ANNEX F: INFLUENCE OF DOSE AND DOSE RATE ON STOCHASTIC EFFECTS OF RADIATION 665

234. It is now recognized that measurements of radiation-induced transformation need to be made with cells that have been allowed to attain asynchronous growth by plating at low density at least 40 hours before treatment [H9, H10]. Before 40 hours, transient asynchronous growth may cause large fluctuations in observed transformation frequencies for relatively small variations in plating time, because the susceptibility of the cell to transformation varies throughout the cell cycle. This may also be affected by radiation-induced cell cycle delay. The failure to recognize the importance of allowing cells to achieve asynchronous growth may account for some of the more complex dose-response relationships that have been observed. For example, Miller et al. [M8, M9] measured the effect on C3H10T½ cells of x-ray doses down to 0.1 Gy delivered just 24 hours after seeding. They found a plateau in the incidence of transformants per surviving cell between about 0.3 and 1.0 Gy (Figure XVIII). With this unusual dose-response curve there could be substantial underestimation of the effect at low doses if projecting from high doses alone on the basis of a linear model.

235. A similarly shaped curve can be fitted to the results of Borek and Hall [B21], which were obtained by irradiating fresh explants of golden hamster embryos either with single doses or with two fractions of x rays. Because of the greater sensitivity of this system, the apparent plateau in response is at doses below 0.1 Gy. However, a linear relationship cannot be excluded on statistical grounds. Similar dose-response kinetics have been observed for experiments performed with asynchronously growing cells and in some cases with cells irradiated in the plateau phase.

236. C3H10T½ cells irradiated at low density 48 hours or more after initial seeding are determined to be growing asynchronously and increasing exponentially [H9, H10]. The dose-response data reported for low-LET radiation, expressed as transformation frequency per surviving cell, can be fitted to a linear model for doses up to about 2 Gy. However, the quadratic model cannot be excluded on statistical grounds. For single exposures to 60Co gamma rays (1 Gy min⁻¹) Han et al. [H5, H6] reported a linear response up to 1.5 Gy for transformation in C3H10T½ cells described by I(D) = 2.58D 10⁻⁴ Gy⁻¹ (Figure XIX), which agrees remarkably well with the dose response obtained up to 2 Gy for acute x-irradiation (4 Gy min⁻¹) of I(D) = 2.50 ± 0.11D 10⁻⁴ Gy⁻¹ by Balcer-Kubiczek et al. [B1] for 36-hour asynchronous cultures (Figure XX; see also paragraph 245). In both of these experiments the lowest dose used was 0.25 Gy. Little [L8] has compared results for two related mouse cell transformation systems: BALB/3T3 and C3H10T½ cells. Following exposure to up to 3 Gy from x rays, the shapes of the dose-response curves differed significantly: that for C3H10T½ cells appeared to follow a linear-quadratic or quadratic relationship, while that for BALB/3T3 cells was nearly linear (Figure XXI). A linear relationship was also obtained for BALB/3T3 cells exposed to beta particles from tritiated water [L11].

237. A linear dose-response relationship for transformation frequency with no suggestion of a threshold was also observed at doses up to 1.5 Gy for golden hamster embryo cells irradiated 72 hours after culture initiation [W3]. Above this dose a rather more shallow increase in transformation frequency per surviving cell was observed. By contrast, Bettega et al. [B11] irradiated asynchronously growing C3H10T½ cells with 31 MeV protons (~2 keV mm⁻¹), finding a transformation frequency per surviving cell that showed a marked change in slope over the dose range examined but in the opposite direction. Between 0.25 and 2 Gy the frequency was observed to increase slowly with dose, but above 2 Gy and up to 7 Gy it steepened very sharply.

238. X-irradiated contact-inhibited (plateau-phase) C3H10T½ cells have also been used to investigate induced transformation [T1]. A steep increase in transformation frequency up to a dose of about 0.5 Gy was observed with a doubling dose of about 0.2 Gy, followed by a slower increase over 1-4 Gy with a doubling dose of 1 Gy and a plateau above 6 Gy. For plateau cells the D0 was 1.53 Gy. Contact-inhibited cells are perhaps closer to the state prevailing in vivo. However, there are technical problems associated with the cell density of plating that may affect the results from confluent cultures, as well as with the more widely used technique of low-density plating of asynchronously growing cells.

2. Dose rate and fractionation

239. Early results for the exposure of C3H10T½ cells to fractionated doses of x rays [H4] and for exposures to high and low dose rates of 60Co gamma rays [H5, H6] using an experimental system involving irradiation of established asynchronously growing C3H10T½ cells, which had been in culture for at least 40 hours, indicated that transformation frequency per surviving cell was reduced significantly with fractionated or protracted exposure as compared with single acute exposures. Analysis of the experimental data suggested fractionation allowed the error-free repair of subtransformation damage.

240. When considering protracted or fractionated exposures to low-LET radiation, the relative times of cell plating and irradiation are important. Complex dose-response relationships have been shown in the
region of 0.3-1.5 Gy when C3H10T½ cells are irradiated soon after seeding (Figure XVIII). Approximate doubling of the transformation frequency per irradiated cell can be observed when doses in this range are given in two fractions [M8]. Higher numbers of equal fractions, up to three or four, spread over 5 hours lead to an almost proportional increase in the observed transformation frequency [H1]. This enhancement was also observed when freshly plated C3H10T½ cells were irradiated with gamma rays to a dose of 1 Gy delivered over 6 hours rather than 10 minutes [H1]. Above a dose of about 1.5 Gy, no enhancement at reduced dose rate was observed. Thus using this particular experimental approach in the dose range of about 0.3-1.5 Gy, the transformation frequency can be enhanced either by splitting the dose into a number of fractions or by protracting the dose over a similar interval. At 2 Gy, no effect was observed. A similar enhancement in the observed transformation frequency per surviving cell has been observed with freshly seeded Syrian hamster embryo cells irradiated with fractionated doses of 0.5 and 0.75 Gy [B21, B22], for similarly treated BALB/3T3 cells at doses below 2 Gy [L8] and for C3H10T½ cells exposed to 244Cm alpha particles giving doses in the range 2 mGy to 3 Gy [B43].

241. This enhancement in transformation with fractionation of the dose has not been observed for other biological effects of low-LET radiation either in vitro or in vivo, and the explanation appears to lie in the shape of the dose-response curve for cells irradiated soon after seeding, when parasympathetic sensitization effects may apply. In the plateau region between 0.3 and 1.5 Gy, where the effect is roughly independent of dose (Figure XVIII), irradiation with two fractions that are assumed not to interact will approximately double the transformation yield. In addition, from this curve, extrapolation from intermediate and high doses will substantially underestimate the true transformation frequency at low doses, particularly when delivered at low dose rate or in several fractions. These results are in contrast to radiobiological expectations, and in view of the interest surrounding them, further, more extensive experiments have been conducted [B1, B2, H6, H9, H10].

242. Han et al. [H6] have compared the transformation frequency in C3H10T½ cells exposed to either single doses (0.25-1.5 Gy; 1 Gy min⁻¹) of 60Co gamma rays or five equal fractions (0.5-3 Gy; 0.5 Gy min⁻¹) separated by 24 hours. Transiently parasympathetic asynchronous cultures were incubated for at least 40 hours before the beginning of irradiation to ensure asynchronous growth. For both patterns of exposure the dose response could be fitted with a linear function, but for fractionated exposures the transformation frequency for surviving cells (0.8 10⁴ Gy⁻¹) was about a third of that obtained after acute exposure (2.6 10⁴ Gy⁻¹), indicating a DDREF of 3.2 (Figure XIX). The reduction in the slope with fractionated exposure indicates that subtransformation damage can be repaired even in the dose region where transformation is apparently linearly dependent on the dose. This is clearly contrary to the autonomous single-hit interpretation of the linear dose-response relationship. However, it is possible that linear and quadratic terms are both present, but that the data are insufficient to allow them to be resolved.

243. Similar results have been obtained by Terasima et al. [T1], who compared the induction of cell transformation and cell killing in plateau-phase C3H10T½ mouse cells by single doses or two fractions separated by intervals between 3 and 15 hours. On the linear component of the dose-response curve (up to 4 Gy) with total doses of 0.9 and 1.9 Gy, fractionation decreased transformation frequency by about 50%, although very variable results were obtained. At the highest dose used (3.7 Gy) the decrease was by a factor of about 2. Watanabe et al. [W3] have reported that for asynchronously growing golden hamster embryo cells exposed to x rays at various dose rates, lower dose rates (0.5 Gy min⁻¹) were less effective in inducing transformations than high dose rates (6 Gy min⁻¹) by a factor of about 2.

244. The use of C3H10T½ cells in plateau phase also demonstrated the repair of potential transformation damage. Results obtained by Terasima et al. [T1, T13] showed that a rapid reduction of transformation frequency occurred over a period of 6-7 hours after a single dose (3.7 Gy) of 200 kVp x rays, if the irradiated cultures were kept in a confluent state before plating cells at a low density for transformation assay. In two of the three media used, the overall transformation frequency was reduced to about one fourth of that obtained with no post-irradiation period of incubation. The results indicated the repair of potential transformation damage had a half-time of about 3 hours. At times longer than about 7 hours the transformation frequency tended to increase again, although the results were widely variable.

245. Bolcer-Kubiczek et al. [B1] studied the dose-rate effect in C3H10T½ cells in some detail, using protracted exposure to x rays of transformed and non-transformed cells. In an initial study on 36-hour asynchronous cultures, similar survival curves for both cell types at doses up to 2 Gy (0.4 Gy min⁻¹) were obtained, indicating similar repair capacity of transformed and non-transformed cells, a result consistent with that of Hill et al. [H8]. In a second series of experiments, cell transformation from acute exposure was compared with that from protracted exposure. For
protracted exposure the dose rate was proportional to the total dose, giving a constant exposure time, so that the repair time was equal at all doses levels. The dose-response curves for oncogenic transformation in the low-dose range between 0.25 and 2 Gy were consistent with a linear response, giving parameters of $2.5 \pm 0.11 \times 10^{-4}$, $1.5 \pm 0.03 \times 10^{-4}$ and $0.87 \pm 0.05 \times 10^{-4}$ Gy$^{-1}$ for acute (<5 min) and 1-hour and 3-hour protracted exposures, respectively (Figure XX). These results indicate that in the linear dose-response range between 0.25 and 2 Gy, oncogenic transformation is reduced by a factor of up to about 3 with protraction of exposure. A linear-quadratic model could also be fitted to the results, but without a common linear term. The results are consistent with a reduction in slope of the dose response as the exposure time is increased.

246. In an extension of this work, Balcer-Kubiczek et al. [B2] examined the effect of dose protraction in the range 0.25-2 Gy with acute exposure and protracted exposures over 1, 3 and 5 hours. Results similar to those of the previous study were obtained for comparable exposure conditions ($2.33 \times 10^{-4}$, $1.55 \times 10^{-4}$ and $1.01 \times 10^{-4}$ Gy$^{-1}$ for acute, 1-hour and 3-hour exposures, respectively). For protraction of the dose over 5 hours, a transformation frequency of $0.56 \times 10^{-4}$ Gy$^{-1}$ was obtained. Thus, the overall reduction in oncogenic transformation with protraction was by a factor 4.5. Based on an analysis of the dose-response data using a linear-quadratic function, a repair half-time for cell transformation of 2.4 hours (95% CI: 1.8-3.0) was estimated. Interestingly, this compares well with a typical value for chromosomal aberrations of about 2 hours [P5].

247. The effect of dose rate on transformation frequency has also been examined in golden hamster embryo cells exposed to x rays at different dose rates (0.05 Gy min$^{-1}$, 0.75 Gy min$^{-1}$ and 6 Gy min$^{-1}$), giving total doses up to 4 Gy. The transformation frequency increased steeply with increasing dose at all dose rates up to a total dose of 1.5 Gy, with the highest dose rate giving a transformation frequency about 1.5 times that of the lowest dose rate at doses of about 1 Gy. At higher doses the increase in transformation frequency was less steep, and at 4 Gy the transformation frequency at the highest dose rate was about twice that at the lowest dose rate [W3].

3. High-LET radiation

248. An extensive series of studies has examined the effects of high-LET radiation on cell transformation. These studies have been confined largely to neutrons, covering a wide range of energies, although some data on the effects of heavy ions (95 MeV $^{14}$N, 22 MeV $^4$He) have also been published [S24]. For acute exposures, the effectiveness of high-LET radiation on transformation induction follows a pattern similar to that for chromosomal aberration induction, cell killing and other cellular endpoints [I6, S12]. In a review of published data, Barendsen [B9] suggested that a maximum RBE value of about 10 and 20 is typically found for 0.4-1 MeV neutrons. These RBE values tend to be higher than the equivalent values for cell reproductive death by a factor of 2-3 [I7] but similar to those found for dicentric aberration induction [I6, L12, S12] and somatic cell gene mutation by high-LET monoenergetic ions [C11]. Barendsen [B8] interpreted this difference as being due to the relatively large linear component found for cell reproductive death induced by low-LET radiation, in comparison with the corresponding value for cell transformation. In a recent review of data on oncogenic transformation of C3H10T$^+$ cells Miller and Hall [M46] noted that irradiation of cells with monoenergetic neutrons having energies between 0.23 and 13.7 MeV to doses of 0.05-1.5 Gy resulted in a linear response for both transformation and cell killing. When compared with results obtained with 250 kVp x rays, all neutron energies were more effective at both cell killing and induction of transformation. Values of the maximum biological effectiveness, RBE$_m$, were calculated from the initial linear term ($\alpha_t$, equation 11) for a linear-quadratic model fit to data on low-LET radiation such that

$$RBE_m = \frac{\alpha_t}{\alpha_x}$$

that is, the ratio of the initial slopes for cell transformation following exposure to neutrons, $\alpha_t$, and x rays, $\alpha_x$. Both cell survival and the induction of transformation showed an initial increase in effectiveness with increasing neutron energy, reaching a maximum at 0.35 MeV, followed by a subsequent decline (Figure XXII). This pattern of response is generally consistent with microdosimetric predictions, in that the neutron-induced recoil protons are shifted to lower linear energies as the neutron energy increases, and the effect of heavy recoils is lessened by saturation effects. The results obtained with heavy ions gave RBE values, relative to $^{60}$Co gamma rays, of 3.3 for $^{14}$N (530 keV $\mu$m$^{-1}$), 2.4 for $^4$He ions (36 keV $\mu$m$^{-1}$) and 3.3 for $^4$He ions with a 100 $\mu$m Al absorber (77 keV $\mu$m$^{-1}$) [S24].

249. As previously described, fractionated and low-dose-rate exposures to low-LET radiation generally show a decrease in effectiveness for cell transformation. For high-LET radiation, however, such a dose-rate effect is not usually observed, leading to higher values of RBE for low-dose-rate or fractionated exposure conditions. Thus, for fission spectrum neutrons at high dose rate (0.1-0.3 Gy min$^{-1}$), the RBE for transformation of C3H10T$^+$ cells was about 2.5 when compared with high dose rate (1 Gy min$^{-1}$) gamma-ray
exposure from $^{60}$Co. With protracted exposure (0.86 mGy min$^{-1}$) or fractionated exposure (five fractions over 4 days at high dose rate) the RBE was about 20. Higher values of RBE might be expected with fractions given at low dose rate [H11]. Some cell transformation experiments have, however, indicated an inverse dose-rate effect, with certain energies of neutrons giving a greater transformation frequency at low dose rates than at high dose rates [H8, H10, H11, M11], although others have not [B3, B4, B12, H7, H20].

250. Hill et al. [H8, H10] first described an inverse dose-rate effect for oncogenic transformation in C3H10T$^{6}F$ cells exposed to fission spectrum neutrons produced by the Janus reactor and suggested that irradiation times of at least 50 minutes were necessary for enhancement of transformation. At low doses, fission neutrons administered either in dose fractions over 5 days [H11] or continuously for 5 days [H8] induced higher frequencies of transformation than cells exposed to single doses (Figure XXIII). Thus at doses in the range 0.025-0.1 Gy, a linear fit to the data at 0.38 Gy min$^{-1}$ gave a transformation frequency of 5.96 $10^{-4}$ Gy$^{-1}$, while at lower dose rates (0.86 mGy min$^{-1}$) the frequency of transformation was 5.3 $10^{-3}$ Gy$^{-1}$. Thus the incidence of transformation increased at the lower dose rate by a factor of about 9, corresponding to a DDREF of 0.11 [H10]. Later studies intended to clarify this effect have failed to find a factor of this magnitude. A two- to threefold enhancement at low dose rates of fission spectrum neutrons has been observed for transformation of fresh cultures of Syrian hamster embryo cells [J2], and a similar response has been found by Redpath et al. [R2, R16] with a Hela x skin fibroblast human cell hybrid system exposed to fission neutrons from both the Janus and TRIGA reactors. An enhancement in transformation frequency has been found by Yasukawa et al. [Y5]. For C3H10T$^{6}$F cells exposed to 2 MeV neutrons from a Van de Graaff generator, fractionation of a dose of 1.5 Gy (two fractions of 0.75 Gy at a 3 hour interval) increased the transformation frequency by about 50%, although with 13 MeV neutrons from a cyclotron the transformation frequency was reduced by about 30% with a similar exposure schedule. Enhancement of transformation was also seen by Yang et al. [Y1], who irradiated confluent cells with accelerated argon ions (400 MeV amu$^{-1}$; 120 keV $\mu$m$^{-1}$) and iron ions (800 MeV amu$^{-1}$; 200 keV $\mu$m$^{-1}$) and found an enhancement of transformation at low dose rates. This enhancement was found to be greater at lower doses.

251. Several laboratories have reported no inverse dose-rate effect with C3H10T$^{6}F$ cells for other high-LET radiations, such as $^{244}$Cm alpha particles [B12] and $^{241}$Am alpha particles [H7]. Balcer-Kubiczek et al. [B3, B4, B39] examined the dose-rate effect in some detail, using fission spectrum neutrons from a TRIGA reactor to irradiate exponentially growing or stationary cultures of C3H10T$^{6}F$ cells. No significant inverse dose-rate effect was obtained following exposure to 0.3 Gy at dose rates from 0.005 to 0.1 Gy min$^{-1}$. These data argue strongly against the hypothesis that differences in proliferative status of C3H10T$^{6}F$ may play a role in the determination of any dose-rate effect. In a second series, consisting of nine experiments, the induction of transformation in actively growing C3H10T$^{6}F$ cells at neutron doses from 0.05 to 0.9 Gy at dose rates of 0.0044 or 0.11 Gy min$^{-1}$ was examined. Again, no discernible dose-rate effect was obtained [B39]. In a third series, concurrent with the second and with the same exposure parameters, mutagenesis at the $hp$ and $a_{r}$ in A$^{r}$ cells was measured, and again no dose-rate effect was observed [B39].

252. Hill [H20], using both 30- and 46-MeV protons on beryllium failed to observe enhancement of transformation for low-dose-rate exposures. No difference in transformation frequency of rat tracheal epithelial cells was obtained in exposures to neutrons at 0.1-0.15 Gy min$^{-1}$ and 0.18 mGy min$^{-1}$. There was also no difference in the induction of metaplasia and tumours in tracheal cells exposed at high and low dose-rates. The exposure times for the low-dose irradiation were between 18 minutes and 3 hours [T14].

253. Saran et al. [S35] examined the effect of fractionation of the dose of fission-spectrum neutrons on exponentially growing C3H10T$^{6}F$ cells. With total doses of 0.11, 0.27, 0.54 and 1.1 Gy given either as single doses or in five equal fractions at 24-hour intervals, no significant difference in either cell survival or neoplastic transformation was obtained. In further studies, C3H10T$^{6}F$ cells were exposed to 1 and 6 MeV neutrons giving doses of 0.25 and 0.5 Gy either as single doses or in five fractions given at 2-hour intervals. Again, no significant difference between acute and fractionated exposures was obtained for survival or neoplastic transformation [S36].

254. Miller et al. [M11], investigated the effects of dose fractionation for monoenergetic neutrons of various energies generated by a Van de Graaff particle accelerator. Comparison of C3H10T$^{6}F$ cells exposed to low doses of neutrons given either in a single acute exposure or in five equal fractions over 8 hours showed that, of the wide range of neutron energies studied (0.23, 0.35, 0.45, 5.9 and 13.7 MeV), significant enhancement of transformation occurred only with 5.9 MeV neutrons. Of the neutron energies examined, 5.9 MeV neutrons had the lowest dose-averaged linear energy and linear energy transfer.

255. From these studies and a comparison of the available transformation data for C3H10T$^{6}F$ cells irradiated with neutrons, a dose-rate enhancement factor
of about 2-3 at low doses (less than 0.3 Gy) and dose rates below 0.01 Gy min\(^{-1}\) was suggested [M12]. It was concluded that the enhancement of transformation by fractionated or low-dose-rate exposures to neutrons appears to depend on radiation quality, with some neutron energies both above and below 5.9 MeV showing no dose-rate effect (Figure XXIV).

256. In a further study, Miller et al. [M28, M46] examined transformation induction in C3H10T\(\text{\textgamma}\) cells exposed to graded doses of 5.9 MeV neutrons given as a single acute exposure (30 mGy min\(^{-1}\)) or in five equal fractions 2 hours apart, or continuously over an 8-hour period at low dose rates (from 0.21 to 1 mGy min\(^{-1}\)). Although cell survival studies showed no differences in effect with a change in dose rate, oncogenic transformation was enhanced by a factor of 2-3 when the dose rate was reduced (Figure XXV). When the neutron dose was divided into five fractions given over 8 hours, the effect was intermediate between that for acute and low-dose-rate exposures. Further irradiation was given with deuterons with a LET of 40 keV \(\mu\)m\(^{-1}\), approximating the measured dose-mean lineal energy deposited in the nucleus of C3H10T\(\text{\textgamma}\) cells by 5.9 MeV monoenergetic neutrons. An inverse dose-rate/dose-fractionation effect for the induction of transformation by these high-LET deuterons was observed when the time between each of three fractions for a 0.3 Gy total dose was at least 45 minutes. Although the transformation frequency increased by a factor of about 2, no further enhancement was seen for longer fractionation periods, suggesting that very protracted exposures of high-LET radiation would produce no additional enhancement.

257. A variety of results have thus been reported on the effects of dose rate on cell transformation \textit{in vitro}. The consistent features that have emerged on the response of C3H10T\(\text{\textgamma}\) cells to various patterns of neutron exposure have recently been summarized [B30, H31]:

(a) enhancement of transformation with dose protraction is not observed with low-LET radiation;
(b) the greatest enhancement for fission neutrons occurred at dose rates below \(-10\) mGy min\(^{-1}\);
(c) for fission (and all other) neutron irradiation at dose rates above \(-10\) mGy min\(^{-1}\), little or no enhancement is apparent;
(d) monoenergetic neutrons produce a significantly smaller enhancement than do fission neutrons;
(e) charged particles with LET much above 140 keV \(\mu\)m\(^{-1}\) produce little or no enhancement;
(f) the effect appears most prominent at doses around 0.2 Gy, with less evidence of enhancement at doses much above or below this.

258. A number of biophysical models have been proposed to account for this inverse dose-rate effect. The relevance of differential radiation sensitivity through the cell cycle was pointed out by Ofedal [O2], and its application to the inverse dose-rate effect observed in transformation studies was first formalized by Rossi and Kellner [R5], who postulated that cells in a particular "window" of their cycle may be more sensitive to radiation (for the end-point of interest) than cells in the rest of the cell cycle. If this is the case, an acute exposure of cycling cells to high-LET radiation will result in some fraction of these sensitive cells receiving (on average) very large deposits of energy, much greater than required to produce the damage that may lead to oncogenic transformation. On the other hand, if the exposure is protracted or fractionated, a larger proportion of sensitive cells will be exposed, although to smaller (on average) amounts of energy deposited; the total energy deposition per cell would still be sufficient to produce a potentially oncogenic change in the cell. To the extent that this later postulate may not apply to low-LET radiation, the inverse dose-rate effect would not be expected to apply. To account for the data first published by Hill et al. [H10], suggesting enhancement by a factor of up to 9 with fractionated exposures, a rather short "window" of only about 5 minutes duration was proposed. With the exception of this early report, the data on enhancement due to dose protraction now all suggest an enhancement factor of up to about 2 or 3, and on this basis the model framework proposed by Rossi and Kellner [R5] has been revised by Brenner and Hall [B30] and Hall et al. [H31], as summarized below.

259. The probability that a particular cell will be exposed to a given number of tracks is given by the Poisson distribution. Thus the probability, \(P\), that a cell will receive at least one track will be

\[ P = 1 - e^{-N} \quad (18) \]

where \(N\) is the average number of tracks, which at a dose \(D\) (given in Gy), delivered acutely, will be

\[ N_a = 5Dd^2/\gamma_F \quad (19) \]

where \(\gamma_F\) is the (frequency) average lineal energy (the microdosimetic correlate of LET (given in keV \(\mu\)m\(^{-1}\)) deposited in the nucleus, which is assumed to be spherical with diameter \(d\) (given in \(\mu\)m). It is assumed that the entire nucleus is the target. Not all the cells will be in the sensitive phase during a short acute exposure; the proportion in the sensitive phase, \(Q_s\), will be

\[ Q_s = \tau/s \quad (20) \]

where \(\tau\) is the duration of the sensitive period of the cell cycle and \(s\) is the total length of the cycle. Now, assuming that any number of high-LET tracks is equally likely to produce the damage that can lead to transformation, the overall probability will be
\[ P_T = Q_s P_s \]  

(21)

where \( P_s \) is given by equations 18 and 19. Thus, the transformation rate due to this process will be

\[ T = KQ_s P_s \]  

(22)

where \( K \) is a constant. It seems unlikely that cells in the rest of the cell cycle will be completely insensitive to the induction of transformation. Based on the low-LET dose response where the effect of the sensitive phase should be less evident, the dose-response relationship for cells damaged in phases other than their sensitive phase can be approximated by a linear-quadratic function. Thus, the total transformation rate is

\[ T_a = KQ_s P_s + \alpha_1 D + \alpha_2 D^2 \]  

(23)

If the dose is not delivered acutely but at a dose rate \( \dot{D} \) over a time \( t = \frac{D}{\dot{D}} \), then the average number of tracks through each nucleus in the sensitive phase will decrease from \( N_a \) to \( N_c \):  

\[ N_c = N_a \frac{\tau}{(t + \tau)} \]  

(24)

However, the proportion of cells exposed in the sensitive phase will be increased from \( Q_s \) to \( Q_c \):  

\[ Q_c = \frac{(t + \tau)}{t}/s \]  

(25)

For \( t + \tau < s \), the overall transformation rate will be

\[ T_c = KQ_c P_c + \alpha_1 D + \alpha_2 D^2 \]  

(26)

where \( P_c \) is given by equations 18 and 19. Finally, for an irradiation that is divided into \( n \) equal fractions, where the time between fractions is longer than \( \tau \), the expressions become

\[ N_f = N_a/n \quad \text{and} \quad Q_f = n \tau/s \]  

(27)

and

\[ T_f = KQ_f P_f + \alpha_1 D + \alpha_2 D^2 \]  

(28)

where \( P_f \) is given by equations 18 and 19.

260. Based on the critical assumption of a target size of 8 \( \mu \text{m} \) (corresponding to the average size of the nucleus of a C3H10T\( \frac{1}{2} \) cell) and a value for \( \alpha_0 \) of 0.29 \( 10^{-4} \), determined from experimental data [M28], the parameters \( \alpha_1 \), \( K \), and \( \tau \) were determined as a best parameter fit for the experimental data shown in Figure XXV for 5.9 MeV neutrons. The model fit to the data was obtained with a period of sensitivity of 61 minutes and values for \( \alpha_1 \) of 4.0 \( 10^{-4} \) Gy\(^{-1} \) and for \( K \) of 1.3 \( 10^{-4} \). This rather longer period of sensitivity, \( \tau \), is more reasonable in terms of the period of the entire cell cycle. A feature of the model is that the time between fractions needs to be longer than \( \tau \), the length of the sensitive window, for a dose-fractionation effect to be observed. As the time between fractions decreases, the exposure will become increasingly similar to an acute exposure. The model appears to give a reasonable fit to much of the reported experimental data on the C3H10T\( \frac{1}{2} \) system and predicts little enhancement of effect for alpha-particle irradiation, as is observed. For intermediate-LET radiation, such as fission neutrons, the effect would be confined to intermediate doses, as the model predicts that both acute and continuous transformation rates will have the same initial slopes.

261. The hypothesis that there is a narrow window (about 1 hour) of sensitivity to oncogenic transformation requires that cells be cycling for the inverse dose-rate effect to be observed and therefore predicts no effect for plateau-phase cells. In a further study, Miller et al. [M17] investigated the LET-dependence of the inverse dose-rate effect using charged particles of defined LET. Parallel studies were conducted with plateau-phase and exponentially-growing C3H10T\( \frac{1}{2} \) cells exposed to single or fractionated doses of charged particles with LETs between 25 and 250 kV \( \mu \text{m}^{-1} \). Doses were delivered in three dose fractions, with various intervals from 0.3 minutes to 150 minutes between the fractions. Dose fractionation with prolonged time intervals enhanced the yield of transformed cells, compared with a single acute dose for a range of LET values between 40 and 120 kV \( \mu \text{m}^{-1} \). Radiations of lower or higher LET did not show this enhancement. This enhanced effect for cycling cells in log phase was not seen for cells in plateau phase, lending strong support to the model by Brenner et al. [B30]. These data by Miller et al. [M17] have also been analysed by Brenner et al. [B16] in the context of their model, but with the additional modification that the constant \( K \) was varied to reflect the specific energy deposition in the nucleus with varying LET. They concluded that the observed LET effects were well explained by the model, assuming a period of sensitivity within the cell cycle of about 1 hour. The inverse dose-rate effect disappears at very high-LET because of a reduction in the number of cells being hit and disappears at LET below about 40 kV \( \mu \text{m}^{-1} \) because the majority of the dose is deposited at low values of specific energy insufficient to produce the saturation phenomenon central to the effect. At even lower LET damage repair will produce a characteristic "sparing" associated with protraction of x- or gamma-ray doses.

262. In a further analysis, the predictions of the model were tested by Harrison and Baic1-Kubiczek [H34]. Their analyses, based on unweighted least-squares techniques, suggested that there is no unique solution for \( \tau \) and that its value is critically dependent on the nuclear diameter. There were also difficulties applying the model to other neutron data on cell transformation. It is clear that the model proposed by Brenner and
Hall [B30], or some future derivative of it, will need to be tested for different doses, dose rates and dose-fractionation schemes to fully examine its general applicability. Ultimately a complete understanding of the inverse dose-rate effect must depend on experimental studies designed to elucidate the mechanistic basis of the observations [B45].

4. Summary

263. Cell transformation studies can yield information of practical use in radiation protection in addition to giving insight into the initial mechanisms of carcinogenesis. At present, the most quantitative data can be derived from cell systems that are not typical of the epithelial cell systems involved in most human cancers. The most commonly used cell lines include cultured embryo cells and the mouse fibroblast cell lines C3H10T½ and BALB/c3T3. Thus, when attempts are made to extrapolate to cancer induction in epithelial tissues in man, the biological limitations of these assay systems must be considered. In addition cell transformation studies have proved to be very difficult to standardize and there are technical uncertainties which must be taken into account in assessing the results of any studies. These include the effects of changes in response during the cell cycle, of plating density and of promoters and suppressors, some of which may be normal components of the growth medium, particularly the serum, and therefore difficult to control.

264. Nevertheless, in carefully controlled experiments where asynchronously dividing cells or, in some cases, non-dividing plateau-phase cells have been irradiated, the resulting observations of dose or dose-rate effects for low-LET radiation are in general agreement with those relating to other cellular effects, such as cell killing and the induction of mutations or chromosomal aberrations. Dose-response curves per cell at risk have a number of features in common with tumour induction in vivo, showing an initial rise in transformation frequency with increasing dose to a maximum and then a decline. When plotted as transformants per surviving cell, the dose response for low-LET radiation generally shows the expected linear or linear-quadratic relationship tailing off to a plateau at higher doses. When low doses of x rays or gamma rays are delivered at low dose rate or in fractionated intervals, a dose-rate reduction factor of between 2 and 4 is commonly found. It is noteworthy that some experimental data suggest that the linear term in the dose response may alter with dose rate, but this may be accounted for by the lack of precise data at low doses.

265. Exposures to high-LET radiation results in a higher transformation efficiency with a tendency towards a linear relationship, in line with data for chromosomal aberrations and again tending to a plateau at high doses. As expected from this pattern of response, there is no tendency for the response to decrease at low dose rates or with fractionation, and in practice, a number of studies have shown an enhanced effect. The main evidence for an inverse dose-rate effect with high-LET radiation seems to be limited to 5.9 MeV or fission spectrum neutrons, and over the past few years estimates of the magnitude of the increased effect have been reduced, from factors of about 9 to factors of about 2 or 3. Results reported from a number of laboratories have become reasonably consistent, and it has been possible to develop a model that can satisfactorily predict many experimental results. The model is based on the assumption that the target in the cell, taken to be the nucleus, has a "window" in the cell cycle during which it is more sensitive to radiation.

266. With protracted or fractionated exposures there is a greater opportunity for this particular "window" to be hit by at least one track and thus make possible an enhancement of transformation frequency with a reduction in dose rate. The magnitude of any effect will depend on the lineal energy, and with alpha-particle irradiation little enhancement would be expected, as is in fact observed. Although such a model appears to be consistent with much of the experimental data, it will need to be tested at different doses, dose rates and dose-fractionation schedules to fully examine its general applicability. Ultimately a complete understanding of the inverse dose-rate effect must depend on experimental studies designed to elucidate the mechanistic basis of the observations.

267. Despite this apparent explanation for the inverse dose-rate effect, there remains the problem that it is largely based on the results obtained with the C3H10T½ cell system and may well have only limited application to human carcinogenesis. The development of epithelial cell systems that are of much more direct relevance to human cancer should be a research priority. While some qualitative information is becoming available from such cell systems, no quantitative assays appear to be available at present.

C. MUTAGENESIS

268. It is generally believed (and pointed out in Annex E, "Mechanisms of radiation onogenesis") that the principal mechanism resulting in a neoplastic initiating event is induced damage to the DNA molecule that predisposes target cells to subsequent malignant development. There is also strong evidence linking a number of tumours to specific gene mutations. After the primary initiating event many genetic, physiological and environmental factors will influence the deve-
development and subsequent manifestation of a tumour. There is, however, a clear need to understand the role of both dose and dose rate in this initial genetic change. Studies on somatic and germ cell mutations both in vivo and in vitro are directly relevant to this question, although the results obtained have been somewhat variable. The effect of dose and dose rate on radiation-induced mutation in mammalian cells has been reviewed by Thacker [5], and a review of specific locus mutation rates in rodents was also prepared by the NCRP [N1].

1. Somatic mutations

269. A number of mutation systems have been described in the literature, but only a few are sufficiently well defined for quantitative studies. Mutation of a single gene is a relatively rare event; the majority of experimental systems are therefore designed to select out cells carrying mutations. Commonly used systems employ the loss of function of a gene product (enzyme) that is not essential for the survival of cells in culture. Thus, cells may be challenged with a toxic drug that they normally metabolize with fatal consequences. If mutation renders the gene producing the specific enzyme ineffective, the cell will survive, and thus the mutation frequency can be obtained by measuring the survivors. A frequently used example of such a system is that employing the loss of the enzyme hypoxanthine-canon phosphoribosyl transferase (HPRT), which renders cells resistant to the drug 6-thioguanine (6-TG), and of the enzyme thymidine kinase (TK) which gives resistance to trifluorothymidine (TFT). HPRT activity is specified by an X-linked gene hprt, while TK is specified by an autosomal gene tk, and therefore has to be used in the heterozygous state.

270. There are a number of difficulties with such somatic cell systems, and these have been reviewed [T5]. In particular, the mutation frequency of a given gene is to some extent modifiable, depending on the exact conditions of the experiment. There may also be a period of time for the mutation to manifest itself. In the unirradiated cell the enzyme would normally be produced and thus will be present for some time in the irradiated cell, even if it is no longer being replenished as a result of a specific mutation. An expression time is therefore normally left after irradiation before a cell is challenged by the specific drug. Ideally the mutation frequency would increase with time after irradiation to reach a constant level. This is not always the case, however, and the mutation frequency may reach a peak and subsequently decline. Thus the true mutation frequency may be difficult to determine, and this can present difficulties in studies of the effect of dose rate when exposures can be spread over varying periods of time.

271. Several established cell lines, derived from mouse, hamster or human tissue, have been used to measure mutant frequencies at different dose rates. The cell lines used experimentally can have sensitivities that depend on the stage of the cell cycle; therefore, to ensure as consistent a response as possible, it is preferable to use a stationary culture in plateau phase in which only a limited number of the cells will be cycling in the confluent monolayer [H21, M30]. The range of published data encompasses both a lack of effect of dose rate and a marked effect on induced mutant frequency [T5]. The data presented here are intended to illustrate the range of results available.

272. The first report on the effect of dose rate on hamster cell lines at low dose rates used hamster V79 cells and the hprt locus system [T2]. The cells were irradiated at dose rates of 1.7 Gy min\(^{-1}\) and 3.4 mGy min\(^{-1}\), with exposures taking up to five days at the low dose rates. A reduction in mutant frequency was obtained at low dose rates with a reduced effectiveness of between 2.5 and 4 at total doses between about 2 and 12 Gy. The dose-response relationship for mutation and survival was approximately the same. Further studies [C17] used growing V79 cells and compared dose rates of 4 Gy min\(^{-1}\) with 8.3 and 1.3 mGy min\(^{-1}\). The authors reported that 8.3 mGy min\(^{-1}\) reduced the mutant frequency compared with the high dose-rate exposure, and that, surprisingly, 1.3 mGy min\(^{-1}\) increased it.

273. A series of studies in Japan on a number of mouse cell lines [F6, N6, N7, S25, U29] reported that mutation frequency in growing cells was substantially reduced with decreasing dose rate over a range of dose rates from about 5 Gy min\(^{-1}\) down to 0.8 mGy min\(^{-1}\). Thus, for mutation resistance to both 6-TG and methotrexate a reduced effectiveness by a factor of about 2, was obtained at low dose rates for L5178Y cells when the linear term (\(\alpha_x\)) of the linear-quadratic model fit to high- and low-dose-rate data were compared [N6]. Similar results were also found with Ehrlich ascites mouse tumour cells used in plateau phase with the hprt gene locus system. At a dose rate of about 11 mGy min\(^{-1}\) compared with 10 Gy min\(^{-1}\), there was a reduction in effectiveness by a factor of about 2, although the extent of the reduction varied with experimental conditions [I5]. It was noteworthy in all these studies that change in mutant frequency with dose rate was paralleled by changes in cell inactivation, which might reflect mechanisms of DNA damage processing [T17].

274. Further studies were reported by Furuno-Fukushi et al. [F7], who used the hprt assay for 6-TG resistance and measured cell killing in growing mouse L5178Y cells exposed to 0.5 Gy min\(^{-1}\), 3.3 mGy min\(^{-1}\)
and 0.1 mGy min⁻¹. A marked increase in cell survival was observed with decreasing dose rate. At the low dose rate no reduction in the surviving fraction of cells was found up to a dose of 4 Gy, although only about 10% survival was obtained for the same total dose delivered at high dose rate. The induction frequency for mutations found at 3.3 mGy min⁻¹ was less than that obtained at the high dose rate (0.5 Gy min⁻¹) by about a factor of about 2. Surprisingly, there was little decrease in mutation frequency at the low dose rate (0.1 mGy min⁻¹) compared with that at 0.5 Gy min⁻¹ up to a total dose of about 3 Gy, and at the highest dose (4 Gy) the reduction was between that found at the high and intermediate dose rates. These results therefore suggest an inverse dose-rate effect for the low dose rate compared with the intermediate dose rate.

275. In a subsequent study, LX830 mouse leukaemia cells, which are more sensitive to cell killing by x-rays than L5178Y cells and 2-4 times more sensitive to mutation induction, were also exposed to 0.5 Gy min⁻¹, 3.3 mGy min⁻¹ and 0.1 mGy min⁻¹ [F8]. A slight, but significant increase was observed in cell survival with decreasing dose rate up to a dose of about 1 Gy. Beyond that, increasing doses at the lowest dose rate (0.1 Gy min⁻¹) did not reduce survival further, although the higher dose rates continued to show an exponential decrease in survival with increasing dose. The mutation frequency increased linearly with dose at all three dose rates, but no significant difference in response was found between the different dose rates. This is consistent with the finding that the LX830 cells are deficient in repair and that this produces a nearly dose-rate-independent response for mutation [E4].

276. A very different sensitivities has been reported by Evans et al. [E5], who assayed for the hprr gene mutant frequency in the radio-resistant L5178Y-R cells. At very low dose rates (0.3 mGy min⁻¹ from x-rays), there was little difference in mutation frequency compared with that at 0.88 Gy min⁻¹. The results also indicated the progressive loss of slow-growing mutants.

277. Evans et al. [E7] also compared the effects of dose rate (0.88 Gy min⁻¹ and 0.3 mGy min⁻¹) on mutation frequency in two strains of L5178Y cells with differing radiation sensitivities. The induction of mutants at the heterozygous tk locus by x-irradiation was dose-rate-dependent in L5178Y-R16 (LY-R16) cells, but very little dose-rate dependence was observed in the case of L5178Y-S1 (LY-S1) cells. This difference may be attributed to the deficiency in DNA double-strand break repair in strain LY-R16. Induction of mutants by x-irradiation at the hemizygous hprr locus was dose-rate-independent for both strains, suggesting that in these strains, the majority of mutations at this locus are caused by single lesions.

278. Suspension cultures of human TK6 cells assayed for mutations at the hprr and rII loci after exposure to multiple acute doses of 10-100 mGy min⁻¹ for 5-31 days showed no significant cell inactivation but linear dose-response functions for mutation. The induction frequency was very similar to that following acute exposures. Similar results were obtained by Koenig and Kiefer [K4], who found no changes in mutant frequency in human TK6 cells at low dose rates (0.45 and 0.045 mGy min⁻¹).

279. In recent experiments Furuno-Fukushi et al. [F2] examined the induction of 6-TG resistance in cultured near-diploid mouse cells (mSS) in plateau and log phase following exposure to gamma rays at dose rates of 0.5 Gy min⁻¹, 3 mGy min⁻¹ and 0.22 mGy min⁻¹. In plateau-phase culture, lowering the dose rate from 0.5 Gy min⁻¹ to 0.22 mGy min⁻¹ resulted in an increase of cell survival and a marked decrease in induced mutation frequency. A reduction factor of more than about 3 was obtained at 2 Gy from data obtained for high- and low-dose-rate exposures. The frequency at 0.22 mGy min⁻¹ was not higher than that obtained at 3 mGy min⁻¹, contrary to previous findings on growing mouse L5178 cells [F7]. In contrast, in log-phase culture, the magnitude of the dose-rate effect was not marked, and up to about 5 Gy almost no differences in mutation frequency were found at the three dose rates examined. These results, together with those indicating an inverse dose-rate effect in growing mouse L5178 leukaemia cells [F7], show that cell growth during protracted irradiation significantly influences the effects of gamma rays, particularly for mutation induction.

2. Germ cell mutations

280. The measurement of germ cell mutation rates presents additional difficulties, as animal studies are needed to demonstrate the mutational response. The effect of dose rate on the induction of specific locus mutations has been reviewed by Searle [S26], by the NCRP [N1] and by Russell and Kelly [R11]. No repair of radiation damage has been demonstrated in mature sperm [N1, R6], reflecting the lack of cytoplasm and enzymic activity. A series of studies involving in vitro fertilization and embryonic culture of mouse oocytes has demonstrated, however, that x-ray-induced damage in mature sperm following exposure to 1-5 Gy can be repaired in the fertilized egg. Assay of chromosome aberrations in fertilized eggs treated with various DNA inhibitors has demonstrated that DNA lesions induced in sperm comprise
mainly double-strand breaks and base damage. It remains to be determined if the specific involvement of repair of a particular type of DNA damage leads to chromosome aberrations and mutations in fertilized eggs, and whether there is a dose-rate effect for such damage. No dose-rate effects appear to have been demonstrated so far [M48, M49, M50, M51]. Unlike mature sperm, spermatogonial cells are metabolically active, and repair processes can modify the yield of mutations or chromosomal aberrations with protracted irradiation. Mouse spermatogonial stem cell studies provided the first demonstration of a dose-rate effect for mutational changes.

281. Russell et al. [R6, R11] first showed that specific locus mutation frequencies after chronic exposures to $^{137}$Cs gamma rays ($\geq$8 mGy min$^{-1}$) were lower than after comparable acute x-ray exposures (0.72-0.9 Gy min$^{-1}$) at doses up to about 6 Gy (Figure XXVI). Similar results were reported by Phillips [P6]. The data available have been summarized by Searle [S26]. For chronic exposures the dose-response data were fitted with a linear function, but for acute exposures a peaked response was obtained; thus, the relative effectiveness of acute and chronic exposures (i.e. the magnitude of the dose-rate effect) varies with the exposure level considered. By comparing the linear fits of the data from 0, 3 and 6 Gy points following acute x-ray exposures with all the data obtained following chronic exposures (at 0.01 and 0.09 mGy min$^{-1}$), Russell [R7] obtained a ratio of 3.23 $\pm$ 0.62. Alternatively, fitting a linear function to the acute data obtained up to 3 Gy, on the assumption of a cell killing function being present at higher doses, gives a ratio of 4.0 [S26].

282. More information on the dose-rate effect for mutation frequencies in spermatogonia has been obtained with various dose rates and fractionation regimes. Russell et al. [R7, R11, R17] reported that mutation frequency decreased markedly as the dose rate is reduced from 900 mGy min$^{-1}$ to 8 mGy min$^{-1}$, although there appeared to be no further reduction at dose rates down to 0.007 mGy min$^{-1}$. Because this independence of dose rate had been shown over a more than one thousand-fold range, it was thought unlikely that mutation frequency would be further reduced at even lower dose rates. The mutation frequency obtained at dose rates from 720 to 900 mGy min$^{-1}$, with total doses up to about 6 Gy, was compared with that obtained at low dose rates, on the basis of linear fits to the data, to give a DDREF of 3.0 $\pm$ 0.41, in close agreement with previous estimates [R11].

283. To examine further this dose-rate effect, Lyon et al. [L17] compared the effects of single doses of about 6 Gy from x rays or gamma rays with those of various fractionation regimes. They found that if the gamma-ray exposure was split into 60 equal fractions of 100 mGy, given daily at 170 mGy min$^{-1}$, the mutation frequency (4.17 $10^{-5}$ per locus) was less than one third of that from a single gamma-ray exposure at the same dose rate (15.39 $10^{-5}$ per locus) and similar to the frequency obtained after giving a comparable dose at 0.08 mGy min$^{-1}$ over 90 days (3.15 $10^{-5}$ per locus). However, if 12 weekly doses of 0.5 Gy from x rays were given acutely the mutation frequency was similar to that found after a single acute exposure (12.61 $10^{-5}$ per locus). It may be concluded that repeated small doses, even if given at a moderately high dose rate, have less mutagenic effect than the same dose given at one time. With fewer fractions (i.e. larger doses per fraction) the effect is intermediate between the response for an acute exposure and chronic exposure (Table 16).

284. These results are very similar to those obtained for lung tumour induction in mice by Ulrich et al. [U26] (Section II.A.2.b), where the incidence of tumours for a given dose again depended on the dose per fraction. A similar explanation can be invoked, namely that with small doses per fraction, in this case $\sim$100 mGy given at a moderately high dose rate, the effect of each fraction will lie predominantly on the linear portion of the dose-response curve, and thus the overall response is similar to that for low-dose-rate exposure. With larger fractions (0.5 Gy) the quadratic function makes an increasing contribution to the response, and thus an effect between acute and chronic exposure conditions is obtained.

285. Based on the above results of dose-rate effects on mutation rates in spermatogonia, a DDREF of 3 has been applied by the Committee since the UNSCEAR 1972 Report [U5] for assessing the risks of hereditary disease at low dose rates. This value of DDREF was also applied in the UNSCEAR 1988 Report [U1].

286. It is also possible to examine the effects of radiation on translocations induced in spermatogonial cells by subsequent examination of the spermatocyte stage. Clear evidence of dose fractionation effects have been observed in the mouse, and these were reviewed by the NCRP [N1] and more recently by Tobari et al. [T9]. Dose-rate reduction factors from 3 to $>$10 have been obtained.

287. In a recent study [T9], the induction of reciprocal translocations in the spermatogonia of the adult crating monkey (Macaca fascicularis) was examined following chronic gamma-irradiation to total doses of 0.3, 1.0 and 1.5 Gy (0.018 mGy min$^{-1}$, about 0.024 Gy in 22 h d$^{-1}$). Two or three monkeys were used for each dose level, and in each testis reciprocal translocations were scored in 1,000-1,250 spermatocytes.
The dose-response relationship for the frequency of translocation per cell could be represented by a linear function \( l(D) = 0.09 + 0.16D \), where \( l(D) \) is the frequency of translocations (\%) and \( D \) is the dose in gray. After acute exposure to x-rays at high dose rates (0.25 Gy min\(^{-1}\)) the dose response was also found to be linear, at least below 1 Gy, and fitted by the equation \( l(D) = 1.08 + 1.79D \) [M18]. Thus, at high dose rates the incidence of translocations was higher than at low dose rates by a factor of about 10.

288. In contrast, van Buul et al. [B24] found that, when the testis of the rhesus monkey was exposed to a gamma-ray dose rate of 0.2 mGy min\(^{-1}\) to give a total dose of 1 Gy, the yield of translocations was 0.38%, about one half the yield obtained at the same x-ray dose delivered at 0.3 Gy min\(^{-1}\) (0.83%). If a correction is made for the RBE of gamma rays, which is possibly about 0.5-0.7, the translocation yield would become more than one half that at high dose rate. It would appear from these results that the dose-rate effect is less pronounced in the rhesus monkey than in the crab-eating monkey.

289. These results suggest that a wide range of dose-rate effectiveness factors may be obtained, depending on the species and strain used for particular study. Reciprocal translocations are, however, two-bit aberrations, and the yield will be very dependent on recovery processes occurring between successive events. The marked difference in dose-rate effects between species may be accounted for by variable rates of repair in different species.

290. Effects of dose rate have also been studied in some of the germ-cell stages present in female mice. Mature and maturing oocytes have a much larger dose-rate effect than that found in spermatogonia [R18], and unlike the situation described earlier for spermatogonia one study has reported that the size of the dose-rate effect continues to increase when the dose rate is lowered below 8 mGy min\(^{-1}\).

291. Selby et al. [S38], using the specific-locus method, examined the effect of dose rate on mutation induction in mouse oocytes irradiated just before birth. Female mice were exposed to 3 Gy of whole-body x-irradiation at dose rates of 0.73-0.93 Gy min\(^{-1}\) and 7.9 mGy min\(^{-1}\) at 18.5 days after conception. The frequency of specific-locus mutations was assayed in the offspring of both control and exposed animals. The radiation-induced mutation frequency decreased from 6.1 \(10^{-5}\) to 4.2 \(10^{-6}\) mutations per gray per locus, i.e. by a factor of about 14, between acute and chronically exposed animals. Although the confidence limits of this estimate of the magnitude of the dose-rate effect are wide with an upper bound of infinity, the results indicate that mutational damage in females irradiated just before birth has a pronounced dose-rate effect. The mutation rate following exposures at low dose rates did not differ significantly from that in controls. Similar calculations, based on results of irradiating mature and maturing oocytes at the same dose rates (0.8-0.9 Gy min\(^{-1}\) and 8 mGy min\(^{-1}\)) [R18, R19], suggest an approximately fourfold reduction in the induced mutation frequency in the adult. With prolonged exposure and lower dose rates (0.09 mGy min\(^{-1}\)), a further reduction in mutation frequency was obtained. It was concluded that although the confidence limits on these estimates of the reduction factor at low dose rates were large, the results suggested that females irradiated just before birth had a more pronounced dose-rate effect for mutational damage to oocytes than those irradiated later [S38].

292. Irradiation of mice with high-LET radiation from fission neutrons has shown average values of RBE of about 20 (range: 10-45), relative to chronic irradiation with gamma rays, both with spermatogonial and oogonal irradiation [I6, S12]. Spermatogonia show little or no dose-rate effect with fission neutrons [R8] except at high doses (>2 Gy), where there is a suggestion of a reduced effectiveness, presumably due to selective cell killing of the spermatogonial population [B32, R8].

3. Summary

293. Studies on somatic mutations in vitro and germ cell mutations in vivo are relevant to assessing the effect of dose and dose rate on the primary lesion in DNA involved in tumour initiation, although subsequent tumour expression will depend on the influence of many other factors. The results obtained in different studies on somatic cell mutations in mice have been somewhat variable, but the overall extent of the dose-rate effect indicates a maximum value of about 2-3. A DDREF of about 3 for specific-locus mutations has also been found in mouse spermatogonia for dose rates that vary by a factor of more than 1,000, and for reciprocal translocations DDREFs up to about 10 have been reported, although there appear to be considerable differences between species. Based on these results, a DDREF of 3 for damage to spermatogonia has been applied by the Committee since the UNSCEAR 1972 Report [U5] for assessing the risks of hereditary disease at low dose rates. The DDREF in mature and maturing mouse oocytes appears to be larger than that in spermatogonia, with the main difference being that the mutation rate continues to decrease when the dose rate decreases below 8.0 mGy min\(^{-1}\). Mouse oocytes present just before birth appear to show a more pronounced dose-rate effect than mature or maturing oocytes, with a DDREF of about 14.
III. DOSE AND DOSE-RATE EFFECTS IN HUMAN CANCER

294. In general, epidemiological studies on the induction of cancer in human populations following exposure to low-LET radiation do not provide information on exposures at different dose rates that allow estimates to be made of dose-rate effectiveness factors. Furthermore, dose-response data are generally not available at the low doses needed to make good estimates of the linear component of the dose response (slope $\alpha$, Figure I). There are, however, some human data that can be used to assess likely dose-rate effects; these have been reviewed by the Committee [U1, U2].

295. In the UNSCEAR 1986 Report [U2] it was concluded from a review of dose-response relationships for radiation-induced tumours in man that for low-LET radiation the data available in some cases (lung, thyroid and breast) were consistent with linear or linear-quadratic models. For breast cancer linearity was considered more probable, as the incidence is little affected by dose fractionation. The Committee considered that for low-LET radiation linear extrapolation downwards from effects measured at doses of about 2 Gy would not overestimate the risk of breast and possibly thyroid cancer, would slightly overestimate the risk of leukaemia and would be likely to overestimate the risk of bone sarcoma (see paragraph 16). For radiation-induced cancers of most other organs only experimental data from animals were available on dose-response relationships, for which upward concave curvilinear dose-response relationships with pronounced dose-rate and fractionation effects are commonly found. The Committee concluded that if similar curves are applied to cancers in humans, a linear extrapolation of risk coefficients from acute doses in the intermediate dose region (0.2-2 Gy) to low doses and low dose rates would very likely overestimate the real risk, possibly by a factor of up to 5. Although some reference was made to the data on the survivors of the atomic bombings in Hiroshima and Nagasaki, the data were not fully utilized because of the uncertainties regarding the revision of the dosimetry. It was also noted that bone sarcoma induction after intake of radium isotopes shows a pronounced inverse relationship of latency to dose, resulting in an apparent threshold at low doses. For assessing the risk of lung cancer from exposure to radon the flattening of the response at higher cumulative exposures could result in an underestimation of the risk by linear extrapolation to low doses.

296. In the UNSCEAR 1988 Report [U1] epidemiological data on the effects of low-LET radiation relevant to assessing risks at low doses and dose rates were also summarized. The Committee considered the then most recent data on the atomic bomb survivors in Japan [P4, S9, S10], which took account of the new (DS86) dosimetry. For leukaemia, a significant difference in the excess relative risk per Gy of organ absorbed dose among survivors exposed to 0.5 Gy or more, as opposed to those exposed to lower doses (5.53 versus 2.44, respectively) was noted, suggesting a curvilinear dose-effect relationship for haemopoietic malignancies. For all cancers except leukaemia the excess relative risk associated with higher doses does not differ significantly from that at lower doses (0.41 versus 0.37, respectively) suggesting a linear response. No significant excess risk was observed at doses below 0.2 Gy, however. The scatter of the data points in the low dose region was such that they could be fitted almost equally well by a quadratic, linear-quadratic or linear dose-response relationship [S9].

297. The Committee also reviewed epidemiological studies of individuals exposed to $^{131}$I, which suggested that radiation doses from chronic internal exposures are less carcinogenic than similar doses of acute external radiation by a factor of at least 3 [N2] and possibly even 4 [H15], although non-uniformity of dose distribution within the thyroid gland may be a contributing factor. Breast cancer studies involving fractionated exposures provide some information on low-dose and low-dose-rate effectiveness factors. No fractionation effect was evident in a Massachusetts study of breast cancer following multiple fluoroscopic examination [B15]. However, in a similar but larger Canadian study, a non-linear dose response, especially at high dose, appeared to have been found. This would suggest a low-dose and low-dose-rate effectiveness factor greater than 1.

298. From examination of both experimental and human data the Committee concluded that reduction factors will vary with dose and dose rate and with organ system but will generally fall within the range 2-10. No dose or dose-rate reduction factor was considered necessary for high-LET radiation at low doses.

299. Since the publication of the UNSCEAR 1988 Report [U1], more information has become available from epidemiological studies that relate to considerations of dose-rate effects for low-LET radiation. The relevant studies are reviewed below.

A. LEUKAEMIA AND ALL OTHER CANCERS

1. Survivors of the atomic bombings in Japan

300. The follow-up study on the survivors of the atomic bombings in Hiroshima and Nagasaki continues to provide the main source of information on the effects on a population of exposure to ionizing radia-
tion. Information is available from 1950 to 1985 on mortality in just under 76,000 survivors for whom revised estimates of doses based on the new DS86 dosimetry system [R4] have been calculated [S9, S10].

301. The dose-response relationship for cancer mortality among the survivors of the atomic bombings in Japan has been examined by Pierce and Vaeth [P2, P3]. Their aim was to determine the degree of curvature in a linear-quadratic dose-response model that is consistent with the data. From this, possible values for a linear extrapolation overestimation factor (LEOF), which is equivalent to the dose and dose-rate effectiveness factor (DDREF), were derived.

302. Figure XXVII gives dose-responses for leukaemia and all cancers except leukaemia on the assumption of an RBE for neutrons of 10. For both sets of data any estimates of dose above 6 Gy (shielded kerma) have been reduced to 6 Gy. In both cases the data indicate a levelling off in the relative risk at doses above about 3 Gy. This apparent plateau at high doses may be due, at least in part, to cell killing, as appears to be the case in a number of animal studies (see Chapter II) and other human studies [S45], although it may in part be attributed to errors in exposure estimates.

303. Because of uncertainties as to the reason for this plateau, two approaches were taken by Pierce and Vaeth [P2, P3] in evaluating the dose-response data, namely:

(a) the dose range was limited to 0-4 Gy as well as 0-6 Gy. While this restriction in the range of exposures studied reduces the statistical power in studying the dose response, it should alleviate any bias in this relationship due to errors in estimates of high exposures. The linear-quadratic model assumption is also less critical if made over a restricted range of exposures;

(b) adjustments were made for random errors in the dosimetry of about 35% across the whole range of exposure estimates. Again, such errors could bias the shape of the dose-response curves and would lead to risk estimates higher by about 10%. Results of the unadjusted analysis were given for comparison.

The model fit adopted for all cancers except leukaemia was taken with excess relative risk constant in age-at-risk, but depending on age-at-exposure and sex.

304. Estimates of the LEOF were obtained based on the exposure range 0-4 Gy (DS86), with or without adjustment for random errors in dose estimates [P2]. Data were given for leukaemia, for all cancers other than leukaemia as a group and for combined inferences, assuming common curvature in these two disease categories. Estimates of the LEOF from analyses based on the range 0-6 Gy were lower than those based on the 0-4 Gy range. However, even after allowing for random errors in the exposure estimates, there is an indication that the analyses based on the 0-6 Gy range are unduly affected by the levelling off in the dose response beyond 4 Gy. Hence, the analyses based on the 0-4 Gy range are likely to be more relevant for the extrapolation of risks to low doses.

305. For the grouping of all cancers other than leukaemia, the maximum likelihood estimate of LEOF was 1.2, with a 90% confidence interval (CI) ranging from less than 1 to 2.3. However, after adjusting for random errors in the dose estimates, the best estimate of LEOF was 1.4 (90% CI: <1->3.1). Thus the data for all cancers other than leukaemia are fitted well by a linear dose-response model, although they are also consistent with a linear-quadratic model for which the linear extrapolation overestimation factor is between 1 and 3. For leukaemia, the maximum likelihood estimate of the LEOF from the Japanese data was 1.6 (90% CI: 1.0->3.1) without adjustment for random dosimetry errors and 2.0 (90% CI: 1.1->3.1) with adjustment for these errors. Thus, these data for leukaemia suggest that a linear dose-response model does not provide a good fit and that a linear-quadratic model with an LEOF of the order of 2 is to be preferred. For all cancers together an LEOF of 1.7 (90% CI: 1.1-3.1) was obtained with adjustment for random errors. Pierce and Vaeth [P2, P3] emphasized that the use of LEOFs much above 2 would need to be based upon information from experimental studies and that their inferences depended strongly on the assumption that a linear-quadratic model is appropriate for extrapolation to low doses.

306. It is clear that there are a number of limitations in the analysis of these data. The plateaus in the dose response at intermediate doses (Figure XXVII) imply that analyses of the shapes of the dose-response curves that include groups exposed at doses much above 3 Gy are likely to underestimate the contribution of the quadratic component to the dose-response function. Yet it is these same groups that make a significant contribution to the overall assessment of risk at high doses and high dose rates. A further problem lies in determining the initial slope of the dose-response function when only limited data are available at low doses.

2. Exposures from the nuclear industry

307. Several studies have been conducted of nuclear industry workers. In the United States, Gilbert [G14] performed a joint analysis of data from about 36,000 workers at the Hanford site, Oak Ridge National Laboratory and Rocky Flats weapons plant. Neither for
the grouping of all cancers nor for leukaemia was there an indication of an increasing trend in risk with dose. The upper limit of the 90% confidence interval for the lifetime risk corresponded to a value of 8.2 \(10^{-2}\) Sv\(^{-1}\) for all cancers and 0.6 \(10^{-2}\) Sv\(^{-1}\) for leukaemia.

308. A recent study of just over 95,000 individuals in the National Registry for Radiation Workers (NRRW) in the United Kingdom examined cancer mortality in relation to dose [K11]. For all malignant neoplasms, the trend in the relative risk with dose was positive but was not statistically significant (p = 0.10). Based on a relative risk projection model, the central estimate of the lifetime risk based on these data was 10 \(10^{-2}\) Sv\(^{-1}\) (90% CI: c0-26 \(10^{-2}\)). For leukaemia (excluding chronic lymphatic leukaemia, which does not appear to be radiation-inducible), the trend in risk with dose was statistically significant (p = 0.03). Based on a BEIR-V type projection model [C1], the central estimate of the corresponding lifetime risk was 0.76 \(10^{-2}\) Sv\(^{-1}\) (90% CI: 0.07-2.4 \(10^{-2}\)). The NRRW therefore provides evidence of a raised risk of leukaemia associated with occupational exposure to radiation, but, like the combined study of workers in the United States [G14], is consistent with the risk estimates for low-dose, low-dose-rate exposures derived for workers by ICRP [I2] from the Japanese survivor data (4 \(10^{-2}\) Sv\(^{-1}\) for all cancers and 0.4 \(10^{-2}\) Sv\(^{-1}\) for leukaemia) which include a DDREF of 2. In particular, combining the results of the NRRW and the United States studies produces central estimates for the lifetime risk of 4.9 \(10^{-2}\) Sv\(^{-1}\) (90% CI: c0-18 \(10^{-2}\)) for all cancers and 0.3 \(10^{-2}\) Sv\(^{-1}\) for leukaemia (excluding chronic lymphatic leukaemia) [K11]. These values are similar to the ICRP [I2] risk estimates, and generally support the use of a low DDREF in assessing risks at low doses and dose rates from high dose and dose-rate studies.

309. Information has recently become available from a number of low-dose-rate studies in the former USSR. Kossenko et al. [K10] have followed up the population of about 28,000 persons exposed as a result of the release of radioactive wastes into the Techa river in the southern Urals. The study shows a statistically significant increase in the risk of leukaemia estimated to be 0.85 (CI: 0.24-1.45) per \(10^{4}\) PY Gy. This is substantially smaller than the value of 2.94 per \(10^{4}\) PY Gy derived for the atomic bomb survivors [S9]. Some risk estimates are also available for cancers in a number of organs and tissues that are similar to those obtained from the atomic bomb survivors, but the confidence intervals are wide. The risk estimates for leukaemia therefore suggest a reduction in risk at low dose rates by a factor of about 3, although the data must be regarded as preliminary. Further extended analyses are planned. Data are also available on the incidence of leukaemia among the workers at the Chelyabinsk-65 nuclear weapons plant [K12]. Film badge data are available on 5085 men in two facilities. Average cumulative doses varied between 0.49 and 2.45 Sv. When compared with USSR national rates for the period 1970-1986, the relative risk of leukaemia appeared to be increased with a relative risk of 1.45 Gy\(^{-1}\), which is about 2.7 times less than that based on the atomic bomb survivors (≥20 years, excess RR = 3.92 Gy\(^{-1}\) [S9]).

B. THYROID CANCER

310. A substantial number of studies have reported excesses of thyroid cancer in populations exposed to external radiation. Many of these studies were summarized in the UNSCEAR 1988 Report [U1] and by the NCRP [N2]. The information summarized in [N2] suggested risks of radiation-induced thyroid cancer are greater in children than in adults, by about a factor 2, and that females appear to be more sensitive than males by a factor of 2 to 3. Radiation-induced thyroid cancer risks in a population were calculated to be 7.5 \(10^{-4}\) Gy\(^{-1}\) and in adults to be about 5 \(10^{-4}\) Gy\(^{-1}\).

311. Information on the dose-response relationship for radiation-induced thyroid cancer is available from studies by Shore et al. [S11] on about 2650 persons who received x-ray treatment for purported enlarged thymuses in infancy. The 30 thyroid cancers detected in the irradiated group (<1 expected), when allocated to 5 dose groups, could be fitted by a linear dose-response relationship (Figure XXVIII) I(D) = 3.46 ± 0.82 per \(10^{4}\) PY Gy (±1 SE, p < 0.0001), although a linear-quadratic relationship could not be excluded.

312. Shore et al. [S11] also examined the effect of dose fractionation, as the number of dose fractions ranged from 1 to 11, with most subjects having 3 or fewer. Three semi-independent variables were tested: number of fractions, dose per fraction, and average interval between fractions. No evidence was obtained for a significant sparing effect for thyroid cancer associated with any of these three fractionation variables, although numerically the excess cancer risk per Gy was greater in the lowest dose-per-fraction group (0.01-0.49 Gy) than in the higher dose-per-fraction groups (0.5-1.99 Gy and 2.5-9.9 Gy), namely by a factor of 2-3, again possibly reflecting an effect of cell killing.

313. Data on thyroid cancer induction also comes from patients given \(^{131}\)I for diagnostic reasons [H13, H15, H35]. Holm et al. [H13] reported a retrospective study of 10,133 subjects given \(^{131}\)I for suspected thyroid disease. The population (79% females) had a mean age of 44 years. For the 9,639 adults (≥20 years of age) the mean calculated thyroid dose was 0.6 Gy,
whereas in the 494 younger subjects the mean dose was 1.6 Gy. Patients were followed for a mean time of 17 years after exposure to $^{131}$I. Only patients diagnosed more than 5 years after $^{131}$I exposure were included in the analysis. No excess of thyroid cancer was found, although the number of observed cases was small (8 observed, 8.3 expected).

314. For 35,074 patients in Sweden examined for suspected thyroid disorders between 1951 and 1969 the mean follow-up was 20 years [H15, H22]. The mean age at administration of $^{131}$I was 44 years; 5% were under age 20 years and the mean dose to the gland was about 0.5 Gy. Persons with a history of external radiotherapy to the head and neck region, or who had been given internal emitters, were excluded from the study. No overall excess risk of thyroid cancer in this group was observed.

315. Further information on thyroid cancer induction is available from groups given $^{131}$I for the treatment of hyperthyroidism. Although a number of studies have been reported, no evidence for radiation-induced cancer in these groups has been obtained. Treatment for hyperthyroidism, however, involves the administration of large quantities of $^{131}$I giving substantial doses to the thyroid (>20 Gy), which would be expected to result in substantial cell killing [H32].

316. An increased incidence of thyroid nodules has been seen in the inhabitants of the Marshall Islands who were exposed to weapons fallout [C19]. However, although a large proportion of the dose was contributed by short-lived isotopes of iodine ($^{132,133,135}$I), there was also a contribution from external radiation with only a small proportion of the dose coming from $^{131}$I. It is therefore difficult to use the data to assess any effect of dose rate on tumour induction.

317. There are some uncertainties regarding dosimetry in the studies of Holm et al. [H14, H15, H22]. The main factors influencing the calculated thyroid dose are the mass of the gland and the initial uptake of $^{131}$I. Animal studies suggest differences in distribution throughout the gland will be of less importance (see Section II.A.2.e). The mean thyroid weight was estimated on the basis of information in the records and available thyroid scintigrams to be <30 g in 42% of the patients, 30-60 g in 38%, and >60 g in 12%. In 8% of patients the thyroid weight was not assessed. No information is given in the paper on the uptake of $^{131}$I by the gland, but the calculated doses suggest 30% has been used, in line with recommendations by the ICRP [I3]. Both these parameters may affect the dose calculations, but taken together are unlikely to alter the average doses calculated by more than a factor of 2. The studies therefore suggest that $^{131}$I is less carcinogenic than acute exposure to external radiation, although these studies mostly involved adults who appear to be less sensitive to the induction of thyroid cancer than young persons.

318. Since the publication of the UNSCEAR 1986 Report [U2] further information has become available on possible effects of dose rate on breast cancer induction. Miller et al. [M32] have reported data from a number of provinces in Canada on mortality from breast cancer in tuberculosis patients irradiated during fluoroscopic examinations. Mortality data have been obtained for 31,710 women treated at sanatoriums between 1930 and 1952, known to be alive in 1950 and followed to 1980. A substantial proportion (26.4%) had received doses to the breasts of 0.1 Gy or more from repeated fluoroscopic examinations during therapeutic pneumothoraces. The principal difference among sanatoriums was that in Nova Scotia the patients usually faced the x-ray source, whereas in other provinces they were usually turned away from it. Various dose-response models were fitted to the data. The best fit was obtained with a linear dose-response relationship, and it was notable that a greater effect per unit dose was found in Nova Scotia than in the other provinces. Thus, the increases in relative risk were 1.80 and 0.53 Gy$^{-1}$ for Nova Scotia and the other provinces, respectively. In the BEIR V Report [C1] the difference in relative risk was given as a factor of 6. Even allowing for the differences in orientation during exposure this difference in response is surprising, and the authors considered that it could be due to a dose-rate effect. Although the mean numbers of fluoroscopic exposures were similar in the two groups, the dose rate in Nova Scotia was higher by more than an order of magnitude, although not higher than that in the atomic bomb survivors. These results would therefore be consistent with a dose-rate effectiveness factor greater than 1.

D. SUMMARY

319. The human data that are available for assessing the effects of dose rate on tumour induction from low-LET radiation are limited. In general, the information available is from exposures at high dose rates, and little information is available at doses of less than about 0.2 Gy. Analyses of dose-response relationships for solid tumours in the atomic bomb survivors are generally consistent with linearity but also with a small reduction in the slope of the dose-response at lower doses. For leukaemia among the atomic bomb survivors, however, the data are inconsistent with linearity, and the central estimate of the DDREF at low doses is about 2. Model fit to the dose-response
data for the atomic bomb survivors over the dose range 0.4 Gy kerma for all cancers combined, suggests a DDREF in the range of about 1.7 (when adjusted for random errors). For solid cancers alone, however, linearity provides a good fit, although the data are also consistent with a DDREF of the order of 2. This interpretation of the data depends on the assumption that a linear-quadratic model is appropriate for extrapolation to low doses and that the linear term can be adequately resolved. Information on thyroid cancer induction by acute external irradiation compared with low dose-rate exposure from intakes of $^{131}$I are consistent with a DDREF of about 3, although there is some question over the contributions that heterogeneity of dose and uncertainties in the dose estimates as well as the effect of age make to the overall reduction in risk. For female breast cancer the information is conflicting. Dose-response relationships for acute exposures and for fractionated exposures at high dose rates are consistent with a linear dose-response relationship. However, comparative data from Nova Scotia and from other Canadian provinces suggest a DDREF greater than one may be appropriate for assessing cancer risks at low dose rates. Although epidemiological studies of low dose-rate exposure should be more relevant for the purposes of radiological protection than studies at high dose rates, the former type of study at present lacks sufficient statistical power to allow risks to be estimated with tight confidence limits. However, the results of studies such as those of radiation workers are consistent with low values of DDREF.

IV. DESIGNATION OF LOW DOSES AND LOW DOSE RATES

320. The choice of bounds for low and high doses of low-LET radiation that are appropriate for decisions on whether to apply dose and dose-rate effectiveness factors (DDREFs) is not straightforward, as it is essential to understand both the physical and biological factors involved and their possible interactions. The physical factors, unlike the biological factors, are well understood as a result of the advances that have taken place in recent years in microdosimetry at the cellular and subcellular levels [B18, B20, G6, P1, R14]. This Chapter reviews the physical, experimental and epidemiological data that can be used as a basis for assessing either the doses or the dose rates below which it would be appropriate to apply a DDREF.

A. PHYSICAL FACTORS

321. The microdosimetric approach to defining low doses and low dose rates uses fundamental microdosimetric arguments that are based on statistical considerations of the occurrence of independent radiation tracks within cells or cell nuclei (Section I.A.3). Photons deposit energy in cells in the form of tracks, comprising ionizations and excitations from energetic electrons, and the smallest insult each cell can receive is the energy deposited from one electron entering or being set in motion within a cell. For $^{60}$Co gamma rays and a spherical cell (or nucleus) assumed to be 8 μm in diameter, there is on average one track per cell (or nucleus) when the absorbed dose is about 1 mGy [B18, B20]. This dose, corresponding to one track per cell, on average, varies inversely with volume and is also dependent on radiation quality, being much larger for high-LET radiation [G4, 14].

322. If the induction of cancer by radiation at low doses depends on energy deposition in single cells, with no interaction between cells, there can be no departure from linearity, unless there have been at least two independent tracks within the cell. The number of independent tracks within cells follows a Poisson distribution, as illustrated in Table 17, with the mean number of tracks being proportional to dose. For average tissue doses of 0.2 mGy from $^{60}$Co gamma rays, spherical cells (or nuclei) of diameter 8 μm each receive, on average, about 0.2 tracks (Figure III). Hence, Table 17 shows that, in this case, just 18% of the cells receive a dose and 90% of these cells receive only one track. Thus less than 2% of cells receive more than one track. Halving the dose will simply halve the fraction of the total cells affected, and so at such low doses the dose-effect relationship should be linear. There should be no dose-rate effect, because this only affects the time interval between energy deposition in different cells (Section I.A.3). This argument applies to all biological effects where the energy deposited in a cell produces effects in that cell and in no other cell. It is generally thought to apply to cell killing, chromosome aberrations and mutations. Its applicability to transformation and cancer is less certain. It would need modification, for example, if the probability of effect were so enhanced by a second track at a later time that the small minority of such cells were dominant. This could conceivably be the case for multi-stage carcinogenesis if more than one essential stage was likely to be caused by radiation.

323. To employ the microdosimetric argument for assessing low doses, a knowledge of the autonomous sensitive volume within a cell is required. Biological
effects are believed to arise predominantly from residual DNA changes that originate from radiation damage to chromosomal DNA. It is the repair response of the cell that determines its fate. The majority of damage is repaired, but it is the remaining unrepair or misrepaired damage that is then considered responsible for cell killing, chromosomal aberrations, mutations, transformations and cancersous changes. The link between DNA damage and cellular effects leads to the notion that the cell nucleus is the critical volume that should be used for these microdosimetric estimations of a low dose. A sphere of 8 μm diameter is representative of some cell nuclei; others may be smaller or larger. On this basis a low dose would be estimated to be less than 0.2 mGy. If part of the nucleus alone responds autonomously to radiation insults and repair, then a smaller volume may be appropriate, and the estimate of a low dose would increase. Conversely, if the entire cell or adjacent cells can be involved in a cooperative response, a larger volume may be appropriate. Figure XXIX shows, for various volumes and radiations, the doses that would correspond to this microdosimetric definition of a low dose. The most fundamental corresponding criterion for a low dose rate is that the dose should not be exceeded in a lifetime (say, 60 years), so that there should be negligible scope for radiation to cause multiple changes in a single cell or its progeny. By this criterion, a low dose rate would be less than about 10^{-8} mGy min^{-1}. A less cautious criterion, applicable to single-stage changes only, is that a low dose should not be exceeded in a time characteristic for DNA repair, say a few hours. In this case, a low dose rate would be less than about 10^{-3} mGy min^{-1}.

B. BIOLOGICAL FACTORS

324. A second approach to estimating a low dose and low dose rate is based on direct observations in animal experiments. The results of animal studies designed to examine the effect of dose and dose rate on tumour induction (see Section II.A and Table 8) suggest that an average dose rate of -0.06 mGy min^{-1} over a few days or weeks may be regarded as low. The choice by the Committee in the UNSCEAR 1986 Report [U2] of a low dose rate to include values up to 0.05 mGy min^{-1} appears to have come directly from dose rates used in animal studies. If it is assumed that dose-rate effects arise when sufficient damage accumulates in a cell within repair times characteristic for DNA damage (a few hours), then a rounded value of 20 mGy may be regarded as a low dose.

325. It should be noted, however, that experimental studies at "high" dose rates were mainly carried out in the range from about 100 to 800 mGy min^{-1} (Table 8), i.e. dose rates more than a thousand times those at the "low" dose rates for which a DDREF between 2 and 10 has been obtained. It seems likely that a reduction in tumour yield similar to that obtained at about 0.06 mGy min^{-1} would have been obtained at dose rates a few times higher, or lower, than this. There are analogies here with the data on mutation yield in mouse spermatogonia, for which a threefold reduction in yield was obtained at 8 mGy min^{-1} compared with 720-900 mGy min^{-1} (Section II.C.2), with no further reduction at 0.007 mGy min^{-1} [R18]. It may be concluded, therefore, on the basis of animal experiments that a low dose rate can be taken to be 0.1 mGy min^{-1} when averaged over about an hour.

326. A third approach to estimating low doses comes from parametric fits to observed dose-response data for cellular effects. As described in Section I.A.2, the effect can be related to dose by an expression of the form

\[ I(D) = \alpha_1 D + \alpha_2 D^{-2} \]  

(29)

in which \( \alpha_1 \) and \( \alpha_2 \), the coefficients for the linear and quadratic terms fitted to the radiation response, are constants and are different for different end-points. This equation has been shown to fit data on the induction of chromosome aberrations in human lymphocytes, for example, and also data on cell killing and mutation induction. For some types of unstable chromosome aberrations in human lymphocytes, the \( \alpha_1/\alpha_2 \) quotient is about 200 mGy for \( ^{60}\text{Co} \) gamma rays [L12], and thus the response is essentially linear up to 20 mGy, with the dose-squared term contributing only 9% of the total response. At 40 mGy the dose-squared term still only contributes about 17% to the overall response. On this basis it could, therefore, be estimated that 20-40 mGy is a low dose.

327. A fourth approach to estimating a low dose is based on the analysis of data from epidemiological studies, in particular from data on the survivors of the atomic bombings in Japan. Analysis of the dose response for mortality from solid cancers in the range 0-4 Gy (adjusted for random errors) has suggested an \( \alpha_1/\alpha_2 \) quotient from a minimum of about 1 Gy with a central estimate of about 5 Gy [P2, P3]. An \( \alpha_1/\alpha_2 \) quotient of 1 Gy suggests that at a dose of 100 mGy the dose-squared term contributes less than 10% to the response and at 200 mGy the contribution of the dose-squared term is still less than 20%. This would suggest that for tumour induction in humans a low dose can be taken to be less than 200 mGy. There is, in practice, little evidence of a departure from linearity up to about 3 Gy. In the case of leukaemia in the atomic bomb survivors, where there is significant departure from linearity at doses above about 1.5 Gy, the central estimate of \( \alpha_1/\alpha_2 \) has been calculated to be
1.7 Gy, with a minimum value less than 1 Gy [P2, P3]. On the basis of this central estimate the dose-squared term would contribute about 10% to the response at a dose of 200 mGy and about 23% at 500 mGy.

C. SUMMARY

328. A number of approaches based on physical, experimental and epidemiological data have been examined for assessing either doses or dose rates for low-LET radiation below which it would be appropriate to apply a dose and dose-rate effectiveness factor (DDREF). The fundamental microdosimetric argument indicates that a low dose, at which fewer than 2% of cells receive more than one track (assuming a cell diameter of 8 \( \mu m \)), is about 0.2 mGy. Since halving the dose will simply halve the fraction of cells affected, at such low doses the dose-effect relationship should be linear. This fundamental microdosimetric approach would have severe practical limitations in radiological protection, and there do not appear to be any experimental or epidemiological data that suggest that it should be applied.

329. Dose-response studies for cells in culture suggest that doses of less than about 20-40 mGy are low; however, epidemiological studies on the induction of solid tumours in the survivors of the atomic bombings in Japan indicate a linear dose response up to about 3 Gy, which suggests that for tumour induction a low dose would be at least 200 mGy. For leukaemia induction there is a significant departure from linearity at doses above about 1.5 Gy, but again a low dose can be taken to be less than 200 mGy.

330. Information on low dose rates for tumour induction can at present be obtained from animal studies. The results of a series of studies in experimental animals that are summarized in Table 8 suggest that a low dose rate can be taken to be less than about 0.1 mGy min\(^{-1}\) given over a few days or weeks.

331. The Committee concludes that for the purposes of assessing the risk of tumour induction in man a dose-rate effectiveness factor (DDREF) should be applied either if the total dose is less than 200 mGy, whatever the dose rate, or if the dose rate is below 0.1 mGy min\(^{-1}\) (when averaged over about an hour), whatever the total dose.

CONCLUSIONS

332. Information on dose and dose-rate effects on radiation response has been reviewed in this Annex with the aim of providing a basis for assessing the risks of stochastic effects at low doses and low dose rates from information available at high doses and high dose rates.

333. The conventional approach to estimating both the absolute and the relative biological effectiveness of a given radiation at minimal doses is based on the assumption, derived in general terms of target theory, that the induction of an effect can be approximated by an expression of the form

\[ I(D) = (\alpha_1 D + \alpha_2 D^2) e^{-\beta_1 D - \beta_2 D^2} \]  \hspace{1cm} (30)

in which \( \alpha_1 \) and \( \alpha_2 \) are coefficients for the linear and quadratic terms for the induction of stochastic effects and \( \beta_1 \) and \( \beta_2 \) are coefficients for linear and quadratic terms for cell killing. This equation has been shown to give a fit to much of the published data on the effects of radiation on cells and tissues, including cell killing, the induction of chromosome aberrations, mutation in somatic and germ cells, cell transformation and tumour induction. For tumour induction it is generally assumed that at sufficiently low doses \( \alpha_1 \) will be constant and independent of dose rate. In practice, however, tumour induction has rarely been observed either in experimental animals or in epidemiological studies at acute doses of much less than 200 mGy.

334. The reduction in effect per unit dose observed at low doses and low dose rates, compared with effects at high doses and high dose rates, is termed a dose and dose-rate effectiveness factor (DDREF), although the terms dose-rate effectiveness factor (DREF), linear extrapolation overestimation factor (LEOF) and low-dose extrapolation factor (LDEF) have also been used. At sufficiently low doses, when cell killing can be disregarded, the DDREF can be defined from the previous equation as

\[ DDREF = (\alpha_1 D + \alpha_2 D^2)/\alpha_1 D = 1 + (\alpha_2/\alpha_1)D \]  \hspace{1cm} (31)

where \( D \) is the dose (in gray) at which the effect is measured.

335. In the absence of clear information on the shape of the dose-response curve for tumour induction at low doses, the initial slope, \( \alpha_1 \), of the response at low doses can be determined, in principle, from exposures
at low dose rates. There are, however, limited data on
dose-rate effects on tumour induction in human popu-
lations and no information on the mechanisms in-
fluencing tumour development from which quantitative
data from numerous studies that violate this simple
estimates of dose-rate effects can be inferred. Animal
expectation, for both low-LET and high-LET radiation.
Studies and experiments on cell transformation and on
Many of these imply that multi-track effects can occur
somatic and germ cell mutation rates are therefore
in the intermediate-dose region (II) and that even
needed to provide insight into the likely effects of
when the dose response appears linear it may exhibit
both dose and dose rate on tumour induction. Biophys-
dose-rate dependence and non-linearity at lower
ical models of radiation action also provide an
doses.
effect on understanding how the fundamental inter-
actions of radiation with cells can play a part in dose-
rate effects.

336. Models of radiation action. Guidance on
expected effects at low doses and low dose rates can
be sought from radiobiological and epidemiological
data in terms of the quantitative models that have been
developed to describe them. Radiobiological data for
effects on single cells under a variety of conditions
have led to the development of many quantitative
models, mechanistic or phenomenological, for single
radiation-induced changes in cells. Multi-stage models
of radiation carcinogenesis, based on epidemiological
or animal data, assume that one or more changes are
required before a cell becomes malignant and that
radiation can induce at least some of these changes
(see Annex E, "Mechanisms of radiation oncogene-
sis"). The biophysical concepts underlying the
different models are described in terms of general
features of target theory, based on the insult of
ionizing radiation always being in the form of finite
numbers of discrete tracks. In this way fundamental
expectation can be sought on the nature of overall
dose responses, their dependence on dose rate and
their features at the low doses of practical importance.

337. Dose-response relationships can be subdivided
into regions. In region I a negligible proportion of
cells are intersected by more than one track, and hence
dose responses for single-stage effects can be confi-
dently expected to be linear and independent of dose
rate. In region II many tracks intersect each cell, but
multi-track effects may not be observed in the experi-
mental data, and hence independent single-track action
is commonly assumed, although true linearity and
dose-rate independence hinge on the validity of this
assumption. In region III multi-track effects are clearly
visible as non-linearity of dose response and hence
dose-rate dependence is likely. The simpler forms of
dose response can be expanded as a general poly-
nomial, with only the dose and dose-squared terms
being required to fit most experimental data, although
sometimes a separate factor is added to account for
competing effects of cell killing at higher doses. In
this approach it is common to regard the fitted linear
coefficient as being constant and fully representative
of the response extrapolated down to minimally low
dose and dose rate. However, the literature contains

338. Low-dose and low-dose-rate expectations based
on multi-stage processes of carcinogenesis depend
crucially on the radiation dependence of the individual
stages and on the tissue kinetics. Expectations could,
in principle, readily range between two opposite
extremes. On the one hand there could be the total
absence of a linear term, implying vanishing risk as
the dose tends to zero, as should be the case if two (or
more) time-separated radiation steps were required. On
the other hand, there could be a finite slope of the
dose response down to zero dose, and this could even
increase with decreasing dose rate, as may occur if
either of the stages can occur spontaneously and if
there is clonal expansion between them (see Annex E,
"Mechanisms of radiation oncogenesis").

339. Life shortening in experimental animals.
Radiation-induced life shortening in experimental
animals following exposure to both low- and high-
LET radiation at low to intermediate doses is mainly
the result of an increase in tumour incidence. There is
little suggestion that there is a general increase in
other causes of death into the lethal range, although
degenerative diseases in some tissues may be in-
creased at higher doses. On this basis, life shortening
can be used to assess the effect of dose fractionation
and protraction on tumour induction.

340. The majority of comprehensive studies on the
influence of fractionation of low-LET radiation on
life-span have used the mouse as the experimental
animal. The effect of fractionation appears to be very
dependent on the strain of mouse and the spectrum of
diseases contributing to the overall death rate. For
example, in some strains thymic lymphoma incidence
is increased by fractionation. Where this is a major
contributor to the fatality rate, fractionation can lead
to a greater loss of life expectancy than acute
exposures. Overall there is no clear trend, and the
results from a number of studies suggest that, when
compared with acute exposures, the effects of
fractionation on life-span shortening are small and, at
least for exposure times of about a month, simple
additivity of the injury from each dose increment can
be assumed. For fractionation intervals over a longer
time there is a tendency to a longer life-span with an
increasing interval between the doses, but the increases
in life-span observed are generally less than those
found with protracted exposures.
341. When the effects in mice of acute exposures to low-LET radiation are compared with those of protracted irradiation given more or less continuously, the effectiveness of the radiation clearly decreases with decreasing dose rate and increasing time of exposure. With lifetime exposures there is some difficulty assessing the total dose contributing to the loss of life-span. However, the results available suggest that with protracted exposures over a few months to a year the effect on life-span shortening is reduced by factors between about 2 and 5 compared with acute exposures. The effect of dose rate on tumour induction and life-span shortening has also been examined in rats and beagle dogs, although no significant differences have been found. In these two studies dose rates varied by factors of 60 or less, whereas in the studies with mice they varied by factors of 100 or more.

342. A number of early studies suggested that fractionated exposures to high-LET radiation induced more life shortening than single exposures. More recent studies have shown, however, that when total doses are low and the dose per fraction is small, there is no significant difference in life shortening between fractionated and acute exposures. Although the data are limited, the available information suggests that protraction of exposure does not affect life shortening.

343. Tumour induction in experimental animals. A number of studies have been published that permit the effect of dose rate from low-LET radiation on tumour induction in experimental animals to be examined. The data that have been reported by various authors cover a wide range of dose-response patterns, and with different dose ranges, differing values of DDREF may be calculated. A wide range of DDREFs for tumour induction in different tissues has been found for dose rates generally varying by factors between about a hundred and a thousand or more. Some of the tumour types for which information is available have a human counterpart (myeloid leukaemia and tumours of the lung, the breast, the pituitary and the thyroid), although the tumours involved may not be strictly comparable to the human disease. Other types either have no human counterpart (Harderian gland) or require for their development substantial cell killing and/or changes in hormonal status (ovarian tumour, thymic lymphomas). In practice, the DDREFs found in these two groups are little different, falling in the range from about 1 to 10 or more, and there is no clear trend with tissue type.

344. Myeloid leukaemia has been induced in RFM and CBA mice, although there are differences in sensitivity between the strains and between the sexes. DDREFs between about 2 and more than 10 have been obtained, but with no consistent trend with changing dose rate. A reasonably consistent finding is that DDREFs for tumour induction in mammary tissue in rodents tend to be low, although even here one author has reported a substantial effect of dose fractionation on the tumour response in mice. DDREFs for lung tumour induction also tend to be low, with values falling in the range of about 2-4 following exposure to both external radiation at different dose rates and to inhaled insoluble radionuclides with different effective half-times in the lung. The results of the principal studies that have been reviewed are given in Table 8, together with the dose ranges over which the DDREFs have been estimated.

345. It has also been demonstrated that the effect of fractionation on tumour response depends on the dose per fraction. With small doses per fraction, which lie predominantly on the linear portion of the dose-response curve, the tumour response is similar to that obtained at low dose rates. At higher doses per fraction, the response approaches that obtained for single acute doses.

346. The main conclusion to be drawn from the results of the studies on radiation-induced life shortening and those on the induction of specific tumour types following exposure to low-LET radiation is that tumour induction is dependent on the dose rate, with a reduction in incidence at low dose rates. While the absolute value of the DDREF varies with the conditions of exposure, the animal strain and gender, tissue/tumour type and the dose range over which it is calculated, there is a consistent finding of a difference in tumour yield per unit dose for dose rates varying by factors of between about 100 and in excess of 1,000.

347. The animal studies also indicate that the presence of a dose-rate effect could not necessarily be inferred from dose-response relationships obtained at high dose rates alone, since for a number of studies the dose-response data for tumour induction up to a few gray could be adequately fitted by a linear function. This would imply the absence of a visible quadratic (i.e. multi-track) function in the dose response, which according to conventional interpretation would appear to be a prerequisite for an effect of dose rate on tumour yield. Clearly, when information is available only for exposures at high dose rates, any attempt to assess the effect at low doses and low dose rates, and hence a value of the DDREF, by simply fitting a linear-quadratic or similar function to the dose response is unlikely to be fully successful. The limiting factor is the amount of information available at low doses from which the linear term ($\alpha_1$ of equation 30) can be accurately defined. For planning future animal studies it is clear that most information is likely to come from studies on animals exposed at different dose rates, rather than from attempting to obtain information on the risks at very low doses. It is
to be hoped that more studies will be carried out to supplement the information presently available.

348. From the limited and somewhat disparate data on high-LET radiation it is difficult to generalize. There is, however, little experimental support for applying a DDREF to high-dose or high-dose-rate exposures to calculate risks at low doses and dose rates. Similarly, there is little evidence to suggest that, in the absence of cell killing, there is an appreciable enhancement of tumour yield when the dose from high-LET radiation is protracted or fractionated.

349. **Cell transformation.** Cell transformation studies can yield information of practical use in radiation protection in addition to giving insight into the mechanisms of carcinogenesis. At present, however, the most quantitative data is derived from the least physiologically relevant cell systems, such as cultured embryo cells or the mouse fibroblast cell lines C3H10T1/2 and BALB/c3T3. Thus, when attempts are made to extrapolate to cancer induction in man, which occurs mainly in epithelial tissues (lung, gastrointestinal tract), the biological limitations of these assay systems must be considered. In addition there are a number of technical uncertainties that must be taken into account. These include the effects of cell cycle time, of plating density and of promoters and suppressors, some of which may be normal components of the growth medium, particularly the serum, and therefore difficult to control.

350. Nevertheless, in carefully controlled experiments where asynchronously dividing cells or, in some cases, non-dividing plateau-phase cells have been irradiated, the resulting observations on dose or dose-rate effects for low-LET radiation are in general agreement with those relating to other cellular effects, such as cell killing and the induction of mutations or chromosomal aberrations and to tumour induction in animals. Dose-response curves per cell at risk have a number of features in common with tumour induction in vivo, showing an initial rise in transformation frequency with increasing dose to a maximum and then a decline. When plotted as transformants per surviving cell, the dose response for low-LET radiation generally shows the expected linear or linear-quadratic relationship tailing off to a plateau at higher doses. When low doses of x rays or gamma rays are delivered at low dose rate or in fractionated intervals, a DDREF of between about 2 and 4 is obtained. Because of the limitations of the experimental system, the range of dose rates applied in experimental animals has not been used, with the maximum range being a factor of about 40. It is noteworthy that some experimental data suggest that the linear term may alter with dose rate, but this may be accounted for by the lack of precise data at low doses. 351. Exposures to high-LET radiation result in a higher transformation efficiency with a tendency towards a linear relationship, in line with data for chromosomal aberrations and again tending to a plateau at high doses. As expected from this pattern of response, there is no tendency for the response to decrease at low dose rates or with fractionation, and in practice, a number of studies have shown an enhanced effect. The main evidence for an "inverse" dose-rate effect with high-LET radiation seems to be limited to 5.9 MeV or fission spectrum neutrons, and over the past few years estimates of the magnitude of the increased effect have been reduced from factors of around 9 to about 2 or 3. Results reported from a number of laboratories have become reasonably consistent, and it has been possible to develop a model that can predict many experimental results.

352. The model is based on the assumption that the target in the cell, taken to be the nucleus, has a "window" in the cell cycle lasting about 1 hour during which it is more sensitive to radiation. With protracted or fractionated exposures there is a greater opportunity for this particular window to be hit by at least one track, and thus the possibility for an enhancement of transformation frequency with a reduction in dose rate. The magnitude of any effect will depend on the linear energy, and with alpha-particle irradiation little enhancement would be expected, as is in fact observed. Although such a model appears to be consistent with much of the experimental data and has been tested in one series of studies, it is critically dependent on the target size and will need to be examined at different doses, dose rates and dose-fractionation schedules to fully examine its general applicability. Ultimately a full understanding of the inverse dose-rate effect must depend on experimental studies designed to understand the mechanistic basis of the observations.

353. Despite this possible explanation of the inverse dose-rate effect, there remains the problem that it is largely based on the results obtained with the C3H10T1/2 mouse-embryo-derived fibroblast cell line and may well have only limited application to human carcinogenesis. The development of epithelial cell systems that are of much more direct relevance to human cancer should be a research priority.

354. **Mutagenesis in somatic and germ cells.** Studies on somatic mutations in vivo and germ cell mutations in vitro are relevant to assessing the effect of dose and dose rate on the primary lesion in DNA involved in tumour initiation, although subsequent tumour expression will depend on the influence of many other factors. The results obtained in different studies on somatic cell mutations in mice have been somewhat variable, but the overall extent of the dose-rate effect
indicates a maximum value of about 2.3. A DDREF of about 3 for specific-locus mutations has been found in mouse spermatogonia for a dose rate of 8 mGy min\(^{-1}\), although no further reduction in effect was obtained at lower dose rates down to 6.007 mGy min\(^{-1}\), i.e. an overall range in dose rates in excess of a factor of 10\(^2\). Based on these results, a DDREF of 3 for damage to spermatogonia has been applied by the Committee since the UNSCEAR 1972 Report [US] when assessing risks of hereditary disease at low dose rates. For reciprocal translocations, DDREFs up to about 10 have been reported, although there appear to be considerable differences between species. Reciprocal translocations are, however, two-hit aberrations, and the yield will be very dependent on recovery processes between successive events. The marked differences in dose-rate effects between species may be the result of variable rates of repair. The DDREF in mature and maturing mouse oocytes is larger than that in spermatogonia, with the main difference being that the mutation rate continues to fall when the dose rate decreases below 8 mGy min\(^{-1}\). Mouse oocytes present just before birth show a more pronounced dose-rate effect than mature or maturing oocytes, with a DDREF of about 14.

355. Epidemiology. The human data that are available for assessing the effects of dose rate on tumour induction from low-LET radiation are limited. In general, the information available is from exposures at high dose rates, and little information is available at doses of less than about 0.2 Gy. Analyses of dose-response relationships for solid tumours in the atomic bomb survivors are generally consistent with linearity but also with a small reduction in the slope of the dose-response at lower doses. For leukaemia among the atomic bomb survivors, however, the data are inconsistent with linearity, and the central estimate of the DDREF at low doses is about 2. Model fits to the dose-response data for the atomic bomb survivors over the dose range 0-4 Gy kGy for all cancers combined, suggests a DDREF in the range of about 1.7 (when adjusted for random errors). For solid cancers alone, however, linearity provides a good fit, although the data are also consistent with a DDREF of the order of 2. This interpretation of the data depends on the assumption that a linear-quadratic model is appropriate for extrapolation to low doses and that the linear term can be adequately resolved. Information on thyroid cancer induction by acute external irradiation compared with low dose-rate exposure from intakes of \(^{131}\)I are consistent with a DDREF of about 3, although there is some question over the contributions that heterogeneity of dose and uncertainties in the dose estimates as well as the effect of age make to the overall reduction in risk. For female breast cancer the information is conflicting. Dose-response relationships for acute exposures and for fractionated exposures at high dose rates are consistent with a linear dose-response relationship. However, comparative data from Nova Scotia and from other Canadian provinces suggest a DDREF greater than one may be appropriate for assessing cancer risks at low dose rates. Although epidemiological studies of low dose-rate exposure should be more relevant for the purposes of radiological protection than studies at high dose rates, the former type of study at present lacks sufficient statistical power to allow risks to be estimated with tight confidence limits. However, the results of studies such as those of radiation workers are consistent with low values of DDREF.

356. Dose criteria. The designation of low doses and low dose rates below which it is appropriate to apply dose and dose-rate effectiveness factors (DDREFs) in assessing risks of human cancer resulting from radiation exposure have been considered by the Committee. A number of approaches based on physical, experimental and epidemiological data have been reviewed. It was concluded that for assessing the risks of cancer induction in man a DDREF should be applied either if the total dose is less than 200 mGy, whatever the dose rate, or if the dose rate is below 0.1 mGy min\(^{-1}\) (when averaged over about an hour), whatever the total dose.

357. Summary. The dose-response information on cancer induction in the survivors of the atomic bombings in Japan provides no clear evidence for solid tumours for a DDREF much in excess of 1 for risk estimation at low doses and low dose rates of low-LET radiation. For leukaemia, the dose response fits a linear-quadratic relationship with a best estimate of the DDREF of about 2. There is only limited support for the use of a DDREF from other epidemiological studies of groups exposed at high dose rates, although for both thyroid cancer and female breast cancer some data suggest a DDREF of possibly 3 may be appropriate.

358. The results of studies in experimental animals conducted over a dose range that was similar, although generally somewhat higher, than the dose range to which the survivors of the atomic bombings in Japan were exposed, and at dose rates that varied by factors between about 100 and 1,000 or more, give DDREFs from about 1 to 10 or more with a central value of about 4. Some of the animal tumours have no counterpart in human cancer. Similar results to those obtained with animal tumour models have been obtained for transformation of cells in culture, although the DDREFs obtained have not been as large. In a number of these experimental studies linear functions would give a good fit to both the high- and low-dose-rate data in the range from low to intermediate doses. This indicates that if the cellular response can, in principle,
be fitted by a linear-quadratic dose response, in practice it is not always possible to resolve the common linear term for exposures at different dose rates.

359. If the human response is similar to that in experimental animals, then it can be envisaged that at lower dose rates than were experienced in Hiroshima and Nagasaki, a DDREF greater than that suggested by analysis of the dose-response data could be obtained. However, information from human populations exposed at low dose rates suggests risk coefficients that are not very different from those obtained for the atomic bomb survivors, although the risk estimates have wide confidence intervals. Taken together, the available data suggest that for tumour induction the DDREF adopted should, on cautious grounds, have a low value, probably no more than 3. Insufficient data are available to make recommendations for specific tissues.

360. For the purposes of applying DDREFs for assessing cancer risks in man, the Committee concluded either that dose rates less than 0.1 mGy min\(^{-1}\) (averaged over about an hour) or acute doses less than 200 mGy may be regarded as low.

361. For high-LET radiation, a DDREF of 1 is at present indicated on the basis that experimental data suggest little effect of dose rate or dose fractionation on tumour response at low to intermediate doses. It is noted that a DDREF of somewhat less than 1 is suggested by some studies, but the results are equivocal and cell killing may be a factor in the tissue response.

362. In the case of hereditary disease, the adoption of a DDREF of 3 is supported by experimental data in male mice, although a somewhat higher value has been found with one study in female mice.
### Table 1
Summary of reduction factors for estimating cancer risk at low dose and low dose rates for low-LET radiation

<table>
<thead>
<tr>
<th>Source</th>
<th>Year</th>
<th>Reduction factor</th>
<th>Alternative conditions for applying a reduction factor</th>
<th>Ref.</th>
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<td></td>
<td></td>
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<td>BEIR III</td>
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<td>2.25</td>
<td>*</td>
<td>[C4]</td>
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<td>BEIR V</td>
<td>1990</td>
<td>2</td>
<td>*</td>
<td>[C1]</td>
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<td>Leukaemia</td>
<td></td>
<td></td>
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<tr>
<td>Solid cancers</td>
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<td>ICRP</td>
<td>1977 2</td>
<td>b</td>
<td>[I1]</td>
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<tr>
<td></td>
<td>1991</td>
<td>2</td>
<td></td>
<td>[I2]</td>
</tr>
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<td></td>
<td></td>
<td>&lt;0.1</td>
<td>&lt;0.1 Gy h⁻¹</td>
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<td>&lt;0.2</td>
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<td></td>
<td></td>
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<td>National Radiological Protection Board (United Kingdom)</td>
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<td>1988 3</td>
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<td>2</td>
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<td>&lt;0.1 mGy min⁻¹</td>
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<td></td>
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<td>[S31]</td>
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<tr>
<td>United Nations Scientific Committee on the Effects of Atomic Radiation</td>
<td>UNSCEAR</td>
<td>1977 2.5</td>
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<td>up to 5</td>
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<td>1988</td>
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<tr>
<td>United States Nuclear Regulatory Commission</td>
<td>NRC</td>
<td>1989 3.3</td>
<td>*</td>
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<td></td>
<td>1991</td>
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<td></td>
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* Not specified.
* For radiological protection purposes.