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DOSE-RATE MODELS FOR HUMAN SURVIVAL AFTER EXPOSURE TO IONIZING RADIATION[a]

Troyce D. Jones
Health and Safety Research Division
Oak Ridge National Laboratory
Oak Ridge, Tennessee 37831

M. D. Morris
Engineering Physics and
Mathematics Division
Oak Ridge National Laboratory
Oak Ridge, Tennessee 37831

R. W. Young
Division of Radiation Policy
Defense Nuclear Agency
Washington, DC 20305-1000

ABSTRACT This paper reviews new estimates of the LD_{50} in man by Mole and by Rotblat, the biological processes contributing to hematologic death, the collection of animal experiments dealing with hematologic death, and the use of regression analysis to make new estimates of human mortality based on all relevant animal studies. Regression analysis of animal mortality data has shown that mortality is dependent strongly on dose rate, species, body weight, and time interval over which the exposure is delivered. The model has predicted human LD_{50}s of 194, 250, 310, and 360 rad to marrow when the exposure time is a minute, an hour, a day, and a week, respectively.

I. BACKGROUND

A. Mechanisms of Death

When mammals are exposed to high doses of ionizing radiations, blood lymphocytes and stem cells of the active bone marrow are killed. Mammals may die from infection or hemorrhage when these cell populations drop below certain critical levels. The time to death depends upon the number of cells killed; the species and strain of the mammal; and the cage/hospital care given, including therapeutic support, barrier nursing, nutrition, etc. This mode of death is commonly referred to as hematologic syndrome (or death from hemapoietic depression).

Hematologic death and modes of death resulting from gastrointestinal (GI) and central nervous (CN) system damage are described in Langham (1967) and many other sources (e.g., Baum et al., 1984). However, this review will discuss, in some detail, the biological and physical conditions contributing to hematological depression, the relevant animal studies from radiation biology, and human radiation accident and therapeutic experiences. This background section will establish the justification for new analytical tools to be used in modeling the LD_{50} for man.

Bergonié and Tribondeau (1906) proposed that the level of radiosensitivity of an organ or tissue is related to (1) the degree of differentiation of its cells morphologically and physiologically, (2) the mitotic activity, and (3) the length of time that the cells remain in an active stage of proliferation, which includes the number of divisions between the youngest precursor cell and the mature functional (or differentiated) cell. This proliferation of cells, which has commenced terminal differentiation, is commonly referred to as amplification and is especially important in maintaining sufficient numbers of lymphocytes (to fight infection) and platelets (to prevent post-irradiation hemorrhage). Because stem cells of the marrow are more radiosensitive than the rapidly proliferating crypt cells of the GI system or the highly differentiated cells of the CN system, survival of the organism is dependent upon the bone marrow although the time to death of a lethally irradiated animal may be determined by damage to the GI or CN systems (Langham, 1967; Baum et al., 1984).

According to Alper (1979), the killing of animals by radiation is determined by the death of "target cells" in "target tissues," and this concept is now a "basic part of the framework of radiological thinking." The United Nations Scientific Committee on Effects of Atomic Radiation (UNSCEAR, 1982) has further broadened this concept by proposing the basic premise that the nonstochastic response of a tissue depends upon the level of cell killing. ("Nonstochastic" is used to describe radiation-induced injuries where both the frequency of occurrence and the severity of the injury are porportional to the radiation dose.) Thus, for hematopoietic deaths, there is no controversy about the sequela of effects that precede death. Following whole-body exposure to lethal doses of radiation

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(below about 1000 rad given over a short time interval), death in small mammals occurs within 30 days and in larger mammals within 60 days.

When the radiation is delivered over a longer time, the magnitude of the lethal dose is increased, and the time to death becomes longer and less sharply defined. These changes can derive from two processes. First (if the radiation dose is from photons), subcellular or enzymatic repair of sublethal lesions in nuclear DNA can occur before a second photon (or photon-induced lesion) can further damage the site and kill the cell. Second, when the dose rate is sufficiently low (i.e., the dose is given over a time interval greater than 30 minutes), compensatory cellular proliferation begins in an attempt to restore tissue homeostasis. Thus, for low-dose-rate exposures to either high or low linear energy transfer (LET) radiations, the survival time can be quite long. The process has been described by Bond, et al. (1965):

> Proliferating cell systems like those found in hemopoiesis can, in operation, be likened to a retail dealer vending several items. If the factory manufacturing a particular item is damaged so that production is reduced or stopped, the retail dealer is not affected until stocks in the chain of supply lines are exhausted. Each individual item (cell) in the store even then remains as good or as "functional" as ever, and the segment of the vendor's business (organ) represented by that item is not affected until the number of individual items falls below a critical level or is exhausted. The entire business (mammal) is not seriously hurt or destroyed unless that particular item represented a major part of (was vital to) his operation. Survival will then be possible only if the factory can be put back into operation reasonably quickly (rapid regeneration), or if a substitute source or product can be used temporarily (symptomatic or substitution therapy) until restoration of the factory eventually takes place.

When humans have been accidentally or therapeutically exposed or when test animals have been irradiated, mortality is commonly an "all or none" event with respect to proportion killed in a population of individuals. That is, there is some high sublethal dose where no subjects die and some dose about twofold higher where very few, if any, individuals survive. The narrow transition zone (wherein some individuals die) is defined by a dose range where the upper dose is only 2 to 3 times that of the lower dose. Thus, because the mortality function is extremely steep, the dose that is lethal to 50% of the exposed individuals can in effect characterize the entire response function for most practical considerations with respect to nuclear safety, civil defense, and radiotherapy.

In spite of the large numbers of documented human exposures (Lushbaugh, 1969), there are inadequate human data to serve as a basis for promulgating an LD_{50} for man or to study how the human LD_{50} changes with different biological and physical conditions.

Historically, the most commonly accepted LD_{50} value for man has been that of the National Council on Radiation Protection and Measurements (NCRP) (NCRP, 1974). For high dose-rate exposures such as those that might occur following the explosion of a nuclear weapon, the NCRP has promulgated a value of 450 R (in air), which has been taken by the NCRP to be about 315 rad (to marrow). This NCRP LD_{50} value "is the median of a number of educated guesses made by a group of U.S. experts in 1949," and there is still insufficient human data to substantiate or change the 1949 value.

Lushbaugh et al. (1967) treated 93 terminally ill patients with a dose rate between 0.75 and 1.6 R/min. They also gave therapeutic aid to seven victims of the Y-12 radiation accident. From this combined population, Lushbaugh et al. derived an LD_{50} of 425 R (in air) or 281 rad (to marrow). Of course, all of the 93 terminally ill patients died, but 18 died within a time interval that suggested that the radiation treatment may have predominated slightly over the progression of death naturally associated with the disease. In contrast to studies of all-accidental human exposures, this study was supported by accurate dosimetry (Beck et al., 1971), and the numbers of patients were sufficient to permit a good statistical analysis of mortality.

In Lushbaugh's study, the patients were terminally ill, a state frequently speculated to result in increased radiosensitivity. On the other hand, the patients were given state-of-the-art hospital care, which would be expected to decrease radiosensitivity (NRC, 1975). Thus, although this study is without doubt the only accurate source of data that measures the LD_{50} of man, there is much uncertainty as to how to extend the results to different dose rates or to "non-sick" humans exposed under accident conditions.

Mole (1984) chose to consider the Y-12, Vinca, and Ewing Sarcoma patients of Rider and Hasselback (1967). Mole bases his LD_{50} of 600 R (in air) and 450 rad (to marrow) on survival of 28 individuals from a population of 29 exposed. Mole's analysis is strengthened somewhat because he used animal data to describe the shape of the mortality curve in the dose-normalizing technique of Jones (1981).

However, doses to accident victims have been determined from calculations and experimental "mock up" and thus are quite unreliable on an individual basis. Mole made a series of assumptions that combine to build a very high LD_{50}. These assumptions include Mole's belief that barrier nursing, antibiotics, platelet transfusions, and marrow grafts did not enhance survival. There are, however, several sources of experimental data to suggest that such procedures are likely to enhance survival by a significant amount, but these studies were not acceptable to Mole (NRC, 1975; Evans et al., 1985).

As a basis for evaluating the LD_{50} of man, Rotblat studied the atomic bomb experience in

Hiroshima. He presented his analysis at a meeting of the Institute of Medicine at the U.S. National Academy of Sciences (NAS, 1985). Rotblat found an LD_{50} of 220 rad tissue kerma in air (~250 R) and 154 rad (to marrow). Although the numbers of deaths and exposed individuals are adequate for a good statistical analysis (i.e., 201 deaths in 765 exposed), Rotblat's analysis is quite controversial because of:

1. extremely inaccurate analytical methods (as only one of several possible examples, Rotblat goes to great effort to compare the shapes of survival curves in a semiquantitative manner by transforming the scales on both the ordinate and the abscissa of only one curve; he then remarks that the similarity between the transformed curve for humans and the untransformed curve for mice "is striking"),

2. an assumption that all deaths after the first day were due to radiation and that combined injury from thermal burns and blast did not increase mortality, and

3. the fact that the survival curve is fivefold flatter than any ever observed in any mortality study (Jones, 1981; Mole, 1984) so that a few humans would die at doses as low as 50–75 rad but some could survive at doses twofold greater than the LD_{50}. Both of these effects have no basis of support in the vast literature on radiation therapy and radiation biology (Jones, 1981; Mole, 1984).

Many others have promulgated human LD_{50} values over time, but the four studies reviewed here illustrate the problem adequately. One is faced with the choice of extrapolating from sick humans to "normal" humans or analyzing data on normal humans where the doses and the number of deaths per number exposed are unreliable. Even with the best analytical methods, a reliable LD_{50} value must depend upon accurate dosimetry and sufficient numbers of exposed individuals and deaths. Some experienced investigators express a great reluctance to use sick humans as analogs of normal humans. However, it is our view that mechanisms of death may not be changed greatly in some populations of sick humans and that mortality models based on carefully done therapeutic populations provide a technically accurate estimate comparable to analytical models based on many species of test animals.

Thus, from the human data collected to-date, it is not possible to define, with acceptable confidence, an LD_{50} value (or a mortality response function) or to anticipate how human mortality varies with dose rate and numerous other physical and biological variables.

Hence, this paper will draw on (1) the vast amount of animal mortality data published in the literature, (2) well-known principles from radiation biology that will help to fit each of these many animal studies into the proper perspective, and (3) simple unifying dose-response models (Jones, 1981, 1984) that permit all data on all species and experimental and biological factors to be analyzed simultaneously instead of the conventional approach of sequentially analyzing a few studies, which then usually cannot be merged into a coherent model that can be evaluated for man.

B. Physical and Biological Conditions That Affect Death

Myelopoiesis is the processes whereby a marrow stem cell divides in order to maintain the homeostatic population of stem cells and to supply differentiated cells to blood, bone, and thymus/lymph. Myelopoiesis is strongly dependent upon species and may vary to a lesser degree within individuals or strains. Myelopoiesis occurs rapidly in small mammals and more slowly in large mammals. The rate within an individual also varies according to homeostatic equilibrium or the need for compensatory cell proliferation to repair tissue injury. Figure 1 is an illustration of the species variation of myelopoiesis (Bond et al., 1965).

From Fig. 1 it is seen that new cells in rat can be observed in the blood within about 3 days following exposure, whereas in man the time increases to about 8 days. Also, cell turnover is more rapid in the smaller species. Blood cell counts reach nadirs at shorter times in the small species so that large species survive longer after low lethal doses. But, because of rapid cell removal kinetics, the smaller species can survive higher sublethal exposures.

Thrombopoiesis results in production of megakaryocytes that secrete platelets, which are essential to prevent hemorrhage. As seen in Fig. 2, fully differentiated megakaryocytes are produced in about 7 days and have a mean lifespan of about 10 days in peripheral blood (Szirmai, 1965).

During thrombopoiesis, megakaryoblasts can increase in number, and this amplification is also common in processes of erythropoiesis and granulopoiesis (Szirmai, 1965). These partially and fully differentiated blood cells are more radioresistant than the stem cells so that, at doses that are just adequately lethal, time to death may be extended through amplification of surviving cell populations. However, lymphocytes (which amplify their numbers greatly within peripheral blood) are quite radiosensitive. As the magnitude of the lethal dose is increased, the survival time is shortened greatly; death results when lymphocytes are killed instead of when stem cells are unable to match the homeostatic demand for new cells. Burros have been found to be quite radiosensitive and die within just a few days following superlethal doses of radiation. Death of lymphocytes may help explain why burros are extra radiosensitive and may die in 5–10 days whereas most hematologic mortality in other large animals is seen at times greater than 10 days. Of course, 5–10-day survival times may be observed in all other species if the treatment dose is sufficiently large.

Radiosensitivity is directly related to cell cycle kinetics. The typical cell cycle is illustrated in Fig. 3. When the need for new cells is low (or zero), cells cease proliferative activity and are commonly referred to as

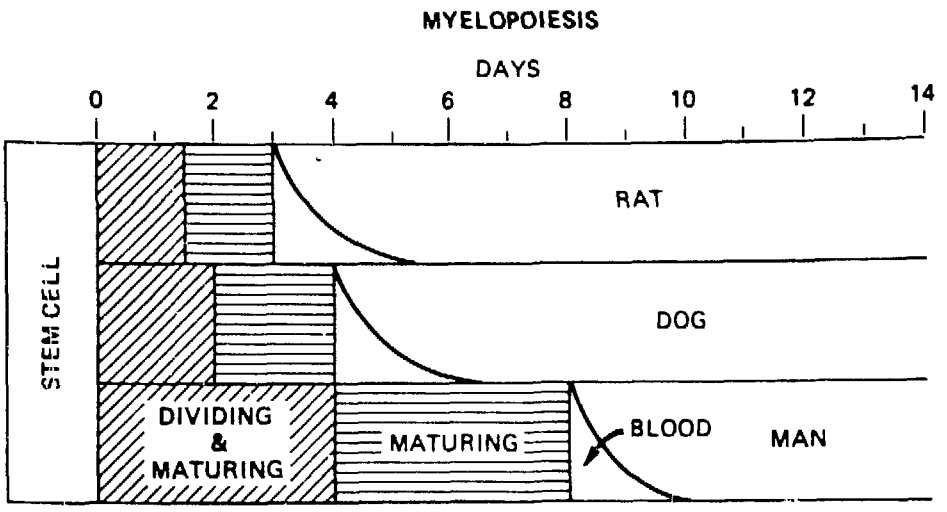

Fig. 1. Variation of myelopoiesis by species. (Reference: Bond et al., 1965.)

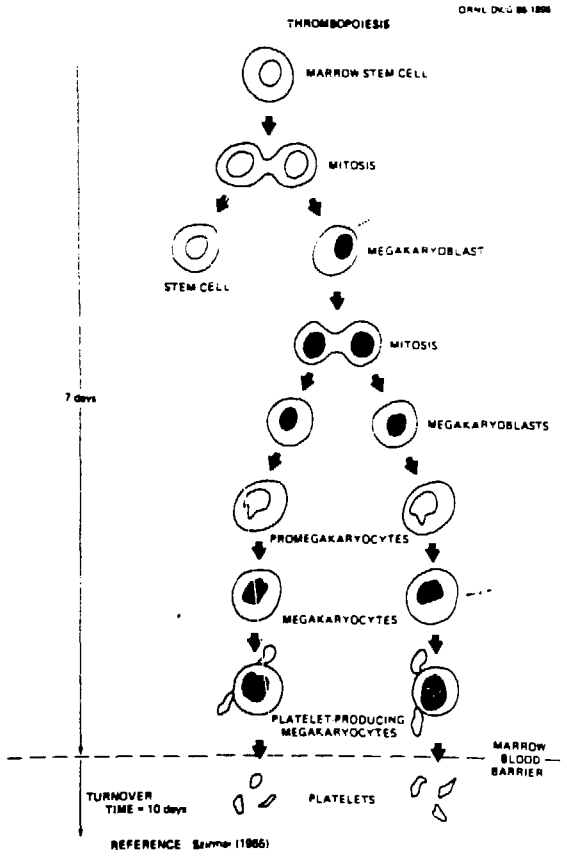

Fig. 2. Process of thrombopoiesis in man. (Reference: Szirmai, 1965.)

being in a resting or G_0 state. As seen in Fig. 3, a cell with the normal amount of nuclear DNA is said to be in the G_1 state (i.e., mitotic inactivity gap with diploid DNA). Following this 12-hour period new DNA is synthesized, and the cell drops into an inactive state with tetraploid DNA preceding binary fission into two new cells.

As illustrated in Fig. 4 (Case I), many radiogenic lesions in non-dividing DNA have a high probability of repair because the enzymes can read the complementary strand of DNA and repair the damage site before the DNA helix separates and a new helix of DNA is synthesized. In each new cell, a DNA helix contains one new and one old strand of DNA. As seen in Case II, radiogenic lesions immediately preceding DNA synthesis have a very low probability of repair, so that it is likely that one of the daughter cells is killed or functionally altered. For most practical considerations, DNA repair ceases when the nuclear DNA replicates. However, about half of the damage can be repaired within 1 hour preceding replication. Thus, in 4 hours between synthesis and mitosis the residual damage could be reduced to about $(1/2)^4$, or 6%. Cells can be killed by damage to other organelles such as mitochondria or membranes, but cells can be ten-fold more resistant during interphase periods than during metaphase periods.

It is obvious that a great many physical and biological factors can effect intracellular lesions, cell death, and, thus, death of the animal. Important physical factors commonly include: type (or LET) of radiation, dose level, dose rate, fractionation of dose with time, dose distribution within the marrow, etc.

Important biological factors that affect intracellular lesions, cell death, and death of

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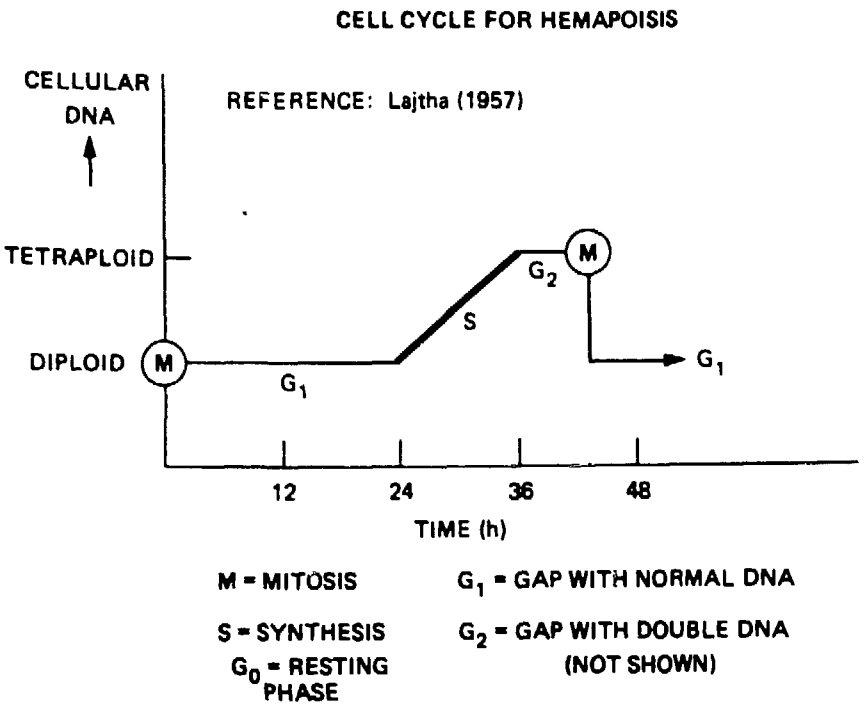

Fig. 3. Cell cycle for hematopoiesis. (Reference: Lajtha, 1957.)

the animal include: DNA content per cell; time periods of various phases of the cell cycle under different in vivo conditions; sensitivity of the individual, strain or species to infection and/or hemorrhage (physical conditions can host the opportunity for infection); capacity of the animal for compensatory repopulation of platelets and granuolocytes; etc.

II. METHOD

Lethality data were collected from many different animal studies. Experiments selected to evaluate the model were restricted to penetrating photons and any combination of body size and irradiation geometry that resulted in a uniform dose profile to all parts of the active marrow. A total of 224 different mortality studies were included in the data base. Data included: 13 different species; body weights from 25 g to 375 kg; sheep, goats, swine, and calves with body weights near man (i.e., 70 kg); radiation sources of ^{60}Co, ^{182}Ta, ^{95}Zr, atomic bombs, and X rays from several voltage potentials and many different moderating materials; and exposures from bilateral, multiple sources, unilateral, rotational, free-moving animals, 4π, and quadrilateral geometries, as long as the dose was uniform over the active bone marrow.

Typically, physical factors can be quantified or ordered on a numerical scale. But biological factors vary with species, strain, age, etc., and with the composite force from the collection of other biological and physical factors. Most biological factors can be treated as "classification" type variables in a regression analysis but usually cannot be quantified. However, the variance in the data set resulting from classification variables can be quantified. Regression analysis methods were used to quantify how much variance is left in the data set after physical factors are considered. Then, we evaluated how much of this variance can be due to individual "classification" variables (such as species) and, finally, how much of the species effect is left unaccounted for after body weight is considered.

Within each species, a model that linearly related the log of LD_{50} to the log of dose rate fitted the data fairly well. Across species, the slopes of these lines were relatively consistent, but their intercepts differed significantly. As evidence of this, a model fitted to all data with a single intercept and slope accounted for less than 1% of the variation in the data ($R^2 < 0.01$). A model that included a separate intercept for each species but only a common slope for the log of dose rate accounted for 84% of the variation; a model that allowed separate intercepts and slopes for each species improved this only slightly, to 86%. Furthermore, when intercepts were fitted for each species, there was a clear inverse relationship between species body weight and the value of the intercept (heavier species had relatively higher response values at a given dose rate). In fact,

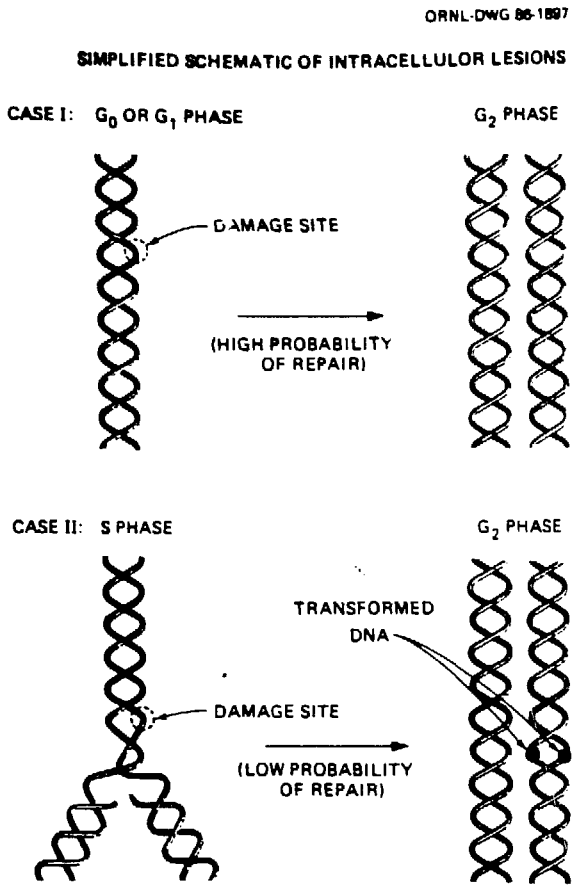

Fig. 4. Simplified schematic of intracellular lesions.

a model that contained a single intercept, a term for the log of dose rate, and a term for standard body weight accounted for 64% of the variation in the data.

In consideration of the above, a two-stage model was adopted.

Stage 1: For species i, a model of form

$$[\log_{10}(LD_{50})]_i = \alpha_i + \beta \cdot \log_{10}(\text{dose rate}) + \gamma \cdot \log_{10}(\text{body weight})_i + \varepsilon$$

was used. β and γ are regression coefficients assumed to be valid across species, α_i is an intercept specific to species i, and ε represents experimental or unexplained error in the reported values of $\log_{10}(LD_{50})$, assumed to be distributed with mean zero and variance σ^2.

Stage 2: Across species, α_i was assumed to be distributed with mean α and variance δ^2. This random intercept can be thought of as a species effect, after correction for species body weight. In order to use the model to predict results for a species not included in this data set (e.g., man), it was assumed that the applicable value of α_i would be a new (unobserved) value from this same distribution.

Using a computational technique described by Laird and Ware (1982), maximum likelihood estimates were calculated for the parameters of the model as follows:

$$\hat{\alpha} = 2.743$$
$$\hat{\beta} = -0.070$$
$$\hat{\gamma} = -0.161$$
$$\hat{\sigma}^2 = 0.0096$$
$$\hat{\delta}^2 = 0.0194$$

So, a point estimate of the LD_{50} for an unspecified or new species is

$$\text{estimated } LD_{50} = 10^{[\hat{\alpha}+\hat{\beta}\cdot\log_{10}(\text{dose rate}) + \hat{\gamma}\cdot\log_{10}(\text{body weight})]},$$

or

$$\text{estimated } LD_{50} = 10^{[2.743 - 0.701\log_{10}(\text{dose rate}) - 0.161\log_{10}(\text{body weight})]}.$$

For man, a species having a 70-kg body weight, this reduces to

$$\text{estimated } LD_{50} = 281\ (\text{dose rate})^{-0.070}.$$

A common slope of -0.070 was used for all species, and the intercepts (i.e., α_i's) are as follows: mouse (2.946), hamster (2.925), rat (2.875), guinea pig (2.508), rabbit (2.967), primate (2.782), dog (2.493), goat (2.490), sheep (2.393), swine (2.500), man (2.743), burro (2.410), and cattle (2.205). Thus, mouse, hamster, rat, primate, dog, swine, goat, burro, and cattle seem to demonstrate a consistent monotonic relationship with body weight, but sheep and guinea pig are more radiosensitive than most other species and rabbit is more radioresistant, on a relative basis.

These formulae are compared with the experimental data, sorted according to species, in Fig. 5. It should be remembered that, although the experimental data in Fig. 5 reflect many other biological and physical variables, only one equation was used for all species. However, the model seems remarkably accurate for each species. This consistency is unique (Baverstock et al., 1985) and offers almost unlimited potential to model human response from the extensive data basis available on test animals.

The midlethal dose for man plotted against dose rate is given in Fig. 6. Marrow dose was converted to tissue kerma in air according to Jones (1977). The equation for man [viz, $281/(\text{dose rate})^{0.07}$] was solved for midlethal dose for continuous dose rates given in 1 minute, 1 hour, 1 day, and 1 week. Results are in Table 1.

III. DISCUSSION

Baverstock et al. (1985) analyzed animal data but did not use a dose-rate dependent model. Instead, they selected exposure times of one hour or less. They found a lack of homogeneity within species. However, according to our analysis, the LD_{50} given in one minute is about 190 rad to marrow, and the LD_{50} given in one hour is about 250 rad. These estimates are for a 70-kg body weight; the spread could be considerable larger for smaller species with

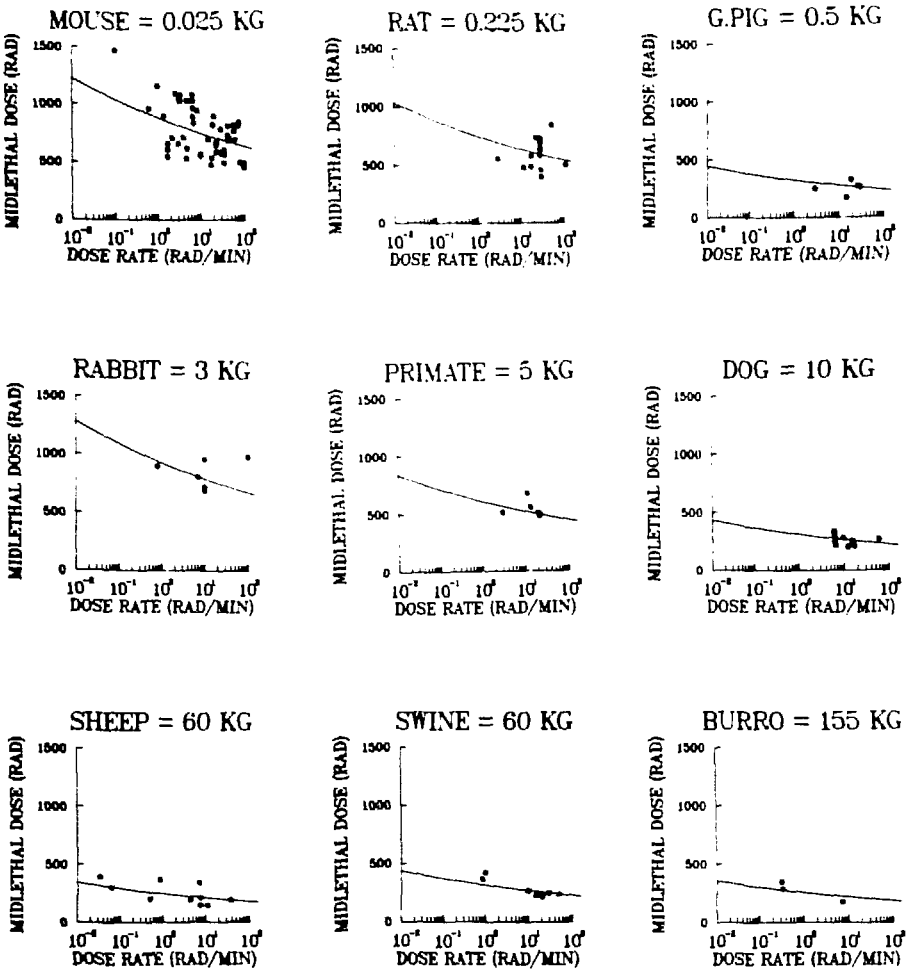

Fig. 5. Comparison of the statistical dose-rate model with experimental data for nine species.

faster mitotic rates. The model of Baverstock et al. did not discriminate between dose rates when exposure times were short compared with cellular turnover times (i.e., dose-rates above 10 R/min were considered equal). However, for low LET radiation (which was being modeled), enzymatic repair must also be considered. Such repair has been found to be significant in times much shorter than cell turnover times (Terraghi and Little, 1975). Thus, the Baverstock et al. model does not seem well suited to analyze exposure intervals ranging from one minute to one hour. In addition, we have made estimates of dose to marrow upon which our model is evaluated. Although the Baverstock et al. model was evaluated twice—once in terms of exposure and again in midline tissue dose—no attempt was made to estimate marrow dose. Because of these significant differences in the two models and because of our much larger data base, it seems that our model has found a coherent pattern in interspecies LD_{50}. Experiments using low LET exposures (to all species) that resulted in uniform marrow dose all seem compatible with a simple interpolation model based on dose rate and body weight.

IV. CONCLUSIONS

There is no unique or practical LD_{50} for man because mortality varies strongly with dose rate and with several physical and biological factors. The NCRP LD_{50} in air may be about 25% too high, and the NCRP marrow LD_{50} may be about 60% too high—excellent agreement considering what was known in 1949 when the NCRP value was promulgated. Mole's LD_{50} in air (Mole, 1984) seems about 70% too high, and his value for marrow seems about 130% too high. However, Mole's mortality curve has the correct shape because he derived it from the animal data in the method of Jones (1981) (i.e., treatment doses were normalized to a multiple of the LD_{50} for that particular experiment).

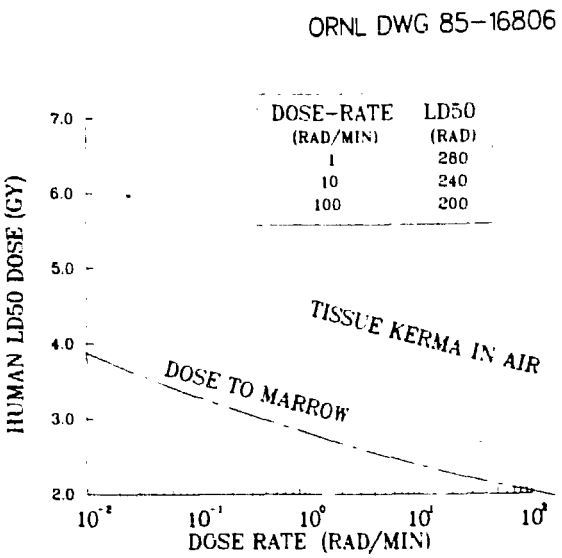

Fig. 6. Midlethal dose for man as a function of dose rate according to the statistical model derived from animal data.

Rotblat's LD_{50} (NAS, 1985) seems about 20% too low, but the slope of his mortality curve is fivefold too flat (Jones, 1981; Mole, 1984).

Lushbangh's estimate of 281 rad to marrow for dose rates between 0.75 and 1.6 R/min seems acceptable. The mathematical model based on the animal data gives 281 rad for 1 R/min and a 70-kg body weight (Lushbaugh et al., 1967). If Lushbaugh had not included the seven Y-12 victims, who were exposed to high dose rates, with his 93 patients treated at a low dose rate, his LD_{50} estimate would probably be a bit higher than the published value of 281 rad.

The United Nations Scientific Committee has undertaken a recent analysis of human mortality. Although that analysis has not been finalized, the analysis described in this paper and our previous experience support several important issues discussed in the UNSCEAR 1982 report. Those issues include:

Table 1. Midlethal dose for man exposed to continuous dose rates given in 1 minute, 1 hour, 1 day, and 1 week

Exposure time	Dose rate (rad/min)	Photon midlethal dose	
		Marrow (rad)	Tissue kerma in air (rad)
1 Minute	194	194	350
1 Hour	4.2	250	450
1 Day	0.22	310	560
1 Week	0.035	360	650

- differences in effects due to different photon energies are considered to be negligible (p. 572),
- sublethal damage can normally be repaired in a few hours (p. 573),
- "For a variety of different types of treatment, different dose rate and LET, the reduction in the proportion of surviving cells resulting in 50% death of the mice was the same for all treatments" (p. 573),
- there is little or no enzymatic repair above 100 rad/min (p. 575) so the LD_{50} should be constant at dose rates above 10^2 or 10^3 rad/min.

Conclusions presented in this manuscript are expected to be firm, but numerical results presented at this time are subject to small changes when a final reporting of this study is made in 1987. Because of the success of this exploratory statistical model, a comprehensive effort is now under way to collect data on all individual dose treatment groups that contributed to the 224 different LD_{50} values analyzed in this study. Also, other studies are being added to the data base. This more comprehensive data base will be analyzed for mortality response as a function of treatment dose expressed as multiples of the LD_{50} value appropriate for a particular study. Thus, a universal mortality function will be derived (Jones, 1981), and 95% confidence limits will be evaluated.

When that effort has been completed, the body weight of man and different dose rates of interest can be used to calculate tables of dose-response values.

V. ACKNOWLEDGMENTS

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