PREFACE

Living organisms are exposed to numerous natural and man-made agents that can interact with each other in a synergistic manner when the biological effect is greater than the sum of the effects from separate exposures to the individual agents. Because of the worldwide expansion of damaging chemical and physical agents, a large body of diseases and even aging are thought to stem from combined action of various deleterious agents. Safety standard assessment generally performed with the simplifying assumption that the agents under consideration act mainly independently on each other. For practical applications in risk analysis, deviation from simple summation of biological effect is virtually expected not very large, the synergistic interaction being expected for acute exposures. However, this problem has not been studied in sufficient detail. Therefore it is of great interest to investigate whether or not the synergistic interaction can take place at low intensities of inactivating and/or mutagenic factors. Since such experiments are very difficult to perform at the real intensities observed in the biosphere, a feasible approach to this problem is to analyze the dependence of the synergistic interaction on the intensity of the agents applied. Several hypothetical possibilities may be realized in principle. If the level of synergism is reduced progressively with a decrease in the intensity of physical factors or concentration of chemical agents, it would mean that the synergistic interaction will hardly be of any importance at low exposure intensity. This conclusion would be also true for the case when a decrease in the intensity of one agent should be accompanied by the increased intensity of another factor to provide the same level of the synergism. The only possibility important for the problem of low doses and intensities safety is the case when a decrease in the intensity of one agent must be accompanied by a decrease in the intensity of another factor used in combination to provide the same level of synergism. This problem has been investigated carefully in our work.

Original data on synergistic effects and cell responses to environmental factors are published. The data will provide some general view regarding the mechanism of synergistic interaction after combined exposures. Before presentation of these data, it is of interest to expound our probability model of cell responses to ionizing radiation that, in fact, combines hit and target model with biological stochastic and predicts the retention of some sublesions in cells surviving after irradiation. We shall use the sublesion idea in our further mathematical modeling of synergistic interaction. Since many authors attribute the mechanism of synergistic interaction with cell recovery inhibition, the relationship of some radiobiological effects with the ability of cells to recover from radiation damage is considered. There are only few papers on the RBE of densely ionizing particles for yeast cells with different capabilities of recovery. Thereby we are going to present a lot of our new data regarding this problem. In particular, we present the data indicating that the recovery processes are not impair after high-LET radiation and the RBE are mainly due to the formation of irreversible damage.

Numerous data are known for the simplest cell objects, which indicate that mechanism of chemical radioprotectors, oxygen and hypoxic cell sensitizers may involve cellular recovery processes. These findings could contribute to the analysis of participation of recovery processes in synergistic effects display. However, similar data for eukaryotic cells are almost missing. New experimental data and theoretical calculations indicating the possible interaction of ionization and excitation of molecules due to Čerenkov emission after ionizing radiation alone are also presented.

Thus, the objective of this Monograph is to develop a unifying conception and mathematical model of synergy, which would not depend on interactive agents, biological objects and tests. The model will predict a number of general rules of interaction, the condition under which the highest synergy can be achieved, its value, and the dependence of synergy on the intensity of the agents applied. Validation of the model will be verified for various physical and chemical factors, biological objects and end points. To achieve this objective, the following subjects are considered.

1. Cell responses to low- and high-LET exposure: the recent peculiarities.
2. Novel direction in study of radioprotecting and radiosensitizing action of chemical compounds.
3. Quantitative regularities of combined action of various agents.
4. Clue for understanding the mechanism involved in synergistic effects.
5. The mathematical approach for synergistic effect: prognosis and optimization.
6. Quantitative prognosis of synergistic effects and recovery for various biological objects.
7. Synergistic effects display for cultured mammalian cells, animals and humans.

We hope the Monograph will be useful for professionals in the fields of radiation biology, medicine, ecology, mathematical biosciences, synergetic, environmental protection, space flights and for students interested in the problems of synergy.

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