphosphate (ATP) hydrolysis energy. Alternative proposal may be in that light absorption does not substitute such hydrolysis, but accelerates it and, thus, accelerates the coupled metabolic reactions.

The first opportunity was associated with the assumption of the role of alpha-helical protein molecules in the ATP hydrolysis energy transfer process. Such assumption was proposed in the late 1970s and was caused by the fact that points where hydrolysis takes place and hydrolysis energy is consumed are frequently separated by distances significantly exceeding the interatomic spacing [19]. To ensure efficient transfer over such large distances, intermediate liner protein molecules are required. The energy is transferred along the peptide group chain. Energy of such oscillations is equal to 0.21 eV and for oscillation excitation ATP hydrolysis energy is sufficient (0.54 eV). Long excitation life in such system compared with their life on an isolated peptide group (11–13 s) is explained by the capability of soliton generation – bound states of intrapeptide oscillations and chain oscillation as a whole. Soliton is a solitary wave with retained form propagating along the protein molecule, it is not susceptible to dispersion and does not lose energy [19].

Soliton excitation is possible not only by chemical, but also by optical way. Such solitons are able to arrive to the area where energy consumption takes place required for metabolism and, thus, to increase their intensity. However, soliton lifetime directly depends on the number of peptide groups involved in its formation by optical exposure, for example, in spectral hydrogen bond excitation range (0.165–0.3 eV, which corresponds to wavelength interval 4–7.5 μm inside which the liner molecule oscillation energy value is present). Thus, when three peptide groups are involved, soliton lifetime is equal to 0.5 s, six groups — 41 s, and when 9 peptide groups are involved whose total size has much lower diameter of optic beam, soliton lifetime corresponding to oscillations in alfa-helical protein molecules in optical excitation of hydrogen bond is equal to 22.5 min! Action of optically generated solitons which are ideal carriers of ATP molecule hydrolysis energy along alfa-helical protein molecules virtually without loss may be greatly enhanced, if the generating light is modulated in GHz range resonant for bonds inside radicals included in protein molecules [10]. In this case, optical excitation and transport of solitons can stimulate removal of oxygen-containing radicals captured by damaged areas of protein molecules that is important for practical medicine.

It should be noted that optically induced soliton can directly influence the ATP hydrolysis process. In this case, optical THz irradiation excites exciton in ATP system whose transport in adenosine ring results in soliton formation followed by increased „exection" probability of phosphate group: ATP + „THz irradiation" $\Rightarrow$ ADP + P. Correspondingly, this process is dramatically enhanced when using GHz modulation of THz irradiation which is manifested, e.g. in optically stimulated ion transport through biological membranes in „sodium-potassium pump" [20].

Results

Literature data analysis has shown that probable action mechanism of THz radiation modulated in GHz band is associated with modulation of biochemical plastic processes and express adaptation to stress impact, e.g. due to heat shock protein synthesis induction. Increased HSP73 heat shock protein gene expression is reported in case of single exposure to uranium compounds [14]. Rats were resistant to repeat-dose of 5 mg/kg uranyl acetate 1–2 weeks after

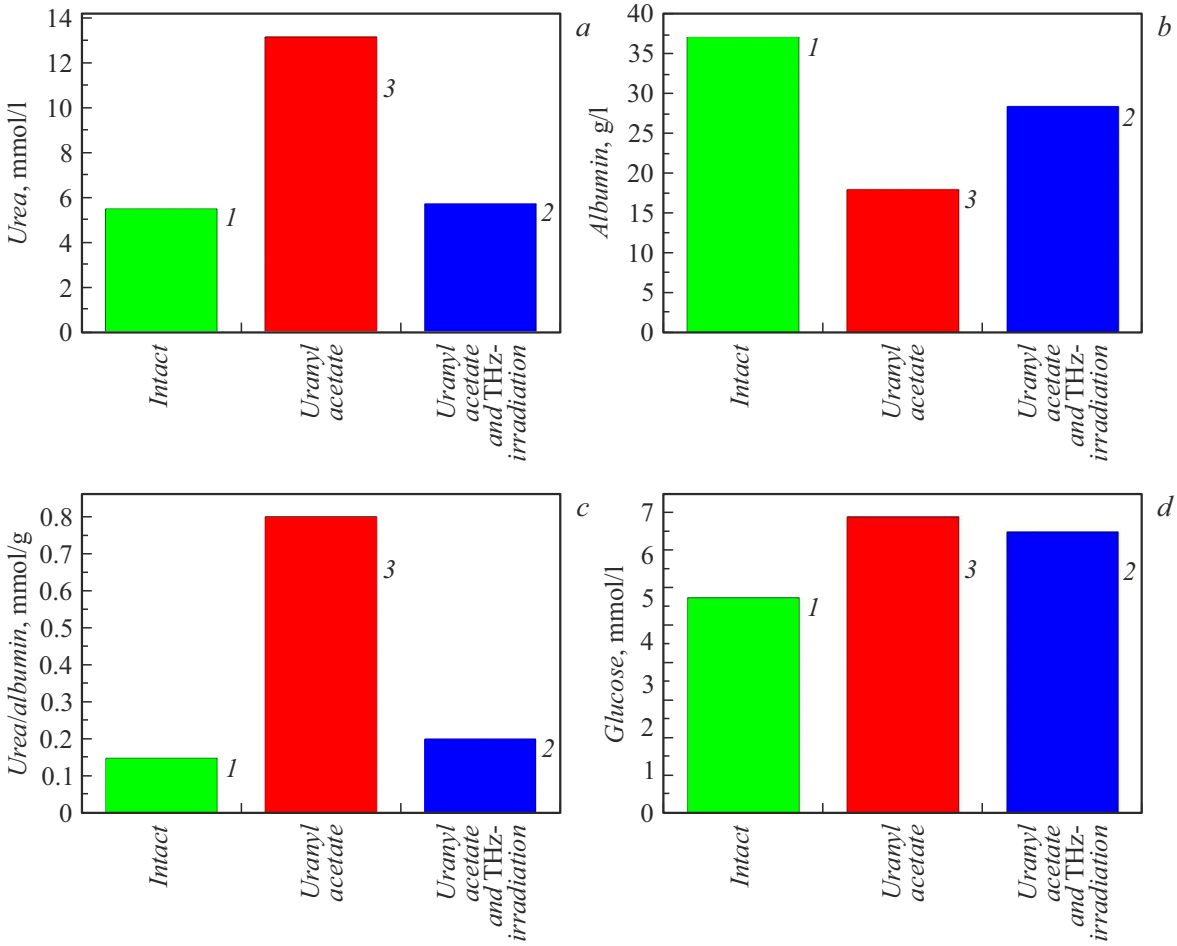

Figure 2. The influence of THz irradiation on some biochemical variables in mice blood serum: *a* — urea, *b* — albumin, *c* — urea/albumin index, *d* — glucose.

the first injection of the same toxicant dose. During this period, renal HSP73 level was increased up to $148 \pm 12\%$ from the initial level, and tubule damage and increase in serum creatinine after the second poison dose were much lower than after the first dose [14].

Due to this, the authors of the paper used „IR-Dipole“ to carry out preliminary experiments *in vivo* in mice that showed high efficiency of total irradiation of animals poisoned by uranium salts in early intoxication period (toxicogenic phase and beginning phase of somatic pathology development). Three series of experiments were carried out on male scrub mice and CBA line mice. After single abdominal introduction of uranyl acetate dihydrate (UAD, CAS Number: 6159-44-0) in lethal dose 5 mg/kg, 3–4 mice per group session were placed into a container where they were exposed to 2 radiation sessions per day. Crystal height above the mice body was 18 cm, exposition time was 22 min per session, 2 sessions per day. Therapy session duration is 7 days after poison introduction.

Comparison of biological effect of radiation was carried out in three experiment series. In first two series, groups of mice administered with UAD and mice administered with UAD and THz physiotherapeutic support were compared with intact mice. The third series additional included a mice group which were warmed in a thermostat in addition to poisoning during the time equivalent to exposure to „IR-Dipole“.

The „IR-Dipole“ has a strong radiation peak in $9-12\,\mu$m range which can be assigned to heat radiation. Therefore, in order to avoid the influence of heat radiation in this experiment on the final result, as heat impact equivalent during the third series, animals were warmed in a thermostat at $+40^\circ$C 22 min per session, 2 sessions per day. Euthanasia was carried out by single-step decapitation. Variables in blood serum on day 10 were defined using Randox (UK) sets in Keylab (BPC BioSed srl) automatic biochemical analyser. Data were processed using GraphPad Prism 6.0 (USA) statistical software package.

Analysis of survival curves (Figure 1) has shown maximum repeatability of the first and third series and reduction of statistical power with reduced animal sampling. Thus, according to Mantel'Cox Log-rank test, during comparison of two groups, statistically and clinically relevant increase in mice survival rate was detected in exposure to THz using „IR-Dipole“ per 50% in the first ($p = 0.0124$) and third ($p < 0.0001$) experiment series, and by 33% ($p = 0.1026$)

Table 1. Impact of THz irradiation on some biochemical variables in mice blood serum (data on experiment day 10, $n = 5$ in each group)

Descriptive statistics	Experimental groups			
	Intact	Control THz	UAD	UAD + THz
	Urea, mmol/l			
Minimum	4.685	5.12	12.13	1.128
25% percentile	4.826	5.14	12.25	3.618
Median	5.764	5.397	12.77	6.226
75% Percentile	5.972	6.438	14.21	7.522
Maximum	6.079	6.576	14.54	7.876
Average value 5.472	5.71	13.14	5.701	
Standard deviation	0.6088	0.6794	1.032	2.657
standard error	0.2723	0.3039	0.4615	1.188
Lower 95% CI	4.716	4.867	11.85	2.402
Upper 95% CI	6.228	6.554	14.42	9
	Albumin, g/l			
Minimum	32	32.14	9.385	18.01
25% Percentile	32.86	32.69	13.58	19.88
Median	37.57	37.59	18.41	29.03
75% Percentile	41.16	38.45	21.96	36.51
Maximum	41.81	38.69	24.89	36.8
Average value	37.12	35.97	17.9	28.36
Standard deviation	4.225	3.047	5.543	8.43
Standard deviation	4.225	3.047	5.543	8.43
Standard error	1.89	1.363	2.479	3.77
Lower 95% CI	31.88	32.19	11.02	17.9
Upper 95% CI	42.37	39.76	24.78	38.83
	Urea/albumin index, mmol/g			
Minimum	0.1226	0.1323	0.5841	0.06263
25% Percentile	0.1302	0.1368	0.6274	0.1172
Median	0.1464	0.1605	0.6714	0.1948
75% Percentile	0.1678	0.1822	1.037	0.2862
Maximum	0.1739	0.1895	1.293	0.362
Average value	0.1485	0.1597	0.8	0.2003
Standard deviation	0.02005	0.0235	0.2843	0.1073
Standard error	0.008966	0.01051	0.1271	0.04799
Lower 95% CI	0.1236	0.1305	0.4471	0.06711
Upper 95% CI	0.1734	0.1889	1.153	0.3336
	Glucose, mmol/l			
Minimum	4.291	4.295	5.812	4.394
25% Percentile	4.414	4.472	5.863	5.054
Median	4.995	4.974	7.267	6.565
75% Percentile	5.578	5.938	7.68	7.965
Maximum	5.897	6.093	7.966	8.218
Average value	4.996	5.159	6.87	6.52
Standard deviation	0.6302	0.7587	0.9577	1.539
Standard error	0.2818	0.3393	0.4283	0.6884
Lower 95% CI	4.213	4.217	5.681	4.609
Upper 95% CI	5.778	6.101	8.06	8.432

Table 1. (*contd*).

	LDH, Unit/l			
Minimum	377.2	397.1	647.7	624.4
25% Percentile	388.1	441.4	653	652.2
Median	445.3	496.8	807.6	794.9
75% Percentile	565.8	799.1	934.6	878.2
Maximum	578.5	979.5	944.1	919.9
Average value	470.6	595.6	796.5	771.1
Standard deviation	90.75	228.7	141.1	119.2
Standard error	40.59	102.3	63.11	53.29
Lower 95% CI	357.9	311.7	621.3	623.2
Upper 95% CI	583.3	879.5	971.8	919.1
	TBARP, μmol/l			
Minimum	1.82	1.59	3.78	1.78
25% Percentile	1.895	1.7	3.848	1.975
Median	1.98	2.16	4.05	2.3
75% Percentile	2.285	2.447	4.93	2.774
Maximum	2.39	2.49	5.18	2.967
Average value	2.068	2.091	4.321	2.359
Standard deviation	0.2208	0.3845	0.591	0.4452
Standard error	0.09876	0.1719	0.2643	0.1991
Lower 95% CI	1.794	1.613	3.587	1.807
Upper 95% CI	2.342	2.568	5.055	2.912
	Bityrosine, FUnit/l			
Minimum	34679	23618	67687	33807
25% Percentile	35376	28423	68831	36406
Median	40744	46559	82115	54578
75% Percentile	53023	68157	84078	73338
Maximum	53616	70725	84939	82353
Average value	43508	47944	77586	54813
Standard deviation	8981	20252	8096	19622
Standard error	4017	9057	3621	8775
Lower 95% CI	32356	22798	67533	30449
Upper 95% CI	54660	73089	87639	79177

Note. CI — confidence interval, FU — fluorescent units, TBARP — thiobarbiturate-reactive products of lipid peroxidation (including malondialdehyde).

in the second series. As opposed to expectations, animal treatment in thermostat enhanced the animal intoxication development probably due to exsicosis development and facilitated earlier death of mice. Thus, definite increase, compared with control groups of mice, in survival rate of animals exposed to „IR-Dipole“ significant reduction of renal damage, partial normalization of homeostasis variables in blood were obtained. The results are shown in Figure 2 and Table 1 and 2.

Conclusion

The results obtained for the first time indicate that animals who received acute intoxication with depleted uranium compounds experienced terminal renal insufficiency development and death within control time, and increased survival rate in mice by 50%. This data needs clarification and detailed elaboration in order to explain potential mechanisms of positive influence of terahertz radiation modulated in gigahertz band during future experiments.

It's safe to assume that remote consequences formed after therapy with antidot/chelating agent of toxic metals may be prevented by the proposed physiotherapeutic method. Comparison of exposure to „IR-Dipole“ with thermostat warming equivalent to exposure to the spectral band ($9-12\,\mu$m) has shown higher efficiency of terahertz broadband radiation band.

Future investigations and positive solution of the set problem will allow to meet many challenges in occupational health and national population health in case of nuclear power plant accodents.

Compliance with ethical standards

All animals were handled in accordance with animal welfare rules adopted by the European Convention for the Protection of Vertebrate Animals Used for Experimental

Table 2. Group comparison by Dunn criteria

Compared groups	Corrected value p
Urea, mmol/l	
Control THz and intact	> 0.9999
UAD and intact	0.0067
UAD + THz and intact	> 0.9999
UAD and control THz	0.0453
UAD + THz and control THz	> 0.9999
UAD + THz and UAD	0.2229
Albumin, g/l	
Control THz and intact	> 0.9999
UAD and intact	0.0166
UAD + THz and intact	0.5855
UAD and control THz	0.0278
UAD + THz and control THz	0.8073
UAD + THz and UAD	> 0.9999
Urea/albumin index, mmol/g	
Control THz and intact	> 0.9999
UAD and intact	0.0081
UAD + THz and intact	> 0.9999
UAD and control THz	0.0328
UAD + THz and control THz	> 0.9999
UAD + THz and UAD	0.2537
Glucose, mmol/l	
Control THz and intact	> 0.9999
UAD and intact	0.0936
UAD + THz and intact	0.389
UAD + THz and control THz	0.6727
UAD + THz and UAD	> 0.9999
Control THz and intact	> 0.9999
LDH, Unit/l	
Control THz and intact	> 0.9999
UAD and intact	0.0328
UAD + THz and intact	0.0722
UAD and control THz	0.4668
UAD + THz and control THz	0.8073
UAD + THz and UAD	> 0.9999
TBARP, μmol/l	
Control THz and intact	> 0.9999
UAD and intact	0.0198
UAD + THz and intact	> 0.9999
UAD and control THz	0.0235
UAD + THz and control THz	> 0.9999
UAD + THz and UAD	0.1708
Bityrosine, FUnit/l	
Control THz and intact	> 0.9999
UAD and intact	0.0453
UAD + THz and intact	> 0.9999
UAD and control THz	0.0972
UAD + THz and control THz	> 0.9999
UAD + THz and UAD	0.3686

Note: FU —fluorescent units; UAD — uranyl acetate dihydrate, TBA-RP — thiobarbiturate-reactive products of lipid peroxidation (including malondialdehyde).

and Other Scientific Purposes (Strasbourg, 1986), animal care conditions were in accordance with GOST 33215-2014 „Guidelines for accommodation and care of animals. Environment, housing and management. " and „Directive 2010/63/EU of the European Parliament and European Council on the protection of animals used for scientific purposes" (Rus-LASA, Saint Petersburg, 2012. 48 p). This paper did not doubled any previous research. The number and composition of animals used in the experiments were required and ensured statistical reliability of the research.

Conflict of interest

The authors declare that they have no conflict of interest.

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