# THREE-DIMENSIONAL DOSE-RESPONSE MODELS OF RISK FOR RADIATION INJURY AND CARCINOGENESIS*

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## ABSTRACT

The use of computer graphics in conjunction with three-dimensional models of dose-response relationships for chronic exposure to ionizing radiation dramatically clarifies the separate and interactive roles of competing risks. The three dimensions are average dose rate, exposure time, and risk. As an example, the functionally injurious and carcinogenic responses after systemic uptake of Ra-226 by beagles, mice and people with consequent alpha particle irradiation of the bone are represented by three-dimensional dose-rate/time/response surfaces that demonstrate the contributions with the passage of time of the competing deleterious responses. These relationships are further evaluated by mathematical stripping with three-dimensional illustrations that graphically show the resultant separate contribution of each effect. Radiation bone injury predominates at high dose rates and bone cancer at intermediate dose rates. Low dose rates result in spontaneous deaths from natural aging, yielding a type of practical threshold for bone cancer induction. Risk assessment is benefited by the insights that become apparent with these three-dimensional models. The improved conceptualization afforded by them contributes to planning and evaluating epidemiological analyses and experimental studies.

## METHODS

Mathematical relationships for risk distributions.

The bodily intake of radioactive materials, such as Ra-226, can lead to protracted, chronic irradiation of tissues, such as the bone, with subsequent cancer induction or systemic injury. Similar responses may be observed for repeated external exposure to penetrating radiation. The independent risk probability of fatal induced cancer is obscured by the separate independent competing risks of death, especially those that occur near the end of the normal life span. The observed occurrence of fatal cancer induced by exposure to ionizing radiation is the resultant of the convolution of all causes of death, and is a type of dependent risk since it depends upon both the dose-response relationships for the irradiation and as well upon other effects including especially deaths associated with natural aging.

Probability distribution functions are utilized to describe the various risk distributions as functions of time from beginning of exposure until death and as a function of dose rate at any specific time. These relationsnips have the general form that the independent risk distribution for a given effect has a probability density, $f(t,\bar{D})$, and cumulative risk function, $F(t,\bar{D})$, which are distributed with respect to elapsed time, t, but depend on average dose rate, $\bar{D}$, forming three-dimensional mathematical response surfaces. The cumulative risk for a single effect is the independent probability (values between zero and one) of an individual succumbing to the specified response (e.g., dying of bone cancer) assuming that there are no other possible effects. Likewise, the probability density,

*Research supported in part by the Office of Health and Environmental Research of the U.S. Department of Energy.

f, is the fraction of all individuals originally at risk who succumb per unit of time (e.g., per day) after exposure begins. Thus, if T is the time from initial exposure to death from a specified cause and there are no other causes of death, then the probability of dying at a given average dose rate before or at a specified time, t>T, is given by $F(t,\bar{D})$ with t=A-E and A the age of the individuals at risk and E their age at the beginning of exposure.

When several separate risk distributions, $F_i$, are superimposed in the time and dose-rate space, the occurrence of one cause of death, i, is a fraction, $\Omega_i$, of individuals who succumb to that cause at a specific average dose rate. For example, effect i=1 could be spontaneous deaths associated with natural lifespan, effect i=2 could be deaths associated with a specific form of radiation-induced cancer, and effect i=3 could be deaths from systemic injury induced by radiation exposure (Raabe, 1987).

Independent distributions, $F_i$, are mathematically unchanged by the presence of the other risks, but the occurrence of the other risks may reduce the number of individuals that succumb to a specific cause. Thus, the actual occurrence of cancer deaths caused by radiation exposure will be less than if there were no other possible causes of death, and $\Omega_2 \leq F_2$. The occurrence fraction is the dependent risk from exposure to ionizing radiation since it is the resultant of the various causes of death including those associated with natural lifespan. The number of individuals among those exposed who succumb to an effect, i, is predicted by $\Omega_i$, not $F_i$.

Lognormal independent risk model

The independent risks of cancer induction and other effects have been usefully modeled as a lognormal functions of time to effect (Raabe et al. 1980; Raabe et al., 1981a; Raabe, 1984; Raabe, 1987). The lognormal model involves a basic dose-rate/time/response relationship given by:

$$t = K\bar{D}^{-S} \qquad (1)$$

where $\bar{D}$ is the average dose rate to the tissue at risk, t is the elapsed time to death (or other endpoint) after initial exposure, K is a parameter associated with level of risk and exposure conditions, and S is the negative slope of the logarithmic form of the function. At any given $\bar{D}$, both K and t are lognormally distributed with geometric standard deviation, $\sigma_g$. This relationship defines a three-dimensional lognormal dose-rate/time/response surface for a specific effect such that:

$$Z = (\ln t - \ln K_m + S \ln \bar{D})/\ln \sigma_g \qquad (2)$$

where $K_m$ is the fitted median risk value of K, $\sigma_g$ is the observed geometric standard deviation of K values for the individual cases, and Z is the standardized normal deviate which is equal to zero at the median risk (F=0.5). Hence, the cumulative risk for a lognormal dose-rate/time/response distribution for a specific effect can be calculated for each $\bar{D}$ and t by numerical integration of the standardized normal distribution.

Data for $^{226}$Ra-injected beagles.

An example of the use of the three-dimensional models is given in an analysis of bone cancer induction and skeletal injury in lifetime studies of Davis beagles injected with Ra-226 (Raabe et al., 1981b). Briefly, 234 purebred beagles were administered 8 fortnightly intravenous injections of Ra-226 in 0.1 N nitric acid saline solution in five dosage groups beginning at 435 days of age and ending at 540 days of age (midpoint of intake at 485

days of age). Lifetime dosimetry involved whole-body gamma ray spectroscopy of Bi-214 and application of the appropriate radon/radium retention ratios in bone; the irradiation of bone cells was primarily by alpha rays. To compare the Ra-226 dose-response results in beagles to other species including people, available human data (Evans, 1966, Evans, 1974, Argonne National Laboratory, 1985) and female $CF_1$ mouse data (Finkel et al., 1969) involving bone burdens were also evaluated with the three-dimensional models.

Life span distributions.

The distribution of deaths associated with natural lifespan involves many causes including various forms of both communicable and non-communicable diseases, and is commonly represented utilizing the Gompertz function. The Gompertzian cumulative risk from an age E until a time t=A-E is described by $h_o$, the hazard rate at birth, and $\psi$, the exponential coefficient (Raabe, 1987). For beagles, $h_o=2.037 \times 10^{-6}$/day and $\psi=1.104 \times 10^{-3}$/day.

## RESULTS

In the Davis beagle study, a total of 115 cases of fatal bone cancer (primarily osteogenic sarcoma) were fit to the lognormal model by least squares for dose rates spanning 0.3 to 20 cGy/day. The resulting function had $K_m=2500$, $S=-0.29$ and $\sigma_g$ of 1.17 based upon survival time in days and dose rate in cGy/day (Table 1). The time post intake was calculated from the midpoint of the injection period (A=485 days). An approximate (S=3) lognormal bone injury risk function was fit to the observed cases of deaths from systemic injury at high dose rates.

When the combined cumulative risk, $F_c(\bar{D},t)$, for all causes of death is divided into its component constituents using mathematical stripping as described by Raabe (1987), the separate fatal occurrences show that radiation bone injury predominates at high dose rates and bone cancer at intermediate dose rates. Also, low dose rates result in spontaneous deaths from natural aging, yielding a type of practical threshold for bone cancer induction.

To compare the Ra-226 dose-response results in beagles to other species including people, lognormal dose response relationships with identical S=0.29 were fit to available human data and female $CF_1$ mouse data involving skeletal burdens of Ra-226 (Raabe et al., 1980; Raabe et al., 1981a; Raabe et al., 1983). These results for the independent risk functions are summarized in Table 1. The three-dimensional occurrence distribution for people of fatal bone cancer induced by Ra-226 can be assumed to includes a concurrent risk of carcinoma of the head not found in beagles.

Table 1. Parameters of the lognormal dose-rate/time/risk distribution for observed fatal cancer in laboratory animals and man where S is the negative slope and $\sigma_g$ is the geometric standard deviation of K values about the median $K_m$ for n animals with correlation coefficient, r, based upon radiation dose rate in cGy/day and survival time in days.

| Response | Radionuclide | Species | $K_m$ | S | $\sigma_g$ | n |
|---|---|---|---|---|---|---|
| Bone Cancer | $^{226}Ra$ | Beagle | 2,464 | 0.29 | 1.17 | 115 |
| Bone Cancer | $^{226}Ra$ | $CF_1$ Mouse | 850 | 0.29 | 1.30 | 249 |
| Bone Cancer | $^{226}Ra$ | Man | 9,000 | 0.29 | 1.39 | 32 |
| Bone Injury | $^{226}Ra$ | Beagle | $10^7$ | 3.0 | Estimate | |

The same basic three-dimensional lognormal dose-rate/time/response function with S=0.29 was found to describe the results for the three species but displaced in time by a species dependent response ratio (RR). This response ratio can be interpreted as the ratio of the respective median values, $K_m$, for the three species which were well correlated to (but not proportional to) life expectancy (Raabe et al., 1981a). The RR for people/beagles=3.6 and people/mice=10. Thus, people are one-tenth as sensitive as mice for osteogenic sarcoma at the same average dose rate.

## DISCUSSION

The three-dimensional dose-rate/time/response relationships provide for an improved understanding of the interaction of competing risks and natural life span in combination with chronic exposure to ionizing radiation. In particular, the usual methods which utilize cumulative dose tend to obscure or ignore the effects of time and dose rate upon the risk.

It is clear the the convolution of induced cancer risk distributions from chronic exposures and natural life span leads to a steep, nonlinear occurrence function. A type of quasi-threshold describes the occurrence of radiation-induced cancer at low dose rates. Hence, the common use of linear risk functions to describe life span dependent risk will be expected to overestimate the actual occurrence of cancer at low dose rates.

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