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Further Research into the Effect of Ionizing  
Radiation Combined with G-loading during Space Flight

by

V. V. Antipov, B. I. Davydov,  
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In connection with systems design and application, and for protection of spacecrews against ionizing radiation, recent interest in research to establish the maximum possible exposure (MPE) for man has been on the upswing.

MPE is among the criteria dictating spacecraft design, mission programming, and the possible usage of antiradiation drugs, etc. Thus, the endeavor of radiobiologists to establish the MPE and to post a recommended maximum radiation level is understandable.

At the present time, some authors (G. M. Frank, P. P. Saksonov, V. V. Antipov, N. N. Dobrov, 1962; V. V. Antipov, N. N. Dobrov, P. P. Saksonov, 1964; Yu. G. Grigor'ev, Ye. Ye. Kovalev, A. V. Lebedinskiy, et al., 1965; et al.) propose various MPE's for spacecraft crews during brief and prolonged missions. Two very important concepts are emphasized in the recommendations appearing in the various papers in spite of their [quantitative] diversity. First of all, the recommended MPE should be derived as a function of the actual degree of exposure and duration of space mission. Secondly, it should be arrived at with a high degree of accuracy, a condition requiring specialized research. This latter factor is especially true concerning MPE during prolonged space missions.

The problem of deriving the MPE against the background of other spaceflight factors is seen in a new and unusual light. In deriving these maximums, certain considerations are necessary. During spaceflight, a complex of factors is at play, including radiation. Thus, primary considerations must be made taking into account the tolerance of the given irradiated organism to the various extreme stress factors accompanying spaceflight.

Along with studying the combined effect of ionizing radiation and other factors, work directed toward precise determination

of the individual types of cosmic radiation\* and toward the investigation of the long range effects of radiation is of great importance.

In a number of earlier articles (V. V. Antipov, V. G. Vysotskiy, B. I. Davydov, et al., 1963; V. V. Antipov, B. I. Davydov, E. F. Panchenkova, et al., 1964; V. V. Parin, V. V. Antipov, B. I. Davydov, E. F. Panchenkova, G. A. Chernov, 1964; V. V. Antipov, B. I. Davydov, E. F. Panchenkova, P. P. Saksonov, G. A. Chernov, 1965, et al.) we showed that flight dynamics can considerably alter the response of a given organism to ionizing radiation. Here, too, the direction and magnitude of these alterations is a function of the nature and intensity of the stimuli, their duration, and the continuity of the factors brought to bear, the type of subject on which they are brought to bear, etc. The significance of these factors in arriving at the MPE for cosmonauts is self-evident.

In this paper, material is revealed representing further development in our research into the responsiveness of an irradiated organism to various spaceflight factors. In particular, an attempt was made to evaluate the role of processes arising within the irradiated organism as it responds to "chronic" G-loading. Moreover, principles concerning the feasibility of extrapolating our experimental results to man are outlined as well as the manner in which orientational data was collected on the MPE as evaluated in the light of criteria for acceleration tolerance.

*Maximum possible exposure*

Twelve hundred white, male mice were used in the experiments without regard to lineage. The mice were administered either gamma or X-rays in doses of 150 to 4000 BER\*\* (15-18 r/min.)\*\*\*. Beginning on the first day and continuing for 45 days after irradiation, animals were subjected to 44 G's for three minutes (angular acceleration and deceleration 30-50 seconds). Equipment and methods are presented in more detail in other papers (B. I. Davydov, V. V. Antipov, P. P. Saksonov, 1965, 1967).

\*Translator's note: Reference here is to fine structure.

\*\*BER coefficient for gamma-rays is taken as 0.75 (S. P. Yarmonenko, A. G. Kenoplyanninov, 1965).

\*\*\*Tr. note: BER connotes B i o l o g i c a l l y e f f e c t i v e r o e n s .

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Let us turn now to presentation and discussion of the experimental findings.

Earlier (1956), Davydov was able to show that an animal's tolerance to G-loading (44 G's) of varying duration after irradiation was dependent upon dose and could be expressed by a hyperbolic function (Figure 1). In this figure, the function is graphed showing points used to designate the material from which the curve is derived. Figure 1 shows that the segment of the curve between  $1 < t < 9$  is of experimental significance. Subsequently, the curve was checked to insure its validity during more advanced periods of radiation sickness. Also, supplementary experimental data were collected on the tolerance [to G-loading] of an animal during the first days after irradiation. The upper limb of the curve in Figure 1 assumes that mice survived G-loading and 4,000 BER. With a certain degree of reliability, any point lying within the shaded portion of Figure 1 may be assumed to reflect tolerance of irradiated animals to G-loading greater than or equal to the tolerance of control animals thereto. For example, the tolerance to G-loading of animals receiving 2,000 and 4,000 BER the first day after irradiation is equal to that of the controls or somewhat higher. Research showed that the tolerance of irradiated animals is greater than that of nonirradiated animals: [coefficients of] 0.86 and 0.58 at 2,000 and 4,000 BER respectively.

After a second\* centrifugation, the mortality of irradiated animals was 50% at 2,000 BER and 70% at 4,000 BER. The average survival time of mice receiving 1500 to 15,000 BER averaged 3.5 days (B. Rayevskiy, 1959). At doses greater than 15,000 BER, the average survival time is seen to sink rapidly as irradiation is increased. Tolerance to G-loading in animals at  $t < 1$  (Figure 1) may be assumed to lie within the same range as that of the control animals at levels of 10,000 to 15,000 BER. As stated earlier, the curve in Figure 1 is derived from determinations of the threshold tolerance of animals to G-loading nine days after irradiation. The portion of the curve for  $t > 9$  days after irradiation was to be checked experimentally.

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\*Tr. note: literally "repeated".

Animals receiving 100, 200, and 350 BER were exposed to G-loading on the 45th day, and those receiving 300 and 500 BER on the 16th day after irradiation. Doses were arrived at where the effect in test animals was equal to that in control animals. Naturally, in determining the tolerable dose of radiation, certain assumptions were made concerning the relevance of linear relationship of the animals' responses to G-loading and concerning the magnitude of the dose administered per unit time during irradiation. The relevance of these factors has been shown to be more complex during intervals just after irradiation (B. I. Davydov, V. V. Antipov, P. S. Saksonov, 1965). On the 16th and 45th days after irradiation at 481 and 150 BER, the tolerance of the test animals to G-loading was on a par with that of the controls.

In this fashion, the experimental findings show the G-loading tolerance of mice to be dependent on the radiation dose they receive. This dependence may be expressed through a hyperbolic function:

$$Dt = 5 \times 10^5 \quad (1)$$

Where  $D$  = dose in BER's, and  $t$  = time in days after irradiation.

Analysis of the data collected showed that a functional relation exists between the response of irradiated animals to massive G-loading and repeated irradiation. Periods exist wherein the animals display lessened and [again] elevated sensitivity to G-loading and repeated irradiation. The period of increased tolerance to G-loading according to our data (a dose level of 250 to 500 BER), is equal to 8-9 days. The period of increased radio resistance (11 to 12 days) was determined through tests involving second radiation cycles. This period runs for about 12 to 15 days (I. G. Akoyev, M. A. Lagun, 1964) [sic].

A number of authors (S. N. Aleksandrov, K. F. Galkovskaya, 1963) have observed increased or normal resistance to strychnine, Novoembichin<sup>\*</sup>, and Ehrlich tumors even after 50 to 65 days following

<sup>\*</sup>Tr. note: Novoembichin (Babichin 7) is 2-Chloro-N:N-bis (2-chloroethyl)-propylamine hydrochloride used in therapy of lymphogranulomatosis, leukemias, erythremias and mycosis fungoides; Merck Index, 1960-738.

irradiation in mice. This contradicts the theory of Blair (H. Blair, 1962) concerning irreversible components of radiation sickness.

Contrary to Blair, our experimental data indicate that on the 45th day after irradiation, acceleration resistance is seen to decrease thus bearing witness to an irreversible component of radiation sickness.

An attempt was made to evaluate the tolerance of irradiated animals to repeated G-loading. This is of interest in arriving at a tolerable [radiation] dose during multiple G-loading exposures. Without doubt, each exposure alters the responsiveness of an animal, thus, it was of interest to determine how and in which direction an organism's responsiveness is altered after repeated exposure to one and the same factor. In this light, the repeated exposure to G-loading after a specific time period had elapsed since the first centrifugation was an index of responsiveness for those animals which survived.

The response of irradiated animals to repeated centrifugation may be assumed to be a function of the duration of radiation sickness.

If  $A_0^1$  and  $A_0^2$  are taken as percent mortality, and  $A_1^1$  and  $A_1^2$  are taken as percent mortality after the first and second centrifugations,

$$\frac{A_1^1}{A_0^1} = K_1$$

where  $K_1$  is an index of survival after the first centrifugation, and

$$\frac{A_1^2}{A_0^2} = K_2$$

where  $K_2$  is an index of survival after the second centrifugation. When  $K < 1$ , G-loading tolerance of irradiated animals is increased; when  $K > 1$ , it is decreased.

The curves traced in Figure 2 at a dose level of 250 to 500 BRR show the ratio  $K_1/K_2$  on different days after irradiation. This

information is carried over from Figure 1. Figure 2 shows that the ratio  $K_1/K_2 < 1$  on the fourth to seventh day after irradiation, i.e., the tolerance of irradiated animals to repeated G-loading, is lower than their resistance to the first exposure. In the remaining periods, however, the resistance of the irradiated animals to the second centrifugation was greater than to the first. At a dose level of 100 BER,  $K_1/K_2$  is almost equal to 1, therefore at a dose level of 100 BER test animals may be assumed to respond to a second centrifugation in much the same way as control animals.

Moreover, we arrived at a MPE for animals rotated twice in the centrifuge. The findings are represented by small triangles in Figure 1. This figure shows that the MPE is less for two runs than for a single run in the centrifuge. At  $t \geq 5$  days, the tolerance of irradiated animals to a second G-loading may be approximately expressed by the function:

$$D = D_0 e^{-\alpha t}$$

where  $D$  = dose in BER,  $D_0$  = initial dose in roentgens,  $t$  = time in days after irradiation,  $\alpha$  is a coefficient, and  $e$  is the natural logarithm base. Employing the method of least squares, an equation was obtained for the regression:

$$\lg D = 2.993 - 0.065 \times t \times \lg e \quad (2)$$

where  $t \geq 5$ .

We shall now attempt to apply our experimental findings to man by extrapolation.

Earlier, we (B. I. Davydov, V. V. Antipov, P. P. Saksonov, 1965) made an attempt to determine the period required for "half-recovery"\* of normal response to G-loading by comparing curves expressing the relation of response of mice to their acceleration tolerance and to leukocyte depression after  $LD_{50}$  irradiation of man and other animals.

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\*Tr. note: The inference here is probably to a statistical method similar to determining the half-life of a radioisotope.

The duration required for "half-recovery" of radioresistance was arrived at by evaluating response to a second radiation exposure and the resistance of mice to massive G-loading. The values obtained show only slight variance, averaging approximately five days at LD<sub>50</sub> (B. I. Davydov, V. V. Antipov, P. P. Saksonov, 1965). The period for "half-recovery" in man is about 25 to 35 days, a value in close agreement with that arrived at by other authors using different methods (G. O. Davidson, 1960).

Notably, the period of half-recovery as arrived at after evaluating the effect of multiple radiation exposures equals only the half-period of decreased sensitivity of irradiated animals to critical G-loading.

Before deriving a curve showing man's tolerance to massive G-loading at various levels of radiation, the selection of corresponding criteria for the derivation of extrapolated coefficients is essential. Among the criteria from which an extrapolating coefficient may be derived is the diverse radiosensitivity of animals and man. LD<sub>50/30-60</sub> irradiation yielded a coefficient of radiosensitivity of mice/man (based on incidence of mortality) equal on the average to 1.35 at a probable mortality of 0.1--95%.

In our earlier experiments (B. I. Davydov, V. V. Antipov, P. P. Saksonov, 1965) we established that the curve expressing the tolerance of irradiated mice to G-loading is influenced by the mean survival time (MST) of irradiated mice. Conceivably, this correlation is extended to man. Obviously, the duration of normal (or decreased) sensitivity of a given irradiated organism to G-loading cannot be greater than the MST.

Coefficients of extrapolation were derived by computing the divergence of the MST in irradiated men and mice at 300 to 2,000 BER. At doses of 300-600 BER, 700-900 BER, and 1,000-2,000 BER, these coefficients were computed to be 1.77 (1.72-1.88), 2.00 (1.95-2.05) and 2.50 respectively. Substituting these into equation (1) at irradiation levels between 300-2,000 BER,

$$Dt = 5 \times 10^3 \times C$$

where  $C_{300-600 \text{ BER}} = 1.77$ ,  $C_{700-900 \text{ BER}} = 2.00$ , and  $C_{1-2 \text{ KBER}} = 2.50$ , and employing the coefficient of extrapolation [derived above], 1.35,

$$Dt = 3.7 \times 10^3 \times C \quad (3)$$

where  $200 \text{ BER} < D \leq 700 \text{ BER}$ . At  $D < 200 \text{ BER}$  where the probability of mortality as cited by Langham et al. (W. Langham, Ph. Brooks, D. Grahn, et al., 1965) is equal to only 1-3%, use of the coefficient of extrapolation derived through MST studies of mortally injured animals is apparently untenable.

In our opinion, the difference in rate of recovery processes is better employed as the functional criterion at  $D < 200 \text{ BER}$ . The rate of recovery from radiation sickness is known to be a function of the rate of metabolic processes, and consequently dependent upon the type of animal involved.

According to a number of authors, the half-recovery time for radiosensitivity for man is 25-35 days and approximately five days for mice. Davidson (1957) established a mean half-recovery time in man of approximately 28 days. Applying the tolerance of man to massive G-loading in our experiments, we arrived at a value of 26 days (B. I. Davydov, V. V. Antipov, P. P. Saksonov, 1965). The ratio of the half-recovery time in man to mice is 5.6-5.2.

As seen from Figure 1, G-loading resistance in mice receiving 100 BER is equal to that of control mice after 45 days, which is longer than the period required for total recovery from radiation sickness for mice. In man the period of total recovery from the reversible components of radiation sickness is computed to be 200 days. Consequently, the period of total recovery in man is seen to be approximately 4.4 times greater than that of mice. The values for these coefficients derived through various means are significantly close. On the average, this coefficient is taken as  $\sim 5$ . At  $200 \text{ r}^*$ , formula (3) takes on the form:

$$Dt = 1.85 \times 10^4$$

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\*Tr. note: BER and r are used as they appear in original.

where  $D \leq 200$  r. Into formula (2), which describes the response of an irradiated animal to a second [repeated] centrifugation, the coefficients of extrapolation must be substituted so that the data may be made applicable to man.

Figure 3 shows a series of curves derived through extrapolation of the experimental data to man (B. I. Davydov, V. V. Antipov, P. P. Saksonov, 1967). In this figure, curve 3 represents the normal tolerance to acceleration of a man receiving 200-700 BER, and curve 4 shows the same at 200 BER. Duration of the primary response must be taken into account, however. Thus, according to the literature reviewed by Yu. G. Grigor'yeva et al. (1965), the sharp, primary response to radiation doses up to 400 BER continues to the third day. The probability that such a primary response will arise is dependent on the radiation dose. Curve "c" of figure 3, arrived at through information cited by W. C. Brown (1953, 1953a, 1955), H. Gerstner (1960), J. Morton (1957), L. Miller, G. Fletcher, H. Gerstner (1958), J. Burwell, B. Wolfson, C. Perryman, F. Foldes (1961), and curve "b" derived by Yu. G. Grigor'yeva et al. (1965) give some idea of the relation involved here. These curves diverge one from the other, apparently because the first set of data was recorded mainly from people accidentally irradiated, and the second set of data was recorded from patients receiving radiation therapy.

As Figure 3 shows, radiation dosage is functionally related to the time lapse after irradiation\*. To determine the minimal radiation dose at which G-loading tolerance will remain normal, determination of the period which may be assumed as the end point of the abscissa scale in Figure 3 is necessary. Consequently, it is necessary to select a criterion whereby this temporal point might be determined. The end point on the abscissa in Figure 3 may be assumed to fall, with certain allowances, at the end of one of two time intervals. The first interval is the first half of the period required for complete postradiation recovery, in the course of which 90% of the reversible components of radiation sickness are compensated for. The second is the period required for total recovery. The period of total recovery from radiation sickness, evaluated through radiosensitivity restoration studies, runs for 200 days.

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\*Tr. note: Reference here is to the lapse of time before G-loading.

According to curve 4 (Figure 3), the minimal radiation dose which elicits no change in response to G-loading (one run) in the course of 200 days is equal to approximately 90 BER. For a second centrifugation, this dose is equal to approximately 50 BER (curve 5).

Consequently, on the basis of data we arrived at through extrapolation, doses of 50-90 BER elicit little change in the tolerance to G-loading of a man irradiated at that level to that of a healthy person within 200 days after irradiation.

As stated earlier, a number of authors have cited the problem of establishing MPE for men in "flying" craft (G. M. Frank, P. P. Saksonov, V. V. Antipov, N. N. Dobrov, 1962; V. V. Antipov, N. N. Dobrov, P. P. Saksonov, 1964; Yu. G. Grigor'yev, Ye. Ye. Kovalev, A. V. Lebedinskiy, Yu. G. Nefedov, 1965; Yu. G. Grigor'yev, A. K. Gus'kova, M. P. Domshlak, V. G. Vysotskiy, et al., 1965). However in the majority of instances, the criteria by which the authors arrived at their recommended MPE has proved inadequate for space flight.

For this reason, great interest was attendant on attempts to evolve other methods for arriving at the maximum tolerable irradiation which would be more specific for space flight. G-loading was presented as among the first of the possible criteria representing the more dominant factors of space flight (V. V. Parin, P. V. Vasil'yev, V. Ye. Belay, 1965).

As apparent from the material presented above, our evaluation of the MPE is derived solely from quantitative indices. However, this is clearly insufficient, and for a more profound analysis it would apparently be necessary to utilize in addition a number of physiological, biochemical, and other tests.

As has been shown earlier (G. O. Davidson, 1957), extrapolation of experimental data to man has been employed with sufficient success in radiobiological investigations carried out by a number of authors proving extremely useful from a practical point of view.

Recognizing the conditional aspects of such a method, we have also attempted to extrapolate experimental data from animals to man utilizing the quantitative divergence in the radiobiological laws governing mice and men. In this light, however, the similarity of

a number of qualitative radiobiological changes occurring in mice and in men is notable. Thus, Mate (1962) indicates that depression of the various types of blood cells in man occurs in the same chronological order as that in mice, effecting first the lymphocytes, then the reticulocytes, granulocytes, and finally the thrombocytes. As P. P. Saksonov (1959), A. S. Mozhukhin, F. Yu. Rachinskiy (1964) have emphasized, convergence in the clinical profile of acute radiation sickness in man and in the higher animals shows that only quantitative divergences exist in the appearance of the individual symptoms and also in the period of time required for them to develop after irradiation.

Thus, the data presented in this report should be viewed as the first attempt to derive the MPE for cosmonauts involving a new approach. Obviously, the final determination of the coefficients of extrapolation presented in this report should be made during actual flight; however, determining them with a greater degree of precision could be carried out by special experimentation on other types of animals. Further experiments to determine the MPE for cosmonauts involving criteria derived from other major space flight factors will be of paramount significance.

### Legends for the Figures

Fig. 1. Dose plotted against time lapse [after irradiation] to show tolerance of mice to G-loading.

- — after one centrifugation
- △ — after two centrifugations

Fig. 2. Response of irradiated mice to a second centrifugation.

$$K_1 = \frac{A^1}{A_0^1}, \quad K_2 = \frac{A^2}{A_0^2}$$

where  $A^1$  = % test animal mortality,  
 $A_0^1$  = % control mortality

and  $A^2$  = % test animal mortality,  
 $A_0^2$  = % control mortality after a second centrifugation

1 — 500 BER, 2 — 250 BER, △ — 350 BER, ■ — 200 BER,  
o — 100 BER

Fig. 3. Theoretical dose-time lapse relation showing tolerance of irradiated humans to critical G-loading.

- 1 — Mean Survival Time (MST) for man after irradiation
- 2 — Extrapolated curve showing man's tolerance to G-loading (MST extrapolating coefficient)
- 3 — Same as curve 2, but with coefficient of radiosensitivity taken into account
- 4 — G-loading tolerance curve (one exposure) of man at  $D < 200$  BER
- 5 — Same as curve 4 (two exposures)
- a — Maximum period of primary reaction

b — Probability of primary reaction appearance ( $P_p$  in %) after Yu. G. Grigor'yev, et al. (1965)

c — Same as "b" (D = 300 BER,  $P_p = 99.9\%$ ) after Curt Brown (1958, 1955), Gerstner (1960), et al.

$P_D$  — Probability of mortality in man.

Fig. 1

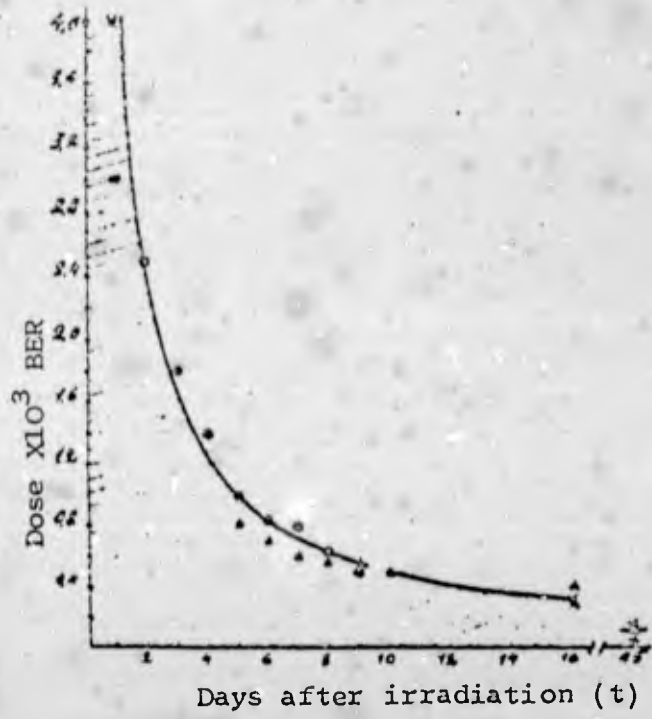


Fig. 2

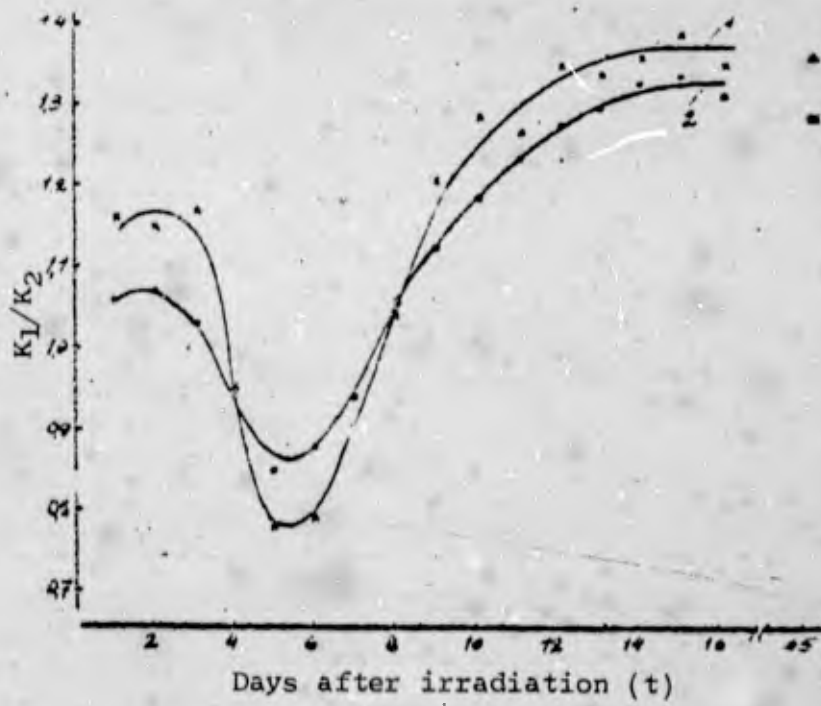
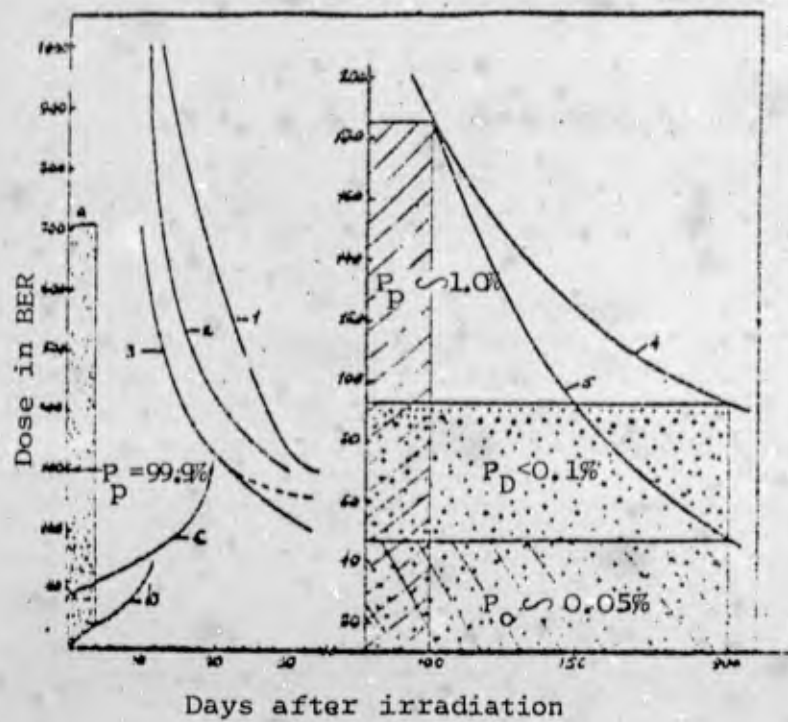


Fig. 3



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