SYNERGISTIC INTERACTION OF ENVIRONMENTAL TEMPERATURE AND MICROWAVES: PREDICTION AND OPTIMIZATION

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A simple mathematical model of simultaneous combined action of environmental agents has been proposed to describe the synergistic interaction of microwave and high ambient temperature treatment on animal heating. The model suggests that the synergism is caused by the additional effective damage arising from an interaction of sublesions induced by each agent. These sublesions are considered to be ineffective if each agent is taken individually. The additional damage results in a higher body temperature increment when compared with that expected for an independent action of each agent. The model was adjusted to describe the synergistic interaction, to determine its greatest value and the condition under which it can be achieved. The prediction of the model was shown to be consistent with experimental data on rabbit heating. The model appears to be appropriate and the conclusions are valid.

Keywords: Mathematical Model, Optimization, Microwave; Hyperthermia; Synergistic Interaction; Rabbit; Body Temperature

1. INTRODUCTION

It was found that an ambient temperature had a profound effect on the thermoregulatory responses of various animals [1–6] and men [7,8] exposed to microwaves. In these experiments, the ambient temperature either exerts a microwave action or both these agents can interact with each other in a synergistic manner. However, none of these papers enables us to optimize the synergistic interaction and demonstrate the existence of the greatest synergistic effect. In our previous paper [9] an extensive number of experimental data have been published for rabbit heating simultaneously exposed to microwave radiation and high ambient temperatures. As mentioned in the paper, the widespread use of radio-frequency electromagnetic radiation (RFR) has greatly increased the possibility of exposure of both occupational and general population to RFR combined with various environmental factors including a higher ambient temperature. The interaction of these agents is of important from theoretical and practical perspectives [9]

It was shown that a number of general features of the synergistic interaction revealed with unicellular organisms [10–14] are also expressed for animals exposed to microwaves at a higher environmental temperature. A new concept of the synergistic interaction and a simple mathematical model based on this conception has been suggested to predict and optimize the synergy when hyperthermia was simultaneously applied together with ionizing radiation, ultrasound, ultraviolet light and some chemical agents [15–18]. The model suggests that a synergism is expected from some additional effective damage arising from the interaction of the sublesions induced by both agents. These sublesions are considered as ineffective when each agent is used individually. The model predicts the dependency of the synergistic interaction on the ratio of the effective damages produced by each agent applied as well as the greatest value of the synergy and the conditions under which it can be achieved. As the model was not based on a particular nature of effective damage or sublesions responsible for the synergy and the mechanism of their interaction was not elucidated, it would be of interest to adopt this model for a description, optimization and prognosis of the synergistic effects between microwave and an ambient temperature on rabbit heating. Therefore, this study, as a succeeding work of our previous paper [9], was designed to implement the following purposes: (a) to adopt a mathematical model to describe the synergistic interaction between microwaves and high ambient temperature; (b) to test the validity of the proposed model for rabbit heating.

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2. MATHEMATICAL MODEL

The availability of a number of common features of synergistic effect display [9–14] indicates the existence of a certain general idea regarding the mechanism of synergistic interaction, which would not be dependent of the object, biological test and agents applied. It is assumed that thermal radiosensitization may be displayed by the inhibition of the repair of sublethal and potentially lethal damages on a cellular level for mammalian [19, 20] and yeast cells [13, 21]. These data indicate that the mechanism of synergistic interaction of heat and ionizing radiation may involve the inhibition of cell capacity to recover damage resulted from the combined action of both modalities. It was shown that the synergistic interaction of heat and ionizing radiation is not related to the impairment or damage of the recovery capacity *per se* but to the production of irreversible damages, which cannot be repaired [13, 22]. Similar results have been observed for yeast cell simultaneously exposed to UV light and hyperthermia [23]. As the synergistic effects are not related with the direct damage of recovery process itself, it is not excluded that synergism would be expected to result from some additional lethal lesions arising from the interaction of sublesions induced by both modalities. Then such an interaction can be considered as an alternative explanatory mechanism of production of irreversible damages. This hypothesis was put forward and applied by many authors [15–18, 24–26]. Therefore, it is of interest to apply such a hypothesis for the description of synergistic interaction of environmental temperature and microwaves.

Let N_1 and N_2 be the yield of some hypothetical effective damage produced by microwaves and ambient temperature, respectively, which resulted in an increase of the rectal temperature. The synergistic interaction takes place when the combined action of two agents exceeds the sum of their individual effects. With the use of this definition, it might be reasonable to assume that some additional effective damage has arisen during the simultaneous action of these modalities. The model suggests that the additional damage may be formed due to the interaction of some sublesions induced by both agents. These sublesions are supposed to be ineffective after each agent is applied separately. We believe here that the effective damage resulting in the rabbit heating and the sublesions responsible for the synergy can be presented by real molecular damage as well as by a disturbance of a regulator mechanism which can be estimated quantitatively. Let p_1 and p_2 be the mean numbers of the sublesions that arise for one effective damage induced by microwaves and an ambient temperature, respectively. Then the whole number of the effective damage N_Σ may be given as

$$N_\Sigma = N_1 + N_2 + N_3, \tag{1}$$

where N_3 is the yield of an additional effective damage responsible for the synergism. As soon as the nature of an effective damage and sublesions can not be established at this stage, for simplicity sake, we suggest that one sublesion induced by microwaves interacts with one sublesion from an ambient temperature to produce an additional effective damage and the number of sublesions is directly proportional to the number of effective damage. In accordance with these suggestions, it can be written that

$$N_3 = \min\{p_1 N_1; p_2 N_2\}. \tag{2}$$

This equation shows that the amount of additional damage is determined by the minimal value of the sublesions produced by the modalities analyzed. Then the synergistic enhancement ratio k can be defined as the ratio of the effective damage produced after a combined action to the sum of damage produced by each agent applied separately, i.e.

$$k = \frac{N_1 + N_2 + N_3}{N_1 + N_2}. \tag{3}$$

Taking into account Eqs. 2 and 3, one can write

$$k = \frac{N_1 + N_2 + \min\{p_1 N_1; p_2 N_2\}}{N_1 + N_2} \tag{4}$$

or, after some mathematical simplification, we have

$$k = 1 + \frac{\min\{p_1; p_2 N_2 / N_1\}}{1 + N_2 / N_1}. \tag{5}$$

The last equation shows that the synergistic enhancement ratio should increase first with N_2/N_1, and then reach a maximum, which should be followed by a decrease. It means that for a constant ambient temperature there an optimal power flux density for maximizing the synergy should exist. Besides, Eq. 5 shows that for any fixed values of p_1 and p_2, the synergism depends only on the ratio N_2/N_1, which is the ratio of the effective damage produced by each of the acting agents applied alone. We can believe that within a certain exposure time, where the temperature increment is linearly related to the duration of an exposure, N_1 should be in direct proportion to an increment of the rectal temperature $\Delta T(RFR + 22℃)$ induced by microwaves only and N_2 should be in direct proportion to the corresponding value of $\Delta T(30℃)$ induced by an ambient temperature only. If this is the case, we can write

$$\frac{N_2}{N_1} = \frac{\Delta T(30^o C)}{\Delta T(RFR + 22^o C)} = \frac{dT/dt(30^o C)}{dT/dt(RFR + 22^o C)}. \tag{6}$$

It means that the ratio N_2/N_1 can be estimated by the ratio of a rabbit heating rate induced by an ambient temperature to that produced by microwaves.

If the number of sublesions from microwaves is less or equal to the number of sublesions induced by an ambient temperature, i.e. $p_1N_1 \le p_2N_2$, then k (Eq. 5) may be expressed as

$$k_1 = 1 + \frac{p_1}{1 + \dfrac{dT/dt(30^o C)}{dT/dt(RFR + 22^o C)}}. \quad (7)$$

From here, parameter p_1 may be represented by

$$p_1 = (k_1 - 1)\left(1 + \frac{dT/dt(30^o C)}{dT/dt(RFR + 22^o C)}\right). \quad (8)$$

In contrast, if $p_2 N_2 \le p_1 N_1$, then k (Eq. 6) may be expressed as

$$k_2 = 1 + \frac{p_2 \dfrac{dT/dt(30^o C)}{dT/dt(RFR + 22^o C)}}{1 + \dfrac{dT/dt(RFR + 22^o C)}{dT/dt(30^o C)}}. \quad (9)$$

From here, parameter p_2 may be represented by

$$p_2 = (k_2 - 1)\left(1 + \frac{dT/dt(RFR + 22^o C)}{dT/dt(30^o C)}\right). \quad (10)$$

A curious feature of Eqs. 5, 6-10 is that they do not include an absolute amount of the damage produced by microwaves (N_1) and an ambient temperature (N_2) which would not be evaluated directly but only their ratio N_2/N_1 that can be, under the suggestion made here, found using Eq. 6.

It can be easily shown mathematically that under the condition

$$N_2 / N_1 = p_1 / p_2 \quad (11)$$

the highest synergistic effect will be observed which is given by

$$k_{\max} = 1 + \frac{p_1 p_2}{p_1 + p_2}. \quad (12)$$

One can see that the highest synergistic effect doesn't depend on the ratio of N_2 / N_1 and is determined only through the free parameters of the model p_1 and p_2. By knowing experimental values of k_1 and k_2, obtained from two experiments which satisfy the requirements of Eq. 7 and Eq. 9, one can estimate the basic model parameters p_1 and p_2 using Eq. 8 and Eq. 10, respectively. Then using Eq. 5 one can predict the k values for any N_2 / N_1 ratio, the highest synergy (Eq. 12) and condition (Eq. 11) at which it can be achieved. Eq. 11 can be rewritten as

$$p_1 N_1 = p_2 N_2. \quad (13)$$

This equation means that the highest synergy should be expected when an identical number of sublesions is produced by both agents used in combination. It is of interest that the dependency of the synergy on the power flux density follows from Eq. 13. Indeed, let Eq. 13 holds for some flux power density and ambient temperature. Then for any higher ambient temperature a smaller time is needed to obtain N_2 which results in a smaller value of N_1. Then to preserve Eq. 13 one must increase N_1 which can be done only by an increase in the power flux density. Analogously, the whole relationship between the synergy and the power flux density should be shifted to higher intensities with an increase in the ambient temperature.

Thus, the considered model predicts the following non-trivial results. First, for every constant ambient temperature, the synergy should be observed only within a certain range of the power flux density that could be different for various biological objects and test effects. Second, within this range, there is a specific power flux density that maximizes the synergistic effect. Any deviation of microwave intensity from the optimal one would result in a reduction in the synergy. Third, the relationship between the synergy and the power flux density should be shifted to higher intensities with an increase in the ambient temperature. It is curiously that quite such rules have been described in our previous paper [9]. So our next purpose is to apply this model to experimental results.

3. THE VALIDITY OF THE MODEL

Taking into consideration the results published in our previous paper [9], we estimated rabbit heating rates for different conditions of exposure to microwaves and ambient temperatures (22 and 30°C). Under conditions of experiment, the first temperature (22°C) was the room temperature. We used ambient temperature of 30°C because of two thoughts [9]: first of all, this temperature may exist at a working place of microwave equipments; secondly, in accordance with literature [3,4], it is an upper limit of relatively comfort temperature both for rabbit and slightly-dressed man. It is worth to add that rabbits used in this study were Shinella rabbits with body masses of 2.5 to 3.2 kg both males and females at an age of 60 days. They were housed individually at an ambient temperature of 22°C, with a relative humidity of 50% under natural lighting. Rabbit chow and water were provided *ad libitum*. Animals were pre-handled and gentled for 10 days prior to exposure.

Table 1 summarizes the following parameters: power flux density and the corresponding specific absorption rate, hating rates (*dT/dt*) at 22, 30 and 38°C, N_2/N_1 ratio calculated by Eq. 6 and the experimental values of the synergistic enhancement ratio (k). The last values have been already published [9]. It is evident that the increase in the ambient temperature from 20°C either to 30°C or 38°C in most cases would greatly enhance the rabbit heating because of rabbit's reduced ability to dissipate the heat accrued from RFR exposure.

Table 1. Heating Rate (*dT/dt*) and Synergistic Enhancement Ratio (*k*) after Different Conditions of Rabbit Exposure.

Power flux density, mW/cm^2	Specific absorption rate, W/kg	*dT/dt* RFR at 22 °C, °C/hr	*dT/dt* RFR at 30 °C, °C/hr	*dT/dt* RFR at 38C °C, °C/hr	N_2 / N_1	Synergistic enhancement ratio, *k*	
						experiment	theory
0	0	0	0.067	0.7	–	–	-
10	0.75	0.033	0.6	-	2.0	6.0	6.0
15	1.12	0.067	1.1	-	1.0	8.2	8.8
20	1.5	0.23	1.7	-	0.61	12.1	10.8
30	2.25	0.74	3.3	-	0.09	4.1	4.1
100	7.5	6.9	7.6	-	0.01	1.1	1.2
100	7.5	-	-	14.4	0.1	1.9	-

Theoretically expected values of the synergistic enhancement ratio are inserted in Table 1 and presented by solid line in Fig. 1, where the synergistic enhancement ratio k of a simultaneous action of microwaves and a high ambient temperature (30°C) is shown as a function of the ratio N_2 / N_1 for rabbits heating. One can see that the theoretically predicted interaction (solid line), calculated by means of Eq. 5, corresponds fairly well with the experimental data (circles). The solid lines were calculated with the following values for the basic model parameters: p_1 = 15,5, p_2 = 37. This set of parameters was obtained from a real experimental value of the synergistic effect for the power flux densities of 10 and 30 mW·cm^{-2} and the corresponding Equations (8 and 10). It can be inferred that the synergy occurred only within a definite ratio of the effects (N_2 / N_1) produced by each agent. It is also apparent that there is an optimal ratio of N_2 / N_1 which results in the greatest synergistic interaction. It follows from the model that the highest synergistic effect, k_{max} = 12, should be expected (Eq. 12) under N_2 / N_1 = 0.42 (Eq. 11). Fig. 1 demonstrates that a good agreement exists between these predicted values and the experimental data. It means that the model presented here can be used to predict and optimize the synergistic effect between radio-frequency electromagnetic radiation and an environmental temperature for rabbit heating. Thus, the first and the second consequences of the model hold fairly well.

To test the third conclusion indicating that the relationship between the synergy and the power flux density should be shifted to higher intensities with an increase in the ambient temperature, a change in the rectal temperature exhibited by rabbits exposed to RFR at 100 mW·cm^{-2} and 38°C was measured. As can be seen (Table 1), for this power flux density there was only a negligible difference in the efficiency of rabbit heating both at the comfort (22°C) and higher temperature (30°C): the synergistic enhancement ratio k = 1.1. Microwave exposure of rabbits at an ambient temperature of 38°C was more effective. As was estimated, the heating rate was 0.7 and 14.4°C·hr^{-1} when animals were exposed to the high temperature alone (38°C) and combined with microwaves at an exposure intensity of 100 mW·cm^{-2}. For this particular case, it might also be thought that the first value is proportional to N_2, while the second one – to the sum of ($N_1 + N_2 + N_3$). It

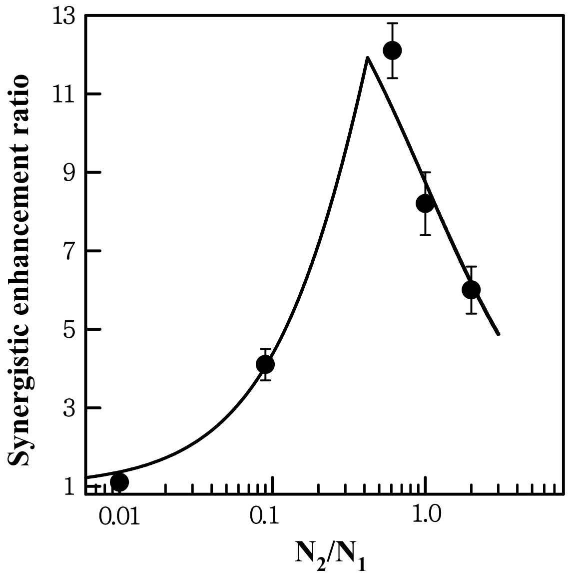

Fig. 1. The experimental (solid circles) and theoretical (solid lines) dependencies of the synergistic enhancement ratio of a simultaneous action of microwaves (7 GHz) and high ambient temperature (30°C) on the ratio of N_2/N_1 for rabbits heating.

gives N_2/N_1= 0.1 (Eq. 6) and k = 1.9 (Eq. 5).

Fig. 2 qualitatively demonstrates the relationships between the synergistic enhancement ratio and the power flux density after a simultaneous action of microwave exposure and an ambient temperatures (30°C, curve 1), and 38°C (curve 2) for rabbit heating. The only experimental point obtained for rabbits exposed to an exposure intensity of 100 mW·cm^{-2} and an ambient temperature of 38°C, shows that the synergistic enhancement ratio was increased for these conditions of irradiation. It was shown that a further investigation of the synergy for lower intensities of the microwaves delivered at 38°C was difficult because the animals did not sustain this high environmental temperature for a long time [9].

The increase in the ambient temperature from 30 to 38°C led to a 10.5-fold increase in the heating rate caused by these temperatures (0.067 and 0.7°C·hr^{-1}, respectively). At an ambient temperature of 30°C the greatest synergy was observed at 20 mW·cm^{-2}, when the heating rate due to microwaves only (exposure at 22°C) was 0.23°C·hr^{-1}.

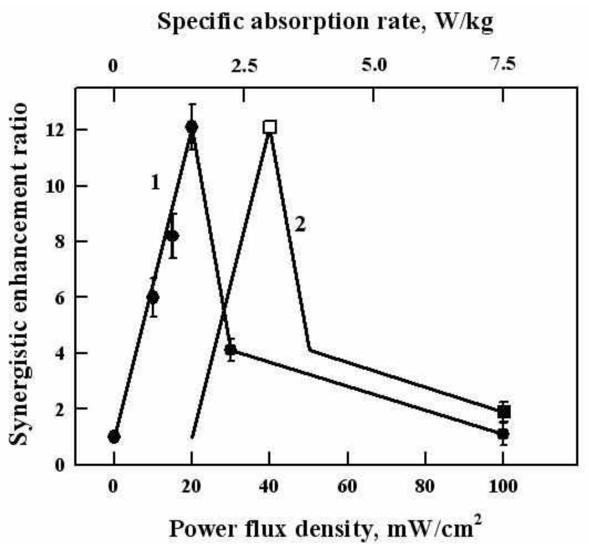

Fig. 2. The relationships between the synergistic enhancement ratio and the power flux density after a simultaneous action of microwave exposure and ambient temperatures (30°C, curve 1), and 38°C (curve 2) for rabbit heating.

Assuming the basic parameters of the model could be unchanged and taking into account Eqn. 11, one can conclude that to keep the same greatest synergistic effect (k = 12.1) observed in the experiments we must provide a 10.5-fold increase in the amount of damage produced by RFR alone, i.e. heating rate should be 2.4°C·hr^{-1}. The data presented in Table 1 shows that this heating rate due to microwaves alone could be observed at about 40 mW·cm^{-2}. It is evident that the results obtained are in accordance to the third consequence from the model indicating that the relationship between the synergy and the power flux density should shifted to higher intensities with an increase in the ambient temperature.

4. DISCUSSION

The data presented here revealed that for a constant ambient temperature the effectiveness of the synergistic interaction of microwaves and a high ambient temperature is observed only inside a certain range of the power flux density. Moreover, within this range an optimal value exists, at which the synergy is the highest one. Both an increase and decrease in the power flux density from this optimal value resulted in a decrease of the synergistic effect. Qualitatively similar results have been observed for the synergy expression for spores radiosterilization [27], bacteriophage killing [28], somatic mutations in *Tradescantia* [29], and yeast cell inactivation [30, 10–12]. To describe this data, a simple model has been suggested to predict and optimize the synergy when hyperthermia is simultaneously applied together with ionizing radiation, ultrasound, ultraviolet light and some chemical agents [15–18]. As the model was not based on the particular nature of both damage and sublesion and the mechanism of an interaction between the sublesions was not defined for certain, in this paper we accommodated this model for the description, optimization and prognosis of the synergistic effects between an ambient temperature and RFR for rabbit heating. The model suggests that the synergism is expected from some additional effective damage resulting in an additional rabbit heating and arising from the interaction of the sublesions induced by both an ambient temperature and microwaves. These sublesions are considered as ineffective after each of these agents is taken alone. The model is not concerned with the nature both of the effective damage and the sublesions and also the mechanism of their interaction is not elucidated.

In the proposed model, the synergistic interaction is given by $\min\{p_1N_1 ; p_2N_2\}$. This means that one sublesion caused by microwaves interacts with one sublesion produced by an ambient temperature. This process is assumed to proceed until the very last sublesion of the less frequent type is used up. However, it does not mean that the model requires some kind of unreal long-range interaction. To estimate the basic parameters of p_1 and p_2 we have used the experimental value of the synergistic enhancement ratio of k_1 and k_2 (Eq. 8 and 10). It means that the model takes into consideration only the actual interaction determining the synergistic effect. The model appears to be appropriate and the predictions are valid. Indeed, it was shown that the model describes the experimental data for rabbit heating, predicts the greatest value of the synergistic effect, the condition under which it can be achieved as well as the dependency of the synergy on microwave power flux density and ambient temperature. From the model standpoint, the highest synergy can be obtained for a specific power flux density at which an equal number of sublesions are produced by each of the agents applied in combination. Any deviation of the microwave intensity from the optimal one resulted in a reduction in the synergy due to a violation of this rule. The increase of the synergy with an increase in the ratio of N_2 / N_1 before the maximum of the synergy has been achieved (Fig. 1) can be explained by an increase in a number of both the effective damages and the sublesions produced by an ambient temperature. Conversely, the fall of the synergistic effect after the maximum of the synergy has already been achieved can be explained by a decrease in the amount of the effective damages and the sublesions produced by the microwaves. Then it can be expected that the greatest synergy would be obtained when an equal number of sublesions are produced by an ambient temperature and microwaves.

In accordance with the considered model the relationship between the synergy and the power flux density should be shifted to higher intensities with an increase in the ambient temperature and *vice versa*. Unfortunately, this prediction could only be tested for rabbit heating only at one experimental condition. Nevertheless, the results obtained here are in a qualitative agreement with the model prognosis and would be, in principle, useful for further solution of the problems related with synergistic interaction of environmental agents.

In conclusion, the widespread and increasing use of RFR has greatly increased the possibility of an exposure of both an occupational and general population to RFR combined with various environmental factors including a higher ambient temperature. The presented mathematical model, predicting the effectiveness of the interaction of microwaves and an ambient temperature, is of important from theoretical and practical perspectives. First is the concept of the interaction to describe and predict the synergistic effect. Second is the concern for an evaluation of a potentially increased health risk to the general public and occupationally exposed population. And third, as these agents are being explored for a cancer treatment, there is a possibility to optimize the acting agents to provide the greatest synergistic effect.

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REFERENCES

1. Michaelson SM. Thermal effects of single and repeated exposures to microwaves – a review. In: Czerski P, Ostrowski K, Shore ML, Silverman Ch, Suess VJ, Waldeskog B, eds. Biological Effects and Health Hazards of Microwave Radiation. Polish Medical Publishers, Warsaw, 1974:1-14.
2. Nikonova KV, Sokolova IP. The characteristics of biologic effects of microwaves combined with the action of soft X-ray irradiation and heat. In: Czerski P, Ostrowski K, Shore ML, Silverman Ch, Suess VJ, Waldeskog B, eds. Biologic Effects and Health Hazards of Microwave Radiation. Polish Medical Publishers, Warsaw, 1974:58-66.
3. Michaelson SM. Thermoregulation in intense microwave fields. In: Adair ER, ed. Microwaves and Thermoregulation. New York: Academic Press, 1983:283-295.
4. Gordon CJ, Long MD, Fehlner KS. Temperature regulation in the unrestrained rabbit during exposure to 600 MHz radiofrequency radiation. Int. J. Radiat. Biol. 1986; 49(6):987-997.
5. Gordon CJ, Long MD, Fehlner RS, Stead AG. Temperature regulation in the mouse and hamster exposed to microwaves in hot environments. Health Phys. 1986; 50(6):781-787.
6. Gordon CJ, Ali JS. Comparative thermoregulatory response to passive heat loading by exposure to radiofrequency radiation. Comp. Biochem. Physiol. 1987; 88(1):107-112.
7. Adair ER, Cobb BL., Mylacraine KS, Kelleher SA. Human exposure at two radio frequencies (450 and 2450 MHz): similarities and differences in physiological response. Bioelectromagnetics 1999; 20(Suppl. 4):12-20.
8. Adair ER, Mylacraine KS, Cobb BL. Partial-body exposure of human volunteers to 2450 MHz pulsed or CW fields provokes similar thermoregulatory responses. Bioelectromagnetics 2001; 22(4):246–259.
9. Kolganova OI, Zhavoronkov LP, Petin VG, Kim JK. Rabbit heating by microwave exposure at various ambient temperature. J. Radiat. Prot. 2010; 35(3):100-105.
10. Petin VG, Komarov VP. Quantitative Description of Radiosensitivity Modification. Moscow: Energoatomizdat, 1989.
11. Kim JK, Petin VG, Zhurakovskaya GP. Exposure rate as a determinant of synergistic interaction of heat combined with ionizing or ultraviolet radiations in cell killing. J. Radiat. Res. 2001; 42(4):361-365.
12. Petin VG, Kim JK, Zhurakovskaya GP, Dergacheva IP. Some general regularities of synergistic interaction of hyperthermia with various physical and chemical inactivating agents. Int. J. Hyperther. 2002; 181(1):40-49.
13. Petin VG, Kim JK. Survival and recovery of yeast cells after combined treatments with ionizing radiation and heat. Radiat. Res. 2004; 161(1):56-63.
14. Petin VG, Zhurakovskaya GP, Kim JK. Synergetic effects of different pollutants and equidosimetry. In: Bréchignac F, Desmet G, eds. Equidosimetry – Ecological Standardization and Equidosimetry for Radioecology and Environmental Ecology. Springer, 2005:207-222.
15. Petin VG, Komarov VP. Mathematical description of synergistic interaction of hyperthermia and ionizing radiation. Mathem. Biosci. 1997; 146(2):115-130.
16. Petin VG, Dergacheva IP, Romanenko AG, Ryabova SV. A new concept of optimization and prediction of synergism effects during the combined action of chemical and physical factors of the environment. Mendeleev Chemistry J. 1997; 41(3):129-140.
17. Petin VG, Zhurakovskaya GP, Komarova LN. Mathematical description of combined action of ultrasound and hyperthermia on yeast cells. Ultrasonics 1999; 37(1):79-83.
18. Petin VG, Kim JK, Zhurakovskaya GP, Rassokhina AV. Mathematical description of synergistic interaction of UV light and hyperthermia for yeast cells. J. Photochem. Photobiol. B: Biol. 2000; 55(1):74-79.
19. Ben-Hur E, Elkind MM, Bronk BV. Thermally enhanced radioresponse of cultured Chinese hamster cells: inhibition of repair of sublethal damage and enhancement of lethal damage. Radiat. Res. 1974; 58(1):38-51.
20. Raaphorst GP. Azzam EI, Feeley M. Potentially lethal radiation damage repair and its inhibition by hyperthermia in normal hamster cells, mouse cells, and transformed mouse cells. Radiat. Res. 1988; 113(1):171-182.
21. Petin VG, Berdnikova IP. Responses of yeast cells to

heat applied alone or combined with gamma-rays. Int. J. Radiat. Biol. 1981; 39(3):281-290.
22. Kim jk, Tkhabisimova MD, Petin VG. Estimation of recovery parameters for mammalian cells after combined action of different modalities. In: *Proceeding of the Korean Association on Radiation Protection*, Daejeon, Korea, 2003, pp. 263-267.
23. Tkhabisimova MD, Komarova LN, Petin VG. Dark recovery of diploid yeast cells after simultaneous exposure to UV-irradiation and hyperthermia. Cytology 2002; 44(6):555-559.
24. Murthy SS, Deorukhakar VV, Rao BS. Hyperthermic inactivation of diploid yeast and the interaction of damage caused by hyperthermia and ionizing radiation. Int. J. Radiat. Biol. 1979; 35(4):333-341.
25. Leenhouts HP, Chadwick KH. An analysis of synergistic sensitization. Brit. J. Cancer 1978; 37(Suppl.III): 198-201.
26. Zaider M, Rossi H.H. The synergistic effects of different radiations. Radiat. Res. 1980; 83(3):732-739.
27. Reynolds MC, Garst DM. Optimizing thermal and radiation effects for bacterial inactivation. Space Life Sci. 1970; 2(3):394-399.
28. Trujillo R, Dugan VL. Synergistic inactivation of viruses by heat and ionizing radiation. Biophys. J. 1972; 12(1):92-113.
29. Leenhouts HP, Sijsma MJ, Cebulska-Wasilewska A, Chadwick KH. The combined effect of DBE and X-rays on the induction of somatic mutations in *Tradescantia*. Int. J. Radiat. Biol. 1986; 49(1):109-119.
30. Petin VG, Zhurakovskaya GP. The peculiarities of the interaction of radiation and hyperthermia in *Saccharomyces cerevisiae* irradiated with various dose rates. Yeast 1995; 11(6):549-554.