OH WUNDER!
THE INVERSE DOSE-RATE EFFECT IS QUELLED BY THE EFFECTIVE THRESHOLD

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ABSTRACT

Three-dimensional dose-rate/time/response mathematical surfaces describe radiation effects in lifetime studies of beagles after intake by injection or inhalation of selected radionuclides (including α-emitters ^{226}Ra, ^{239}Pu, ^{238}Pu, and ^{241}Am and β-emitters ^{90}Sr, ^{91}Y and ^{144}Ce) and in people after intake of ^{226}Ra. For each effect $t_m = K_m \bar{d}^{-s}$, where t_m is the median elapsed time to death with the specified effect after intake, $\bar{d}$ is the time-weighted average absorbed radiation dose-rate to the target organ, K_m is the median distribution coefficient, and s is the negative slope parameter. Using maximum likelihood survival regression methods, s was found to be ⅓ for α radiation and ⅔ for β radiation. The relationships of competing risks of death associated with radiation injury, radiation-induced cancer, and natural aging after initial exposure or intake are graphically portrayed using three-dimensional illustrations of these dose-rate/time/response surfaces. At the higher dose rates (larger organ burdens of radionuclide) the principal deleterious effects are those associated with radiation-induced injury while at intermediate dose rates radiation-induced cancer predominates. For cancer induction, lower dose rates have a higher relative dose effectiveness than higher dose rates (*inverse dose-rate effect*) for either low LET β radiation or high LET α radiation. However, at the lower dose rates the long latency time required for development of radiation-induced cancer may exceed natural life span, yielding a *life-span effective threshold* for death associated with radiation-induced cancer at a lifetime cumulative absorbed dose to the target organ of from about 0.08 to 1.4 Gy for α irradiation or from about 28 to 130 Gy for β irradiation. The beagle results were scaled to predict human bone cancer risks for internally-deposited ^{226}Ra and the predicted life-span effective threshold of about 2.1 Gy agreed well with the U.S.A. human ^{226}Ra data. The predicted occurrence of human lung cancer from inhaled $^{239}PuO_2$ yielded a life-span effective threshold of about 1.4 Gy..

INTRODUCTION

In this report, radiation risk from internally deposited radionuclides is described by an independent risk model in which radiation risk is superimposed in time upon the natural lifetime causes of death and competing risks. In its simplest form there are three separate fatal risk distributions: (a) deaths associated with natural life span and aging including the background incidence of various types of fatal cancer; (b) those deaths associated with radiation-induced cancer; and (c) deaths associated with exposure-related non-neoplastic injury (1-7). Precise data obtained in lifetime studies utilizing beagles provide the basis for understanding these phenomena. Raabe et al. (8-9) used life-span normalization to scale response relationships from laboratory animal species to human risks.

METHODS

Selected data were reviewed from published reports of life-time studies of internally deposited radionuclides in young adult beagles at four laboratories: University of California, Davis (10), Lovelace Inhalation Toxicology Research Institute, ITRI (11), University of Utah (11), and Battelle Pacific Northwest Laboratory, PNL (12). Throughout this report, doses refer to average absorbed target organ doses from parent and decay products, where all x ray and gamma emissions are ignored, and beta emissions are also ignored where alpha emitters predominate. Because of an observed pattern of linearity between the logarithm of time to radiation induced cancer deaths and logarithm of lifetime average dose rate to the target organ, standard log-linear survival models and maximum likelihood regression methods were used to describe the response functions (4). In terms of the natural logarithms, ln, the log-linear regression line is thus given by:

$$\ln t_m = \ln K_m - s \ln \bar{d} \rightarrow t_m = K_m \bar{d}^{-s} \quad (1)$$

where $\bar{d}$ is the time-weighted average dose rate, t_m is the regression value of median survival time, s is the negative slope of the regression line for the specified effect, and K_m is the median risk coefficient.

RESULTS AND CONCLUSIONS

The results are summarized in Figure 1. Alpha emitting radionuclides all yielded cancer risk distributions with slopes of -1/3 and the beta emitting radionuclides all yielded cancer risk distributions with slopes of -2/3, indicating that two beta particles are required to effect the same cellular transformations effected by one alpha particle such as two-strand DNA breaks (6). In addition, the underlying slope of -1/3 indicates that the distance between these events controls the response as a function of survival time as discussed by Raabe (3).

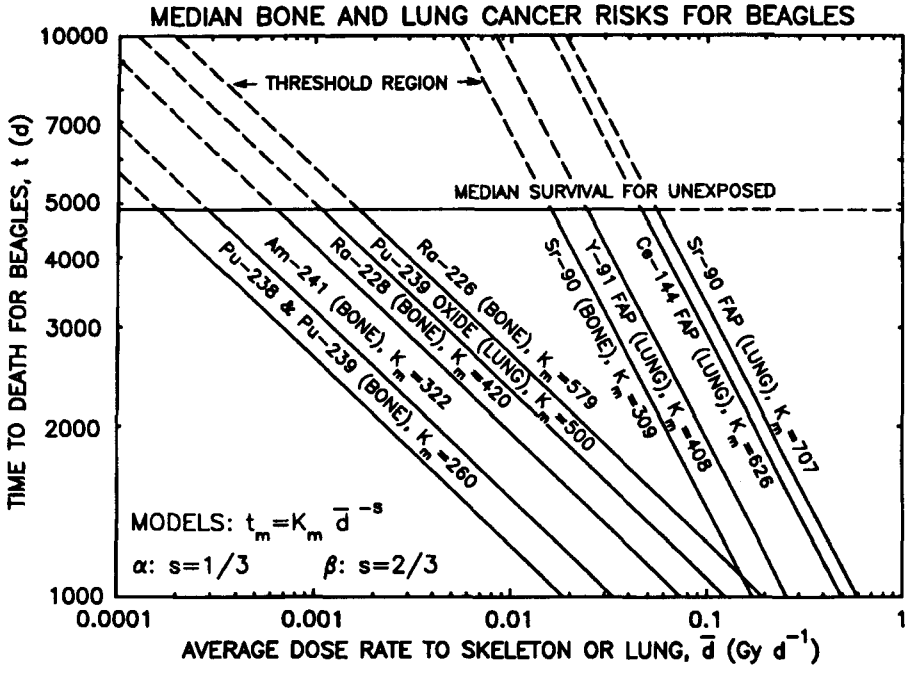

Figure 1. Median bone and lung cancer risks for beagles.

Because of the negative slopes of these distributions, the cumulative absorbed dose required to yield a specified level of cancer risk is less at lower dose rates than at higher dose rates (*inverse dose-rate effect*), but the time required for tumors to manifest tends to be much longer at lower dose rates and can exceed the natural life span, yielding a *life-span effective threshold* for fatal radiation-induced cancer. In other words, *Oh Wunder!* The old-age-related death of the individual preempts the development of radiation-induced cancer. For young adult beagles, this threshold occurs at about 0.08 Gy for ^{238}Pu and ^{239}Pu in bone, 0.2 Gy for ^{241}Am in bone, 0.5 Gy for ^{228}Ra in bone, 0.9 Gy for ^{239}Pu in lung, 1.4 Gy for ^{226}Ra in bone, 28 Gy for ^{90}Sr in bone, 70 Gy for ^{91}Y in lung, 110 Gy for ^{144}Ce in lung, and 130 Gy for ^{90}Sr in lung. Effective thresholds are predicted for human exposures using life-span normalization (8-9). For example, it is about 3.5 Gy for ^{226}Ra in bone; there were no cases of bone cancer for any cumulative dose less than 10 Gy in U.S. radium cases (13). Likewise, the predicted human occurrence of radiation-induced lung cancer (Figure 2) from inhaled $^{239}PuO_2$ has an effective threshold of about 2 Gy (8).

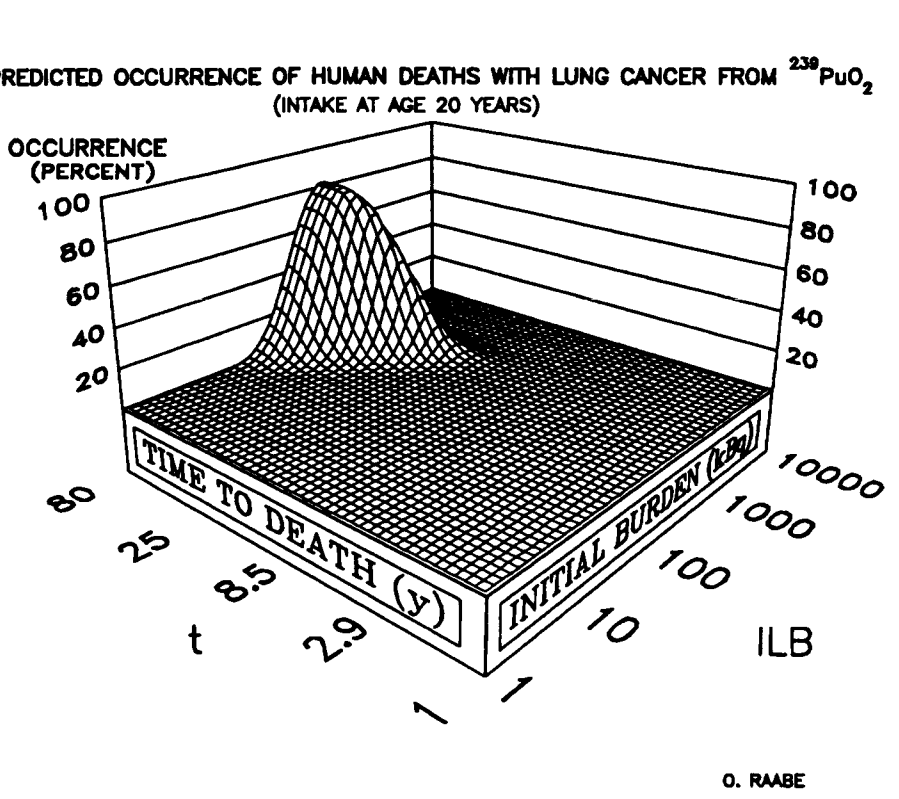

Figure 2. Predicted lung cancer from inhaled $^{239}PuO_2$ by initial lung burden (ILB).

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