Evidence for dose and dose-rate effects in human and animal radiation studies

M.P. Little

Radiation Epidemiology Branch, National Cancer Institute, National Institutes of Health, Bethesda MD 20892-9778 USA; e-mail: mark.little@nih.gov

Abstract-Deterministic and stochastic effects associated with high dose ionising radiation (X-ray) exposure have been known for almost as long as ionising radiation itself. At lower doses radiation risks are primarily stochastic effects, in particular somatic effects (cancer) rather than the deterministic (tissue reaction) effects characteristic of higher-dose exposure. In contrast to deterministic (tissue reaction) effects, for stochastic effects scientific committees generally assume that at sufficiently low doses there is a positive linear component to the dose response, i.e. that there is no threshold; this does not preclude there being higher order (e.g. quadratic) powers of dose in the dose response that may be of importance at higher doses. It is on this basis that models linear (or linear-quadratic) in dose are often used to extrapolate from the experience of the Japanese atomic bomb survivor Life Span Study (LSS) cohort (typically exposed at a high dose-rate to moderate doses (average 0.1 Sv)) to estimate risks from low doses and low dose-rates. The so-called low dose extrapolation factor (LDEF), which consists of the ratio of the low dose slope (as derived via fitting a linear-quadratic model) to the slope of the straight line fitted to a specific dose range, has been used to derive the degree of over- (if LDEF > 1) or under-estimation (if LDEF <1) of low dose risk by linear extrapolation from effects at higher doses. Likewise, a dose rate extrapolation factor (DREF) can be defined, consisting of the ratio of the low dose slopes at high and low dose rate. Here we review a variety of human and animal data for cancer and non-cancer endpoints to assess evidence for curvature in the dose response (i.e. LDEF) and modifications of the dose response by dose rate (i.e. DREF). The most informative human data on dose response curvature are from the LSS, which show strong evidence of curvature (i.e. LDEF > 1) for leukaemia and non-melanoma skin cancer, but only modest indications of curvature for other endpoints. There are indications in both the latest cancer mortality and cancer incidence datasets that curvature for other solid cancer endpoints is more pronounced in the recent time periods, and over the lower dose range, under 2 Sv. There is a body of data, some of it from the LSS, suggesting that the dose response for bone cancer (osteosarcoma) may be non-linear. The only useful information on modifying effects of dose rate (DREF) comes from comparing different populations, exposed at high and low dose rates, and as we review this may be problematic because of other variations (for example in underlying cancer risk) between these groups. There is a large body of animal data investigating effects of dose and dose rate. Among the most substantial is a corpus of murine and other experiments conducted at the JANUS reactor in Argonne National Laboratory from 1970 to 1992 to study the effect of acute and protracted radiation dose from gamma rays and fission neutron whole body exposure. A recently published reanalysis of the JANUS data for 36,735 mice (mostly *Mus musculus*, but some *Peromyscus leucopus*), 16,980 irradiated with neutrons, 13,647 irradiated with gamma rays, found that after gamma ray exposure there was significant non-linearity for all tumours, lymphoreticular, respiratory, connective tissue and gastrointestinal tumours, also all non-tumour, other non-tumour, non-malignant pulmonary and non-malignant renal disease ($p<0.001$). Associated with this the LDEF was significantly elevated for lymphoreticular tumours 1.159 (95%CI 1.059, 1.311), elevated also for a number of non-malignant endpoints, specifically all non-tumour diseases, 1.629 (95% CI 1.419, 1.987), non-malignant pulmonary disease, 1.696 (95% CI 1.175, 2.787) and other non-tumour diseases, 1.474 (95% CI 1.287, 1.851). However, for a rather larger group of malignant endpoints the LDEF was significantly less than 1, with central estimates generally ranging from 0.2-0.8, in particular for tumours of the respiratory system, vasculature, ovary, kidney/urinary bladder, mammary gland and testis. For neutron exposure most endpoints, malignant and non-malignant,

showed downward curvature in the dose response, and for most endpoints this was statistically significant ($p<0.05$). Associated with this, the LDEF associated with neutron exposure was generally statistically significantly <1 for most malignant and non-malignant endpoints, with central estimates mostly in the range 0.1-1.1. There were statistically non-significant decreases of risk per unit dose at low gamma dose rates (5 mGy/hr) for most malignant endpoints, and non-significant increases in risk per unit dose at low gamma dose rates for most non-malignant endpoints. Associated with this, the DREF for many tumour sites was in the range 1.2–2.3, albeit not statistically significantly elevated from 1, while for most non-malignant endpoints the gamma DREF was less than 1. After neutron exposure there were non-significant indications of lower risk per unit dose at low dose rates (5 mGy/hr) for most malignant endpoints, and for all tumours ($p=0.001$), and respiratory tumours ($p=0.007$) this reduction was conventionally statistically significant; for most non-malignant outcomes risks per unit dose non-significantly increased at lower doserates. Associated with this, the neutron dose-rate extrapolation factor is less than 1 for most malignant and non-malignant endpoints, in many cases statistically significantly so, with central estimates mostly in the range 0.0–0.5.