GENETIC AND SOMATIC EFFECTS OF IONIZING RADIATION

United Nations Scientific Committee on the Effects of Atomic Radiation
1986 Report to the General Assembly, with annexes

UNITED NATIONS
New York, 1986

NOTE

The report of the Committee without its annexes appears as Official Records of the General Assembly, Forty-first Session, Supplement No. 16 (A/41/16).

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UNITED NATIONS PUBLICATION
Sales No. E.86.IX.9
ISBN 92-1-142123-3
004800P

ANNEX B

Dose-response relationships for radiation-induced cancer

CONTENTS

Introduction

1. It has long been recognized by UNSCEAR that radiation-induced malignant diseases are the most important late somatic effect in human populations exposed at high doses for which direct observations are available [U6, U7, U9-U12, U24]. For evaluation of radiological risk or detriment [I2] this importance derives from the fact that these diseases are often lethal and they are the only statistically verifiable cause of radiation-induced life shortening at intermediate and low doses [B17, B18, J1, K39, K40, U24]. Radiation-induced cancer belongs to those radiobiological effects whose frequency of occurrence (but not severity) is believed—as a rule—to correlate with dose.[a] The postulated probabilistic nature of the relationship between dose and frequency of malignancy[b] has led to the acceptance of the term "stochastic" for effects of such type.

2. Assessment of risk, from environmental and occupational radiation sources in the dose region from fractions of mGy to a few tens of mGy, would be greatly facilitated by knowledge of the shapes of the dose-response relationships for radiation-induced cancers in humans. This knowledge is not available at present and is not likely to be obtained by direct observation. Two features of the dose-response relations are most important for evaluation of the risk at low doses: the possible presence of a threshold dose below which the effects would not occur, and the shape of the dose-response curve.

3. Lack of threshold for a given effect is usually assumed if the response for this effect, plotted against the independent variable (causal factor, or, specifically, dose), permits extrapolation by eye to the origin of the coordinate system, or when the calculated regression line intercepts the abscissa at values that are not significantly different from zero. Conversely, a threshold is usually assumed when the fitted regression function crosses the abscissa at a value significantly greater than zero. However, proving or disproving a threshold below the levels of direct observation may be impossible, due to statistical fluctuations of the spontaneous level and of the presumably induced response. Therefore, assumptions regarding a threshold are based essentially on theoretical considerations of the mechanisms of radiation interaction with the biological targets for initiation of neoplasia, supplemented by empirical observations to support the hypothesis. Although absence of the threshold is often assumed, this has not been proved for any form of radiation-induced malignancy [U6] and must be regarded as a working hypothesis.

4. In annex I of the 1977 UNSCEAR report [U6], the available data concerning experimental radiation carcinogenesis in numerous animal species were reviewed. The large variation of susceptibility to cancer induction in different tissues was emphasized. Physical and biological factors modifying the frequency of induction were discussed in great detail and interactions of other agents (e.g., viruses) with radiation were also reviewed. The extreme complication and unsatisfactory understanding of the pathogenesis of all forms of cancer, including those induced by radiation, were particularly stressed.

5. Various physical factors, such as dose, dose rate, and quality of radiation, were also considered, and general patterns could be recognized in cases where such factors were systematically studied in a given strain of animals, and for specific tumour types. Among the patterns identified, were a sparing effect of dose fractionation and protraction of low-LET radiation (x or gamma rays) upon the frequency of induced cancer and the absence, or even reversal, of such an effect for high-LET radiation (neutrons, alpha particles).

6. Current theories of cancer induction by radiation and some other agents (viruses, chemicals) were also briefly reviewed in the 1977 UNSCEAR report [U6]. None of these was able to accommodate all the known facts and to allow development of a theory or of

[a] For brevity, the term "dose" is used here instead of the more correct "absorbed dose".

[b] In this annex, the term "carcinogenesis" is used to include carcinoma, leukaemia or any other form of malignancy (sarcoma, lymphoma, etc.). The word "malignancy" is used when the reference is to all such malignant conditions, while "cancer" or "malignant tumour" refer only to solid or focal malignancies. The term "tumour" is used without qualification when it is either clear from the context, or unimportant, whether a malignant or a benign tumour is intended.

comprehensive models of cancer induction by ionizing radiation. It was recognized, however, that known carcinogens have a common target within the susceptible cells, which is most likely the nuclear DNA or genome.

7. Since the 1977 report [U6], new information has been published on experimental induction of cancer by radiation. Some of it refers to observations at intermediate and low doses. Of particular importance is the information dealing with high-LET particles (mostly neutrons). This is reviewed here when it appears relevant to models of radiation-induced malignancies.

8. In annex I of the 1977 report [U6], the response relationships as a function of single acute doses for various forms of experimental radiation-induced cancer—both after whole-body and localized irradiation—were reviewed thoroughly. Tumours could be broadly subdivided into three categories:

(a) Those showing an increasing incidence with increasing dose up to a maximum, with a decline following that maximum (most forms);

(b) Those displaying a negative correlation between incidence and dose, as observed in tumours with an unusually high spontaneous frequency;

(c) Those showing no clear rise with increasing dose up to several Gy.

For occupational and environmental exposure of man, type (a) is the most relevant. Schematic examples of dose-response curves are shown in Figure I.

9. UNSCEAR [U6] also identified a large variability of the net incidence of various tumour types at intermediate to high doses between different species and, within species, between inbred strains. It was also found that in many cases a particular tumour could be induced by radiation in only one or two strains of a given species, an observation that must raise questions as to whether such tumours may represent adequate models of corresponding human diseases. Similar doubts would also apply to some observed forms of dose-response relationships. In some cases, dose-response relationships differ from species to species, although in many cases consistent patterns have been found. For these reasons, the increased incidence per unit dose of a given form of cancer cannot—as a rule—be extrapolated between species.

10. For dose-response relationships of category (a) some regularities were pointed out that appeared to conform to other radiobiological phenomena occurring in single cells (e.g., cell killing, induction of mutations and chromosome aberrations). These common features were as follows:

(a) The RBE values for densely-ionizing radiation relative to x and gamma rays are higher than 1 and decrease as doses increase;

(b) With acute doses of high-LET radiation the dose-response relationship is closer to linearity than for sparsely-ionizing radiation, for which upward concave curvilinearity is usually observed;

(c) The tumour yield often shows little dependence on dose protraction and fractionation for high-LET radiation, while for x and gamma rays the yield usually declines.

11. Since publication of the 1977 report [U6], additional information has appeared on tumour induction and life shortening in the low and intermediate dose region. It shows that after acute (high dose rate) high-LET exposure, in some cases at intermediate and in most cases at high doses, the incidence of tumours per unit dose decreases with increasing dose. For low-LET acute exposures, such a decline is usually observed only at high doses (above several Gy). These and other observations, together with some notable exceptions, will be discussed in detail in chapter IV.

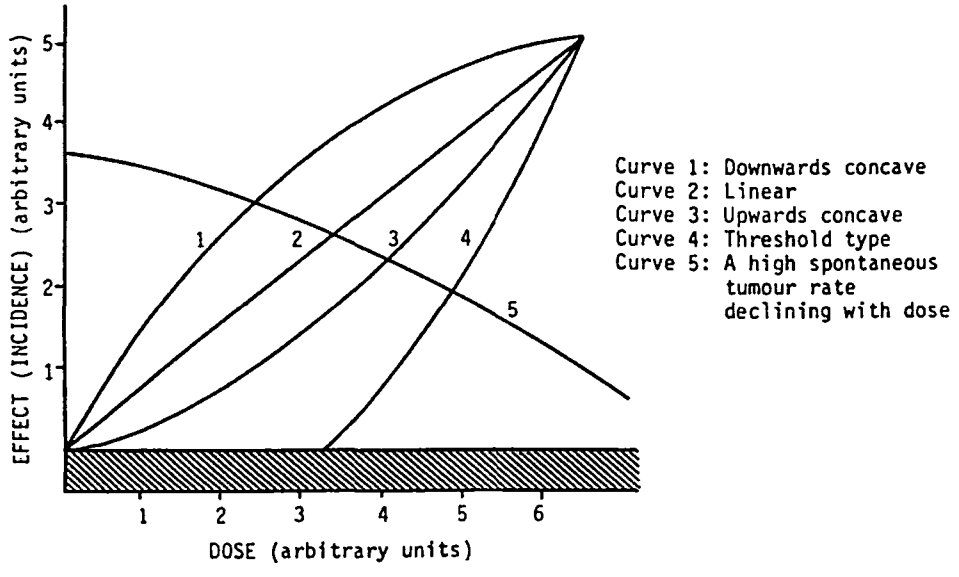


Figure I. Typical dose-response curves for radiation-induced tumours. Curve 1: Downwards concave; Curve 2: Linear; Curve 3: Upwards concave; Curve 4: Threshold type; Curve 5: A high spontaneous tumour rate declining with dose. The shaded area represents the spontaneous (control) incidence.

12. In annex G of the 1977 report [U6], UNSCEAR presented a comprehensive review of epidemiological data on radiation-induced cancer in man. Absolute risk estimates of mortality per unit dose were examined in detail for malignant diseases of various organs, and confidence limits were attached to these estimates, derived in most cases from irradiation with doses at or above 1 Gy. Also, an approximate life-time risk of mortality from cancer at all sites per unit dose was estimated from the ratio of incidence of all non-leukaemic malignancies to the incidence of leukaemias in several groups (atomic bomb survivors, American radiologists, and patients treated for ankylosing spondylitis and metropathia haemorrhagica). However, the previously available dosimetry at Hiroshima and Nagasaki has been questioned, and the new dosimetric system (DS86) is expected to yield improved risk coefficients for atomic bomb survivors, who are one of the most important sources of information.

13. The merit of such risk estimates lies in the fact that they are derived directly from human data and thus avoid interspecies extrapolations of doubtful validity. The precision of the 1977 risk estimates was the best possible under the conditions of exposure and follow-up then available, but many limitations of the estimates were discussed extensively.

14. Uncertainties regarding the shape of the dose-response relationships for radiation-induced malignancies, and the related risk estimates in man, derive mostly from the following conditions:

(a) The short duration of follow-up of irradiated populations compared to the length of latent period of most tumours. Whereas 20 to 30 years may be sufficient for manifestation of leukaemias and bone sarcomas after short-term irradiation, it is not so for other cancers. At present, the time distribution of their latent periods is not known in detail, and for some cancers it depends upon dose (or dose rate for chronic exposure), and also on age at irradiation. In addition, several, if not all, radiation-induced tumours tend to have an age distribution similar to that of their spontaneous counterparts. This means that greater absolute incidence per unit dose will be observed in cohorts of older than of younger ages. On the other hand, the expression of induced cancers will be truncated in cohorts irradiated at older ages, owing to their limited survival. Thus, the shape of the dose-response curve may depend upon the length of follow-up and on the age structure of the irradiated population. In most studies, the mean follow-up period is substantially shorter than the time needed for full tumour expression. In addition, a negative correlation between dose and latent period could, if present, affect the shape of the dose-response relationship, because it could not permit comparable tumour expression after high and low dose;

(b) The sex and age composition of the population under study. Since for certain tumours the age at irradiation and sex have a pronounced effect upon the risk of later development of the malignancy, a given dose-response relationship may not be representative of populations of different composition;

(c) There is a pronounced geographical, socio-economic and ethnic variation of the spontaneous incidence of cancers in most organs. (For a review of this point see [D17, W9].) This suggests that epidemiological observations on radiation-induced cancer cannot be applied indiscriminately to populations of different ethnic, socio-economic or geographic characteristics. On the other hand, such differences are not necessarily reflected in the value of the absolute risk or the shape of the dose-response relationship. For instance, in spite of large differences in the age-specific incidence, the age-corrected excess risk of breast cancer and dose-response curves in Japanese atomic bomb survivors are very similar to those in women irradiated in the United States for medical reasons;

(d) Deficiencies of tumour ascertainment in retrospective studies from available records of incidence or specific mortality;

(e) Difficulties in the selection of suitable comparison groups for the calculation of the expected (control) incidence or mortality due to a given tumour;

(f) Presence of confounding variables and modifying factors (promoters, inhibitors) that, if correlated with dose, or per se, could modify the shape of the dose-response relation;

(g) Questionable accuracy of dosimetric estimates, particularly when these involve retrospective reconstructions of complex situations. Numerous examples of such uncertainties are given in chapter V. In this category belongs also the very narrow range of doses to which a population may have been exposed, as well as the non-uniformity of dose distribution in the target organs. The latter condition may distort the relationship when the mean organ dose is used as the independent variable and induction is not a first-order process;

(h) Statistical uncertainties in the estimates of incidence or mortality at given dose levels.

15. Because of such limitations, in view of the presence of numerous and often unknown biological variables affecting cancer incidence, and of the lack of understanding of the pathogenesis of cancer, UNSCEAR cautioned against the indiscriminate use of risk estimates under conditions other than those for which they had been derived. For example, direct application of the risk coefficients to doses in the range from 1 mGy to 0.1 Gy involves a procedure of linear extrapolation, i.e., an assumption that the incidence per unit dose does not vary with dose. Such a procedure could, however, lead to over- or under-estimates of risk, depending on the actual shape of the dose-response curve. It was generally concluded, in the 1977 report, that the real risk per unit dose of low-LET radiation at low doses and/or dose rates would be unlikely to be higher, but could be substantially lower, than the values derived for the range of a few tens of mGy. The derivation was based essentially on

observations made above 1 Gy, but some reduction of the effect at low doses was already assumed (e.g., for leukaemia by a factor of about 2).

16. The wide confidence limits on the data from man allow various mathematical functions to be fitted to the same epidemiological series [B17, B20, B24, C29, M31, R21, S50]. Consequently, the probability of being able to discriminate between the statistical goodness of fit of various alternatives, or to reject some of them, is too low. In addition, the extrapolation of a relationship beyond the region of direct observation is always questionable when the underlying mechanism is not well understood.

17. In view of all these difficulties UNSCEAR has followed another approach in preparing the present annex. It has reviewed evidence at the subcellular and cellular level, from which inferences could be made as to the possible nature of the dose-response for cancer initiation by radiation. It has also examined how initiation of cancerous clones, and their progression to clinical tumours, may affect the shape of the dose-response relationship. Finally, it has reviewed published models of cancer induction and tested them for compatibility with epidemiological and experimental findings. It is hoped that this complex exercise may help to establish, with some confidence, the shape of dose-response relationships, and thereby limit the uncertainty in the extrapolation of the risk to low doses.

18. Thus, the objectives of this annex may be summarized as follows:

(a) To review the critical assumptions involved in the formulation of models linking radiation-induced cancer to dose;

(b) To review and discuss dose-response relationships for effects at the cellular level that could conceptually be linked with malignant transformation;

(c) To discuss models of cancer induction by radiation from the standpoint of resulting dose-response relationships for tumours of some organs and tissues;

(d) To review the effects of the mode of dose delivery (dose rate, fractionation) and quality of radiation upon the dose-response relationships;

(e) To identify possible general trends, and inter-species similarities, brought about by changes in the above variables upon the dose-response relationships for various types of cancer.

UNSCEAR wishes to stress that in pursuing this exercise it does not intend to give more weight or credit to one or another model of tumour induction, nor to depart from previously established policies in risk estimation adopted within the Committee. This review is meant to be a purely scientific analysis of data aiming at an assessment of systematic errors in the risk estimates derived from existing epidemiological evidence when one or another model is assumed in interpreting such evidence.

I. DOSE-RESPONSE RELATIONSHIPS FOR RADIATION-INDUCED CANCER

19. Radiation-induced cancer, as a stochastic phenomenon, can be analysed in terms of probabilistic concepts such as the distribution function of the time from irradiation to the occurrence of cancer. Depending on the data, the event may be assumed to occur at the time of diagnosis for readily apparent tumours, or at the time of death for rapidly lethal ones. The definitions and procedures of estimation are similar, but the two cases should not be confused because this could lead to serious errors, particularly with cancers for which effective therapy is available.

20. In experimental work, the populations under study consist generally of inbred animals standardized for species, strain, sex and age. They are irradiated under controlled conditions and followed for a specified time or up to death. Appropriately matched control groups are followed concurrently under similar conditions. The time of death and, at least in some experiments, the cause of death, can be ascertained for each animal. Such data may undergo sophisticated statistical treatments.

21. Easily diagnosed or rapidly lethal tumours are readily discovered. For such "manifest" neoplasms, established mathematical procedures can be applied to correct for competing risks, e.g., intercurrent mortality not related to the tumour incidence. Under these conditions, the time to the expression of the tumour is known only for some of the individuals in the collective, while others die or disappear from observation due to unrelated causes before a tumour is observed. For these latter individuals one knows only that the hypothetical time to the tumour would have been longer than the observation time, i.e., it would lie to the right on the time scale. Hence one speaks of "right censored" data.

22. If tumours are "occult", in the sense that they are discovered only incidentally in animals killed or dying for other reasons, one speaks of "double censored" data. In this case, one knows either that the time to the expression of the tumour is shorter than the observed time of death or that the hypothetical time would be longer than the time of death, according to whether the dead animals carry a tumour, or not. Under these conditions the expression "double censored data" is used (meaning that the data are both "left and right censored") and the methods for a competing-risk-corrected analysis are more complex (see paragraph 31). There are special difficulties for partly lethal tumours, but a four-point grading of the tumours is usually practicable and sufficient for the analysis; it ranges from "definitively incidental" to "definitively manifest (e.g., lethal)" [P18, P19].

23. In epidemiological work on human populations, the situation is quite different. The series are, in most cases, retrospective; the final data on morbidity and mortality are frequently incomplete; and the composition of the group is often heterogeneous with respect

to sex, age, socio-economic status, health conditions and exposure to carcinogenic or promoting agents other than radiation. Also, the control population is seldom fully adequate; follow-up to extinction is rarely achieved owing to the long life span of man; and dosimetry is frequently uncertain. The statistical treatment of such data must obviously follow methods different from those applying to prospective experiments.

A. THE INDEPENDENT VARIABLE

24. Dose-response curves are functional relationships between an independent variable, the radiation dose in a given organ or tissue, and a dependent variable represented by a suitable measure of the response. The specific energy, z, absorbed in a cell or in its critical structures, is a random variable. The mean value of z, i.e., the absorbed dose, D, is commonly used as the quantity of reference, but at equal values of absorbed dose the distribution of the values of specific energy can vary greatly, depending on the tissue volume for which the specific energy is determined and the value of the absorbed dose, as well as the radiation quality (see III.B.2). Furthermore, the same dose may be delivered at different dose rates. In the present context, the following terminology will be adopted for sparsely-ionizing radiation: low doses, < 0.2 Gy: intermediate doses, 0.2-2.0 Gy; and high doses, > 2.0 Gy. For densely-ionizing radiation (e.g., fast neutrons) doses < 0.05 and > 0.5 Gy will be referred to as low or high, respectively, with intermediate doses falling between the figures quoted. Low dose rates for all radiations are < 0.05 mGy min^{-1}; high dose rates are > 0.05 Gy min^{-1}; and intermediate dose rates fall between these limits. Other quantities will at times be used as the independent variable, such as the injected activity of a specified radionuclide, or the time-integrated concentration of alpha-energy of short-lived radon daughters ultimately to be released in air. With some oscillations, such quantities are proportional to dose.

B. THE DEPENDENT VARIABLES IN EXPERIMENTAL WORK

25. In experimental work on radiation carcinogenesis, various expressions of the response may be adopted (see annex I in [U6]). The simplest, and most commonly used, is the fraction of animals incurring a tumour after irradiation with a given dose (crude incidence). It has been stressed repeatedly [F1, G17-G19, H15, M32, R9, S37, U2-U5, U20-U22] that such way of expressing the response leads to erroneous results. The reason is the interference of competing risks and of the different duration of life between animals receiving different doses. Actually, animals receiving the highest doses tend to die earlier and thus have less chance of expressing the tumours that may be induced.

26. Corrections for differences in the distribution of survival times between control and irradiated animals may be made by approximate methods, as, for example, in studies by Ullrich and Storer [U2-U5, U20, U21, U23-U26]. In this approach, the data are truncated at the time when the group is extinguished through natural death and the observed incidence in the treated group is corrected by a factor equal to the ratio of the mean lifetime for the control and the irradiated groups. This approach can provide approximate age corrections, but it may be misleading when the frequency of tumour appearance varies considerably with time after exposure.

27. Rigorous corrections for age and intercurrent mortality may be made by following the response of irradiated and control individuals throughout their life after irradiation or during a pre-selected post-irradiation period, with appropriate methods of investigation, including careful post-mortem pathology. The relevant parameter is then the age- or time-dependent rate of tumour appearance [C18, C19, H15, K8, S37] or a related cumulative quantity that can be more readily determined in the experiment. The basic quantities in this approach and their competing-risk-corrected estimates for manifest tumours are:

(a) The tumour rate, r(t), as a function of age or time (t) after irradiation. It is the probability at time t per individual to develop a tumour per unit time. This quantity, r(t), is to be interpreted as a mean value for the population under study. Since, for tumours diagnosed during the lifetime, the actual time of origin of the tumour is unknown, the time of its first observation is generally used; the time of death is used for rapidly developing, lethal tumours. In experimental work one derives r(t) as an average value in a group of animals at time t. If N animals are observed (i.e., are at risk) over the interval $t - \Delta t/2$ to $t + \Delta t/2$, and n tumours appear within the interval, the estimate of the tumour rate is $\hat{r}(t) = \Delta n/N\Delta t$. For incidentally observed tumours a direct estimate of the tumour rate is impossible; the tumour prevalence can, however, be estimated (see paragraph 31);

(b) The cumulative tumour rate, R(t). Estimates of this quantity are less affected by statistical fluctuations and are therefore more readily derived. The quantity is defined as the integral of the tumour rate from the time of exposure ($t = 0$) up to time t:

$$R(t) = \int_0^t r(t)\,dt \qquad (1.1)$$

R(t) is the number of tumours per animal up to time t under the hypothetical condition that one could keep the number of animals at risk constant in spite of intercurrent mortality and the occurrence of tumours. R(t) exceeds, therefore, not only the crude incidence, but also the incidence I(t), corrected for competing risks (see paragraphs 29 and 30). A competing-risk-corrected estimate of the integral tumour rate is [A1, N3, S37]:

$$\hat{R}(t) = \sum_i (n_i/N_i\Delta t)\,\Delta t = \sum_i n_i/N_i \qquad (1.2)$$

for all i with $i\Delta t < t$, where n_i is the number of tumours appearing within the time interval $(i-1)\Delta t$ to $i\Delta t$, and N_i is the actual number of

individuals still at risk at this time, i.e., individuals still without a tumour. The standard error for equation (1.2) can be obtained by the relationship [S37]

$$\sigma_{R(t)} = \sqrt{(\sum_i n_i/N_i^2)} \qquad (1.3)$$

28. If multiple non-lethal tumours occur, estimates of the tumour rate or the integral tumour rate can be based also on all observed tumours [S37]. In this case all animals still at risk are included in N_i (equation 1.2), regardless of whether these animals had developed a tumour or not. With this modification, similar estimates are obtained, provided that the animals without previous tumour had experienced the same tumour rate as the animals that had already incurred a tumour. This is so because both the numerator and the denominator in equation (1.2) are increased. If, on the other hand, there are inherent variations of the tumour rate within a population, or if the occurrence of a tumour increases the probability of subsequent tumours, the tumour rate estimated from all tumours will be larger than the rate estimated from first tumours only. It is mandatory, therefore, to specify whether the estimates of the integral tumour rate are based on the first or on all observed tumours. For partly lethal or rapidly developing lethal tumours the estimate can be based only on first tumours.

29. A frequently used quantity, related to the cumulative tumour rate, is the actuarial incidence, or incidence corrected for competing risks, I(t). It is the probability of an animal at risk up to time t to have incurred a tumour. In the absence of competing risks, the actuarial incidence equals the crude incidence (see paragraph 25). In the presence of competing risks, and for manifest tumours, a quantity can be obtained in terms of the product limit estimate [K1]:

$$\hat{I}(t) = 1 - \prod_{i=1}[1 - n_i/N_i] \qquad t_1 \leq t \qquad (1.4)$$

where the product extends over a number of time intervals (i) up to time t; n_i is the number of animals with tumours appearing within the time interval $t_{i+1} - t_i$; and N_i is the number of animals without tumours still at risk at time t_i. The standard error of the product limit estimate is expressed by the so-called Greenwood formula:

$$\hat{\sigma}_{I(t)} = [1 - \hat{I}(t)] \sqrt{\sum_i n_i/N_i^2} \qquad t_i \leq 1 \qquad (1.5)$$

When N is very small the log-rank test is preferable (see paragraph 33).

30. If few individuals incur the tumour, the actuarial incidence and the integral tumour rate, based on first tumours only, are nearly equal. At high frequencies, the actuarial incidence can approach 1, and the integral tumour rate may exceed 1. The sum limit estimate (equation 1.2) is largely equivalent to the product limit estimate (equation 1.4), i.e., the integral tumour rate can also be obtained from the product limit estimate by the relationship:

$$R(t) = -\ln [1 - I(t)] \qquad (1.6)$$

Similarly, the actuarial incidence can be obtained from the sum limit estimate by the relationship:

$$I(t) = 1 - \exp [-R(t)] \qquad (1.7)$$

31. For occult tumours (see paragraph 22), which frequently occur in short-lived animals, the actuarial incidence (which is then usually called prevalence) or the integral tumour rate are more difficult to estimate. Theoretical analyses have shown that a combination of serial killing and survival data is required for such estimates in the case of tumours with unknown degree of lethality or life shortening [C36, M22, N4, R8]. If occult tumours are definitely non-lethal, estimates can be obtained by serial sacrifices at specified times after irradiation. However, this approach requires large numbers of animals. As Hoel and Walburg have pointed out [H29], the method of isotonic regression (see also [B84, K38]) may be used to estimate the competing-risk-corrected incidence from survival experiments. This provides a maximum likelihood solution with the constraint of monotonicity of the incidence. The algorithm for isotonic regression is straightforward and has been utilized for the analysis of radiation carcinogenesis [C36]. At present, however, there are no methods to derive standard errors.

32. In most experimental studies in which tumours are seen in various organs of the same animals, it is usually assumed that such tumours occur independently of each other. However, Storer has shown [S53] that this is not necessarily so. In irradiated female BALB/c mice, 21 out of the 66 pairs of tumours tested showed significant positive or negative correlations. Some of the negative associations were due to rapid lethality caused by one of the tumours, and this could be corrected for by appropriate methods allowing for intercurrent mortality. Of the remaining 13 significant correlations, 6 involved tumours known to be endocrine-related, and 7 applied to tumours of other organs. Alterations in host factors were believed to be responsible for the observed associations. These possible complications should be borne in mind in the analysis of dose-response relationships on the assumption of random, i.e., independent, tumour occurrence.

33. The logrank test, the Breslow test, or the wider class of non-parametric generalized rank-sum tests are suitable for the comparison of tumour rates in two or more groups in the case of manifest tumours [K37]. Analogous tests do not exist for double censored data from survival experiments, i.e., for tumours found incidentally. With such data, one must use tests based on the assumption of the equality of competing risks in the two groups under comparison, or one requires knowledge of the degree of difference of competing risks. For experiments with serial killing, suitable standard tests exist.

34. The quantities discussed in paragraphs 28-29 are not based on specific models. In experiments where various groups, exposed to different doses, are compared, estimates may be used that are also non-parametric but are based on models. Most frequently, the proportional hazards model is used. This model is based on the assumption that the tumour rate or the integral tumour rate in non-irradiated animals is increased by a dose-dependent factor:

$$r(t,D) = \lambda(D)\, r_0(t) \quad \text{or} \quad R(t,D) = \lambda(D)\, R_0(t) \qquad (1.8)$$

where $r_0(t)$ and $R_0(t)$ are the tumour rates and integral tumour rates for the non-irradiated animals, and $r(t,D)$ and $R(t,D)$ are the tumour rates for the individuals exposed to dose D. By equations (1.1) and (1.6) one could express this model in terms of the actuarial incidence, I(t). However, such expression would be more complicated. The reason is that tumour rates and cumulative tumour rates from independent causes are additive, while the incidence is additive only when its value is small. For manifest tumours, there is a relatively straightforward algorithm for calculation of the proportional hazard coefficients, $\lambda(D)$, employing the method of partial likelihood [K37]. For incidentally observed tumours, one must make use of more complex methods, requiring computer algorithms for non-linear optimization, with the constraint of monotonicity [C36, K38]. The analysis can also be based on the model of accelerated failure times by use of the non-linear optimization methods. This model assumes that the competing-risk-corrected incidence, I(t,D), rises earlier in a way that can be described by a dose-dependent acceleration of the incidence $I_0(t)$ for the control groups:

$$I(t,D) = I_0[a(D)t] \quad \text{and} \quad R(t,D) = R_0[a(D)t] \tag{1.9}$$

A similar model is that of time shift [C36], which assumes that the tumour rates, the integral tumour rates, or the incidence may attain the same values at earlier times, in a manner that can be described by a forward shift in time:

$$I(t,D) = I_0[t+s(D)] \quad \text{and} \quad R(t,d) = R_0[t+s(D)] \tag{1.10}$$

With both the accelerated time or the time shift models, algorithms for non-linear optimization are required for either manifest or incidentally found tumours.

35. As a further step towards the derivation of coherent time and dose dependencies, parametric models have been used. Particularly important among these is the so-called Weibull model [K37], which postulates tumour rates, and integral tumour rates, increasing as a power of time:

$$r(t) = c\,t^p \quad \text{and} \quad R(t) = c\,t^{p+1}/(p+1) \tag{1.11}$$

The coefficient c is assumed to depend on dose, while the exponent p may or may not be treated as a parameter that varies with dose. The Weibull model is a special case both of the proportional hazards model and of the accelerated time model. Another frequently used model envisages a log-normal distribution of the times to the tumour, i.e., of a competing-risk-corrected incidence that depends on time as a log-normal sum distribution. Various other models, for example the logistic model, have also been utilized.

36. The preceding paragraphs refer only to acute irradiation. In case of continuous or fractionated long-term exposure, additional complexities are introduced. Under such conditions, the dose increases with time and it may be difficult to identify the relevant value of the accumulated dose. The process of cancer induction is followed by a period of growth until the tumour becomes observable. The dose absorbed during this period is not relevant to the appearance of the tumour. Corrections may therefore be applied by subtracting from the total dose the portion received after the presumed onset of neoplastic growth.

C. THE DEPENDENT VARIABLES IN EPIDEMIOLOGICAL STUDIES

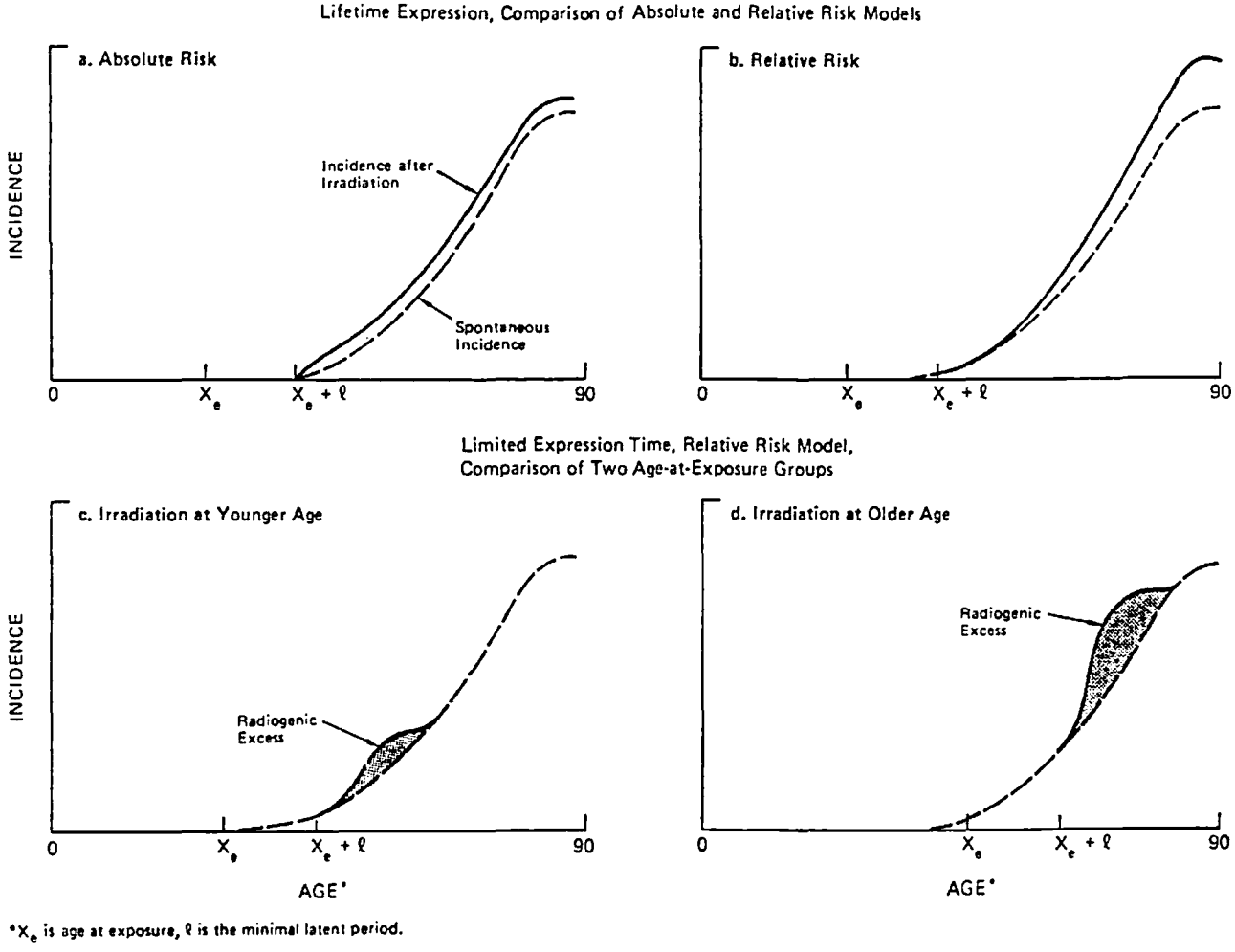
37. Whereas experimental studies use inbred animals that are uniform as regards sex, age at exposure and other conditions, no comparable uniformity is ever encountered in epidemiological human studies. Moreover, various human populations are often subject to a spectrum of influences, of which only some are known or accounted for. In an ideal case, a multivariate analysis should be used to assess the relative importance of factors other than radiation. As this is seldom possible, less rigorous analyses must frequently be accepted which, in addition to the basic quantities previously discussed, use other, somewhat cruder ones. In epidemiological investigations, the follow-up may start shortly after irradiation (prospective studies) or at later times when some or all of the expected tumours may have occurred (retrospective studies). Reliable data collection is more easily achieved in the first case, but the majority of epidemiological studies are based on retrospective analyses.

38. It is not the objective of this annex to deal in detail with all factors and variables affecting the accuracy of risk assessment of radiogenic cancers. However, for the understanding of the following text it is necessary to discuss briefly the expression of the response in absolute and relative terms. The question of risk projection beyond the period of direct observation is intimately linked to the use of so-called absolute and relative risk projection models. These will not be discussed in detail in this annex.

39. As mentioned above, the occurrence of radiation-induced neoplasms may depend on time after irradiation and on the absorbed dose in a variety of ways. In epidemiological investigations it is possible, ideally, to envisage two different situations frequently referred to as the absolute or the relative risk model.

(a) The radiation-induced excess tumour rate—or the incidence rate, as more frequently determined in epidemiological studies—after a latent period increases independently of the spontaneous incidence but as a function of absorbed dose, i.e., the spontaneous and induced rates are additive. Panel (a) of Figure II illustrates this case schematically;

(b) The excess tumour rate, or the net incidence rate, is proportional to the spontaneous age-specific incidence rate, i.e., the dose results in a multiplicative effect of the spontaneous tumour rate over the life span. This relative risk model, corresponding to the proportional hazards model described in paragraph 34, is shown in panel (b) of Figure II [C29].



*X_e is age at exposure, ℓ is the minimal latent period.

Figure II. Radiation-induced cancer incidence superimposed on spontaneous cancer incidence, by age. Relative and absolute risk models.
[C29]

40. For most human tumours, the spontaneous tumour rate is a steep function of age, but quantitatively this dependence varies. For radiation-induced tumours with relatively short latent periods and full expression within a short interval (leukaemia and bone sarcoma) one may distinguish between absolute or relative risk models. A simple absolute model will apply when irradiation at any age is followed by a temporary increase of the tumour rate that does not depend on the magnitude of the spontaneous age-specific rate. A relative model will be preferable when the temporary increase of the tumour rate becomes larger with increasing age at exposure. The latter case is illustrated in panels (c) and (d) of Figure II.

41. The relative risk projection model implies that the absolute (attributable) risk increases with age; on the other hand, the absolute risk model implies that the excess risk when related to the spontaneous incidence rate, decreases with age. Actually, epidemiological data often show an intermediate pattern, and a decision as to which model is most appropriate for risk estimation is not always possible [C29, T12]. However, recent evaluations of cancer incidences in atomic bomb survivors lend rather strong support to the relative model. This is so because, for the same age cohort, excess deaths from cancer other than leukaemia increase with age at death in proportion to the age-specific death rate from these cancers in the population of Japan [K39, S59]. A similar conclusion was reached when the time pattern of appearance of second cancers, presumably radiation-induced, was studied in women treated by radiation for carcinoma of the cervix [B93]. Constancy of the relative risk of lung cancer with time after irradiation was also noted in Swedish iron-ore miners [R41] and in United States of America and Czechoslovak uranium miners [I5]. The two projection models have been used for prediction of the numbers of various tumour types in a population having an age distribution similar to the one in the United States, assuming a series of dose-response relationships and applying the appropriate corrections for intercurrent mortality by the life-table technique [C29]. When considering the risk of radiation-induced cancer, whatever the model applied, it is being currently assumed that the distribution of the sensitivity in human population is unimodal, although the character of the distribution is virtually unknown. The question of the possible exceptionally elevated susceptibility of some individuals is discussed in paragraphs 93-97.

1. The risk expressed in absolute terms

42. The tumour response of an irradiated population may be characterized by the time average net incidence rate, $\dot{I}_{TA}$, which is defined as the number of additional tumours diagnosed per person-year (PY) at risk. This quantity should reflect a net increase above the spontaneous incidence rate in suitably matched controls. It is calculated from the formula

$$\dot{I}_{TA} = X/P - J/Q \qquad (1.12)$$

where X is the number of persons with a diagnosed tumour in the exposed group; P is the number of person-years in this same group, obtained by summing the number of years at risk for all individuals; J is the number of persons with the same type of tumour in a control group that is matched or corrected for sex, age and calendar years; and Q is the number of person-years in the control group.

43. The period at risk for an irradiated subject is the time, usually in years, from irradiation to cancer diagnosis, or death, or to loss from observation, or termination of the survey. For cancers other than leukaemia and bone sarcoma, an assumed minimum latency is usually subtracted from the time at risk. The value of $\dot{I}_{TA}$ is given as "cancer cases/person-year at risk", or more generally as the annual probability of occurrence of a specified cancer in a given population. The dose, D, will commonly be an average of the different doses that the members of the population have received.

44. If a suitable control group is not available, age- and sex-specific incidence rates of tumours in the general population may be used. Under these conditions, however, tumour ascertainment in the groups may not be fully comparable, and possible selection by conditions that prompted irradiation, or by other co-variates, may result in gross errors.

45. In order to obtain the time average net incidence, I_{TA}, the value obtained from equation (1.12) is multiplied by the average time at risk, i.e., by the average period of observation or, for predictions beyond follow-up, by an assumed time for full expression of the malignancy. For leukaemia and bone sarcoma, this time is known not to exceed significantly 30 years (see chapter V). For other radiation-induced tumours, the period of expression is unknown. In order to derive meaningful projections, a correction for intercurrent mortality becomes necessary, i.e., average life expectancies have to be used. When the distribution of the population by age and sex is known, life tables can be used to this purpose, as in [C29]. As the quantities $\dot{I}_{TA}$ and I_{TA} can be affected by significant errors, due to several circumstances, they must be used with caution. First, as the latent period is not known precisely, the correction for it can only be, at best, an approximation. Secondly (and apart from the above correction) it is unrealistic to assume constancy of the incidence rate over time; if the observation periods for two collectives exposed to different doses do not coincide, then the observations cannot be strictly comparable.

46. Annual risk coefficients for radiation-induced cancer can be expressed in terms of the time average net incidence rate per unit dose, $\dot{F}_{TA}$, that is, the probability per unit time per unit dose per person that a tumour can be seen in the observation period. This risk may depend on sex, age at irradiation, genetic disposition, the organ exposed, and a variety of other factors. The quantity is obtained by dividing $\dot{I}_{TA}$ by the mean absorbed dose received in the exposed group. Numerical values are commonly given in "cases 10^{-6} a^{-1} Gy^{-1}".

47. In order to obtain the life-time risk coefficient (net incidence per unit dose), F_{TA}, the quantity $\dot{F}_{TA}$ is multiplied by the time at risk, i.e., by an assumed average time of full expression of the malignancy. The considerations in paragraph 45 that refer to the quantity I_{TA} apply also to F_{TA}.

48. When the risk coefficients F_{TA} and $\dot{F}_{TA}$ are calculated for groups exposed to different average doses, changes of these quantities with increasing dose may provide approximate information about the shape of the dose-response curve. Thus, constancy of the coefficient indicates proportionality between response and dose within the range of doses studied; a rise or a decrease with increasing dose may result from an upward or downward concavity of the dose-response curve. However, if the radiation dose is correlated with a variable that affects the response (e.g., age) spurious effects may be seen and normalization procedures are called for. Furthermore, if the dose-incidence relationship is not linear, expressing the observations in terms of a probability per unit dose distorts the data and introduces additional inaccuracies if individual doses within the exposed population deviate substantially from the average dose to the population. For instance, if the dose relationship contains a dose-squared component, the contribution to the response by individuals with high doses is greater than if linearity applies.

2. The risk expressed in relative terms

49. When the risk is expressed in relative terms, the response is related to the risk of spontaneous cancers (incidence or mortality) in an unirradiated control population. The response variables used are the standardized mortality ratio (SMR), defined as the ratio of mortalities in the exposed group to the mortality in a control group multiplied by 100; and/or the relative risk (RR), which is the ratio of risks observed over expected (each expressed, for instance, per 10^{-6} person and over a given follow-up time). The latter quantity may be applied both to the incidence and mortality indices. The proportional hazard model specifies that if λ_i is the incidence rate of a disease, or the mortality rate for a specific cause of death among subjects in dose group i, it can be expressed as $\lambda_i = \lambda_{i0}\,(RR_i)$, where λ_{i0} is the background or spontaneous rate of mortality or incidence (i.e., the rate experienced by subjects in the absence of exposure to radiation) while RR_i is the relative risk associated with dose group i. The starting point for investigation of a radiation dose-response is the function

$RR_i = 1 + \gamma D_i$, where γ represents the excess relative risk coefficient ((RR −1) per unit dose). Variation of γ with dose provides information as to the form of the RR-dose relationship.

50. Various statistical methods, including multiple regression analysis, have been used to obtain dose-response relationships, and are presented and discussed in detail in numerous publications, e.g., [G36, J8, K42, S60, W17]. Careful corrections for sex, age at irradiation, attained age at observation and other confounding variables (e.g., ethnicity, exposure to other carcinogens and promoters) are necessary when the shape of the dose-response curve is the object of the study.

D. TEMPORAL RELATIONSHIPS

51. As pointed out in preceding paragraphs, the tumour rate, the cumulative tumour rate and the actuarial incidence depend on time after irradiation and on other factors, such as age at exposure or absorbed dose. It has already been mentioned that the absorbed dose may change the time dependence in a variety of ways. It is necessary, therefore, to consider temporal relations in somewhat more detail.

1. Latent period

52. The latent period is the time between irradiation (e.g., single acute exposure) and manifestation of a tumour. It may be divided conceptually into true latency (the time required from initiation to the beginning of unrestrained growth) and tumour growth (time until the neoplasm can be diagnosed). Reported data are usually latent periods, i.e., the sum of the above times. The length of true latency may be obtained by subtracting an estimated time of tumour growth from the observed latent periods. There are considerable differences between the latent periods of various tumours. Two malignancies in man, leukaemia and bone sarcoma, appear to have relatively short latencies and show an upper limit of the latent periods, so that their full distribution in a population having a normal age structure can be observed. For other tumours the distribution of the latent periods is unknown, because it extends to very long times; the distributions are then usually truncated by the length of the observation period. Median times recorded so far are of the order of 20 to 30 years, but they should increase with extension of the follow-up of the respective groups.

53. If the follow-up is shorter than the minimum latent period, radiation-induced tumours cannot be expected. For more extended studies an inferred minimum latent period is frequently subtracted from the total time at risk, as mentioned before. The minimum latent period is often identified with the time after irradiation at which the incidence rate becomes statistically significant at a given level of confidence above the control values. Figure III shows, however, that, for statistical reasons, the minimum latent period so estimated must vary with dose even

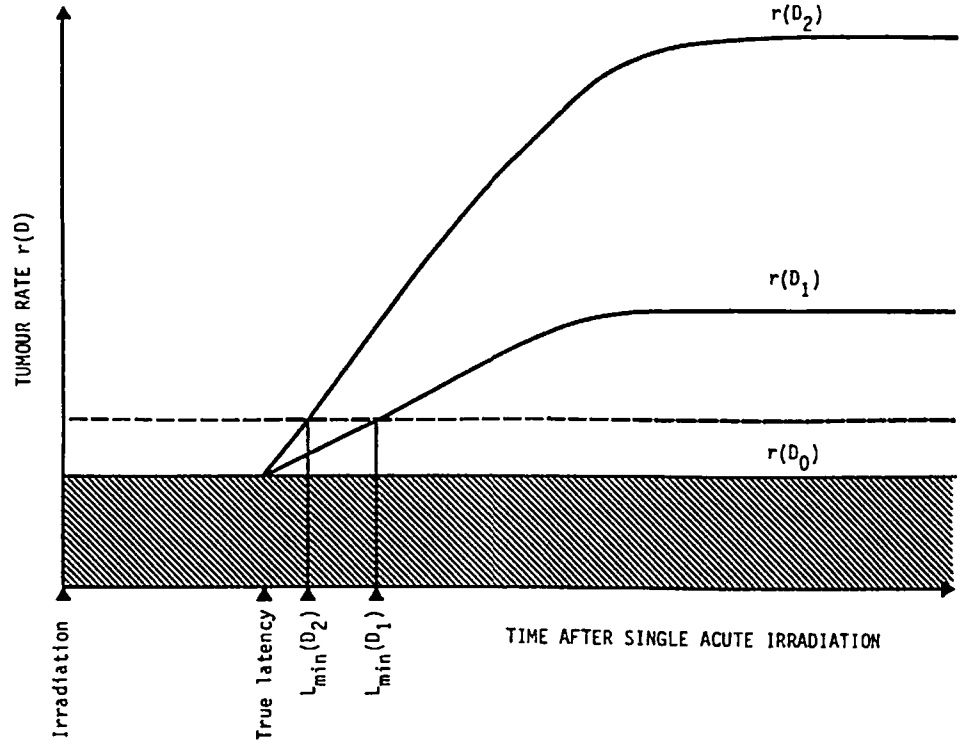


Figure III. Presumed effect of the magnitude of dose upon estimate of minimum latent period. Two doses ($D_1 < D_2$) produce different absolute effects, which have similar time distributions of the latent periods. Shaded area: spontaneous (control) incidence rate; Broken line: upper confidence limit of the spontaneous incidence rate.

under the assumption of the proportional hazard model, i.e., when the tumour rate is increased by a constant factor without change of the underlying temporal dependence. Similarly, shorter minimum latent periods are estimated if the number of individuals in the observed population is larger, because predetermined levels of statistical significance are reached earlier in a larger sample. Other statistical procedures have been developed to analyse the dependence of the latent period on dose [L32].

54. For some cancers, the minimum observable latend periods may change with age at irradiation, as suggested, for example, by studies of human breast carcinoma [B26, M17, S16, T12, T23] and lung cancer incidence in Japanese atomic bomb survivors [K39]. These radiation-induced tumours appear with high frequency at ages when the spontaneous incidence is also relatively high. It follows, therefore, that latency is longer for cohorts irradiated in childhood and adolescence than for individuals exposed in their twenties or thirties. If so, the follow-up to include a complete (i.e., life-time) expression of the effect must vary with age at exposure for different cohorts. It is not known whether this observation can be applied in a general sense to all forms of radiation-induced tumours with long latent periods.

55. In cohorts of advanced age, the life expectancy may be shorter than the average latent periods, and only a fraction of induced neoplasms will be seen. The younger the age at irradiation, the fuller the expression of induced tumours. In the common case of neoplasms with a distribution of latent periods extending significantly beyond the follow-up, the dose-response relationship cannot be based on complete data. The estimate of I_{TA} will then change with the duration of the observation period; however, for those cancers for which the relative risk model appears adequate, the relative risk should be a less susceptible quantity in this respect. Analogous changes of the dose-response relationships have been shown in experimental work [S37]. Whenever the distribution of latent periods varies with the absorbed dose, the form of the derived dose-response relationships will depend critically on the length of the observation period. At low doses, the minimum latent periods may exceed the average life span of the individuals and it has been postulated that so-called practical thresholds may result [E3, M8, M10, R28]. This inverse relationship between latency and dose is most common in studies of continuous long-term irradiation. It was first described for bone sarcoma induced by long-lived isotopes [B48, E3, E4, F8, M4, R18-R20]. The present evidence does not substantiate the existence of such relations for other tumours commonly induced by radiation in man, for which sufficiently detailed data are available, namely cancer of the breast [K39, L22], of the thyroid [S38], and of the lung and stomach [K39, L32]; an inverse relationship between absorbed dose and latent period may exist for leukaemia [L24], but has not been definitely proved.

56. All the above factors must be borne in mind in any discussion of the accuracy and reproducibility of dose-response relationships. Except for tumours with short latencies, such as leukaemia and osteosarcoma, there is generally a lack of data extending to follow-up periods long enough for the dose-response relationship to be assessed with reasonable completeness.

2. Relationships between dose and tumour-free lifetime lost as a result of induced cancers

57. As mentioned above, various malignancies may be characterized by different latent periods. For some malignancies and modes of irradiation the latent periods (mean, median) may vary with dose, the mean values normally increasing with decreasing dose. A quantity that may provide a first approximation to a common denominator for assessment of the harm per induced neoplasm is the tumour-free lifetime lost [I6]. The relationship between this quantity and dose is therefore of interest. Very few papers provide information on the subject, but this will be reviewed, when it is available, in relation to different types of tumour.

E. SUMMARY AND CONCLUSIONS

58. Cancer, as a stochastic radiation effect, can be studied for its dependence on dose and time after irradiation. Different degrees of precision are attainable in experimental and epidemiological studies of radiation-induced tumours. The methods for the estimation of dose-response relationships reflect these differences.

59. The absorbed dose in the relevant tissue is the independent variable for dose-response studies. The magnitude of the dose and its temporal pattern of delivery (dose rate, fractionation) may vary greatly. In the present context, low doses are taken to be those up to 0.2 Gy of low-LET radiation, while those in the interval 2.0-3.5 Gy are regarded as high doses, with the intermediate doses lying between these ranges. Low and high dose rates are taken to be below 0.05 mGy min^{-1} and above 0.05 Gy min^{-1}, respectively. Intermediate rates are those in between these values. For high-LET radiation low and high doses are assumed to range up to 0.05 Gy and down to 0.5 Gy, respectively. Dose rates may be classified in the same way as for low-LET radiation. In certain studies, more readily measurable quantities that are proportional to absorbed dose—at least over some range—may be used as the independent variable.

60. In experiments on radiation carcinogenesis, various measures of the response may be used. The crude incidence, uncorrected for mortality, is not infrequently applied, but it is unsatisfactory because it neglects differences in life span after different exposures; accordingly, it may be strongly affected by intercurrent mortality due to causes other than cancer. Competing risk corrected quantities such as the tumour rate, r(t), the cumulative tumour rate, R(t), or the actuarial incidence or prevalence, I(t,D), can be used for more meaningful expression of the response. These quantities are always dependent on the post-irradiation time, and must be reported accordingly. They are obtained from the observed time sequence of

tumour appearance and from the variable number of individuals at risk during the observation period. They may be calculated by appropriate algorithms that are different for manifest tumours, i.e., rapidly lethal or readily discovered tumours, and for incidentally observed tumours, i.e., tumours that do not contribute to lethality and that are found only at necropsy. Only a few experiments have so far been analysed according to the requirements of the competing risk theory, and this circumstance has often reduced the potentially useful information from numerous studies.

61. In epidemiological surveys, the response is, in most cases, assessed retrospectively, but less accuracy can be achieved than in well-designed controlled experiments. The genetic composition, the distributions of ages and sex, the forces of selection, and the follow-up periods are often different in irradiated and control groups and require appropriate adjustments. Furthermore, the doses to individual members of a cohort are usually subject to substantial variation, making it necessary to group exposed individuals over broad dose intervals. Also, the less rigorous quantities used in epidemiological studies, I_{TA}, F_{TA}, and their rates, are complex functions of time post-irradiation. The scoring of radiation-induced tumours depends therefore, in a complex way, on the age at irradiation, duration and completeness of follow-up, latent period, and life expectancy of the population. The duration of follow-up may especially influence the magnitude of the response and the shape of the derived dose-response relationship in terms of the absolute (attributable) risk. If the tumours of interest show an increment of the relative risk per unit dose that is not strongly dependent on age at irradiation, the shape of the observed dose-response relationship is less susceptible to duration of the follow-up, provided the minimum latent period has been exceeded, the number of tumours is sufficient for verification of the postulated models, and other relevant co-variables have been corrected for.

62. Human tumours with relatively short latent periods, e.g., leukaemia and bone sarcoma, are not expected to appear after about 30 years. For these tumours, the dose-response relationships in young cohorts can be based on complete manifestation of the effect. For other tumours, of longer and unknown latency, dose-response relationships must be based on the incomplete information resulting from truncation of the response by the short follow-up. A possible dependence of latent periods on dose is of critical importance in determining the shape of the dose-response curve. When mean latent periods decrease with increasing dose, the shape of the relation depends on the observation time and, in some cases, practical thresholds may apply. However, except for ^{226}Ra-induced bone sarcoma, little information of this nature is available from data on man.

63. Projection of tumour incidence or incidence rate beyond the period of follow-up for tumours with long latent periods may be achieved by two alternative models: the absolute and the relative risk projection model. In its simple version, the first is based on the assumption that the rates of spontaneous and of radiation-induced tumours are independent, so that the rate of radiation-induced tumours does not increase proportionally to the age-dependent rate of spontaneous incidence. The second model in its simplest form assumes that irradiation has a multiplicative effect on the spontaneous tumour rate and that the rate of induced tumours is a dose-related multiple of the spontaneous rate. Recent data from several epidemiological studies have shown that, in many cases, the relative risk projection model provides a better fit to the data than the simple absolute risk model. For numerous tumours, however, no firm conclusions can be drawn as yet.

II. ASSUMPTIONS AND LIMITATIONS OF EXISTING MODELS

A. BASIC PHENOMENA AND INFLUENCE OF MODIFYING FACTORS

64. Common features of malignant cells are the unrestrained growth, the ability to infiltrate neighbouring tissues, and often the capacity to give rise to metastases. In a general sense, cancerous cells transmit their malignant characteristics from one generation of cells to another, and therefore somatic mutation could be one of the mechanisms involved as an underlying factor [B71, C32, F14, K20, K29, M50, R31, S43]. On the other hand, epigenetic factors such as dis-differentiation, expression of previously suppressed genes, activation of oncogenes (see annex A to this report) or others [B71, K26, S43, R31, S55] may be envisaged, alternatively or in parallel. Continuous growth through cellular divisions might result either from inactivation of operating or regulatory genes, or from the inability of malignant cells to receive or recognize division-restraining signals, whatever their nature might be.

65. Owing to poor understanding of the origin of cancer, quantitative predictions regarding the effects of ionizing radiation (dependence on dose, dose rate, quality of radiation) cannot be developed from basic principles. Formulation of simplified hypotheses under the form of models is at present a practical step towards understanding basic issues. To this end, detailed knowledge of mechanisms of cancer initiation and promotion would be valuable, but even this cannot be secured at present in a comprehensive form. Quantitative models of cancer induction have been reviewed recently by Whittemore [W8] and Parfenov [P2].

66. Before reviewing selected models, it is necessary to discuss the concept of multi-stage development of cancer. Since the classical studies of Berenblum et al. on chemically induced skin cancer in mice (discussed recently with regard to in vitro oncogenic transformation by Borek [B76]) this concept has gained wide acceptance. The subject has been repeatedly reviewed [B71, C32, D18, F13, F16, F20, M50, R31, R42, S43]. It is commonly assumed that cancer induction is started by a phenomenon of initiation, occurring most likely in one cell, although participation or modifying influences from neighbouring cells cannot be excluded. Further development into a cancerous clone probably

requires several stages, covered under the concepts of promotion and progression, which result eventually in an overt malignancy. These concepts have been reviewed by the Committee in annex I of the 1977 report [U6].

67. Cellular phenomena that take place during development of a cancerous clone are not well understood. Direct involvement of DNA in oncogenic cell transformation has been demonstrated [B14, L33, L34]. Lesions affecting its structure and function must therefore be relevant. Somatic mutation(s)—such as changes of the DNA base sequence; transposition, deletion, translocation and transfection (from one cell to another) of genetic material; enhanced instability of DNA, leading to facilitation of non-repairable DNA damage; induction of recombination between nuclear and mitocondrial DNA; disturbances of DNA methylation; activation of oncogenes—may be involved. But some of these mechanisms are largely hypothetical [B71, B83, F21, G33, R31, S43, S45, S55, V2, V3]. Initiation is followed by a long latent period, during which secondary influences (systemic, exogenous) may influence the final outcome of the process. During this period, the action of secondary factors may accelerate and stimulate (promote) or inhibit, or even reverse the process (anti-promoters, suppressors of malignant transformation). Arguments have recently been presented which show rather convincingly that not all initiated cells, or their clones, will eventually give rise to diagnosable tumours [F22].

68. Whatever the nature of initiation, be it radiation-induced somatic mutation in the classic sense (induction coefficient of 10^{-5} to 10^{-6} Gy^{-1} of low-LET radiation per locus at risk), or any other phenomenon similar to in vitro cell transformation (induction coefficient of 10^{-2} to 10^{-4} Gy^{-1}), the yield of recovered malignant tumours per irradiated cell in vivo is lower by many orders of magnitude. The possibility of a symmetrical "tumour-specific" chromosomal translocation was advocated [F21] as a very rare event that would remove part of this difficulty. However, recent studies in vitro and in vivo (chapter IV) suggest that initiation may not be a rare event when expressed per cell at risk. Therefore, if it is assumed that these processes operate in vivo with comparable efficiency, even for a small fraction of the susceptible cells (10^{-4} to 10^{-6}), a significant number of cells would be transformed every day because of background irradiation alone [M31].

69. The theory of sequential development of cancer may help to explain the discrepancy between data in vitro and in vivo, and the rarity of radiation-induced cancer. If a series of consecutive rare events is required for the initiated cell to become malignant, the final probability of emergence of the malignant clone will be the product of the probabilities of each event. Assuming that only the first event (initiation) is radiation-induced, and that the subsequent ones are rare phenomena, perhaps independent of irradiation, clinical cancer could be many orders of magnitude less likely than initiation itself. Yet, clinical cancer could show a relationship with dose similar to that of initiation, even though (owing to the multi-stage nature of the process and possible systemic interferences) less regularity would be expected than that observed for stochastic radiation-induced phenomena in single cells under controlled conditions. That this may actually be the case is suggested by the reproducibility of dose-response relationships for some cancers in animals of selected strains. Also, supporting this contention is the fact that the absolute risk coefficient for cancer of the same organs derived from epidemiological observations of different populations (see chapter V) are often similar, although there are exceptions to this rule (see, for example, Figure XXVIII). This may imply that the modifying influence of secondary factors may not greatly change the final probability of induction and the reproducibility of the dose-response relationships. It has been postulated that for some forms of malignancy, such as leukaemias, radiation may be the causal factor, not for the first, but for the last event in a series of rare phenomena [L24, K39]. In any case, initiation is a necessary step, although only a small fraction of initiated cells may develop into a viable clone and into a clinical tumour.

70. The principal aim of a model is to predict the shape of the incidence curves as a function of dose, dose rate, quality of radiation and possibly other factors. Ideally, a model for radiation-induced cancer could provide some basis for the evaluation of risk at low doses [D9, F12, T15] if it could characterize the following processes:

(a) Probability of malignant transformation of a defined target cell. This will most likely vary with the organ, dose, quality of radiation, and temporal pattern of dose distribution. In this respect, the model should include theoretical concepts concerning the nature of the initiating event(s) and not be purely empirical. Mathematical formulations should be compatible with general knowledge of radiation and cancer biology;

(b) Probability of interaction at the systemic level between transformed cells or between developing clones;

(c) Probability of cell killing with dose, as non-viable cells cannot give rise to cancerous clones. This factor, as discussed in chapter III, depends certainly upon the tissues concerned, some of which are particularly susceptible, and upon dose, dose rate and quality of radiation and on other irradiation conditions (in vitro, in situ) [D7, G14, G16, H8, H10, M31, M52, R2, S26, S27, U6, U7, U17];

(d) Effect of numerous host factors, discussed in annex I of the 1977 UNSCEAR report [U6]. Among promoting factors, cell division is perhaps a good example [B36, B85, M6, N6, P22]. Enhanced proliferation can be induced by various mechanisms, including radiation-induced cell death, a phenomenon which is likely to produce a threshold-type dose response. Other factors could be the differentiation of initiated cells, immunological surveillance that suppresses development of malignant clones with antigenic characteristics foreign to the host-system, and hormonal influences;

(e) Effect of exogenous promoting agents leading to more rapid appearance of tumours, to an increase in tumour yield, and perhaps also to changes in the shape of dose-response curves, as shown by several experiments [F21, L26] including those on in vitro oncogenic transformation [H22, L26].

71. Immunological surveillance may be impaired by numerous factors, including ionizing radiation. The degree of impairment would certainly depend on dose, on whether the whole body or only part of it is irradiated, and then on what part and what proportion. It may be postulated that a reduction of immunological capacity of the organism follows a threshold-type response to irradiation. The importance of the immunological suppression in the low and intermediate dose range remains to be established although recent evidence points to a limited role of the immune system. Studies of Mole et al. [M52] on induction of acute myelogenous leukaemia in CBA/H mice, suggest that, at least in this tumour-host system, impairment of immunological surveillance is not very important. Similar conclusions were also reached by Nolibé et al. in respect to lung cancers induced by $^{239}PuO_2$ in rats [N9].

72. Hormonal dependence is well known for some cancers [U6]. By partly or totally inactivating endocrine organs and creating a hormonal imbalance, radiation may accelerate or impair malignant growth in other organs (e.g., breast, thyroid, ovary). Again, it is likely that this type of response would show pronounced dose thresholds. Hormonal influences could also be responsible for the association of various tumours, as observed in experimental animals [S53].

73. In summary, the action of modifying factors might change the resulting dose-response relationships. It is a basic weakness of the models discussed in chapter III that mathematical functions relating cancer incidence to dose reflect only initiation and sterilization of the initiated cells. This is because the precise effect of other modifying factors on tumour induction—as a function of dose—cannot yet be described with reasonable credibility, even if some attempts have been made [M4, P22]. Models, therefore, provide greatly simplified concepts, based on plausible assumptions and hypotheses, which may help in understanding the role of dose, dose rate and radiation quality. The relative importance of the parameters reflecting these quantities in a model can be deduced by comparing data with predictions. However, some of the parameters are the compounded expression of several elementary phenomena that cannot be resolved at present.

74. From available models, risk coefficients for man in the range from about 1 mGy up to about 0.1 Gy can only be obtained by extrapolation from the recorded values (in most cases above 1 Gy) to zero dose. Effects of the host factors discussed above (cell renewal, immunological surveillance, hormonal balance) and exogenous modifying factors upon dose-response relationships are uncertain, and only approximate evaluations may be given. For the purposes of the present annex, the levels of acute doses of low-LET radiation can be broadly separated as follows:

(a) $<$ 0.2 Gy. At this level, data for most tissues are not directly available, but the damage to tissue functions is considered negligible. Therefore, dose-response relationships could be very close to those postulated by models that disregard host factors;

(b) 0.2-2.0 Gy. Damage to tissues, cell proliferation and influence of other host factors would not be expected to play a dominant role. Distortions in the dose-response relations should be relatively minor, and would not grossly bias the extrapolations;

(c) 2.0-10 Gy. Damage to tissues, to immunological functions (for irradiation of the whole or most of the body) and to hormonal feed-back systems may play a significant role. Extrapolations to low doses must therefore become more complex, particularly from the upper end of this range. Great caution is needed to avoid extrapolating from data that are already strongly affected by killing of initiated cells, as this might result in a substantial under-estimate of the risk at low doses;

(d) $>$ 10 Gy. Severe damage to tissues and organs will dominate the response. Data in this dose region are most difficult to evaluate and so complex that extrapolation to low doses could be meaningless. Induced cell repopulation may also become a complicating factor for irradiation times longer than a few days.

A corresponding approximate classification of fast neutron doses would include the ranges: (a) $<$ 0.05 Gy; (b) 0.05-0.2 Gy; (c) 0.2-2.0 Gy; and (d) $>$ 2.0 Gy. It should be noted that the relation between these ranges of low- and high-LET radiation may not be interpreted in terms of RBE.

B. THE THRESHOLD DOSE FOR CANCER INDUCTION

75. It has already been mentioned that for many types of cancer the epidemiological and experimental information available does not suggest the presence of a threshold dose. If initiation is at least partly autonomous, i.e., if it affects a single or very few cells, present understanding of the mechanisms involved suggests that:

(a) The nature of radiation interaction with the cellular target for cancer initiation is stochastic, in the sense that each increment of dose carries a given probability of effective interaction;

(b) The error-free repair of the DNA, which is the most likely target involved, leaves some fraction of the damage unrepaired and the error-prone repair may produce misrepaired sequences in the DNA structure.

As the product of two probabilities greater than zero cannot equal zero, the presence of a threshold cannot be assumed.

76. A different situation obtains when the lifetime lost per cancer case (instead of the incidence) is related to dose or dose rate. Few malignancies show a definite inverse relationship between dose rate and latent period (see III.B.2), particularly at chronic exposure. In such cases (e.g., bone sarcomas induced by ^{90}Sr or long-lived radium isotopes) practical thresholds may exist below which no life shortening occurs and a very low probability of tumour appearance applies.

C. UNICELLULAR VERSUS MULTICELLULAR ORIGIN OF NEOPLASTIC GROWTH

77. Under the simplifying assumption that dose-response relationships for radiation-induced cancer reflect mainly the kinetics of initiation, they should include both the dose-dependence of the relevant intracellular phenomena and the interactions of individual (contiguous) cells, if indeed the latter play any role in the process [G30]. Therefore, the question whether a malignant clone arises from transformation of a single cell or of several contiguous cells is of critical importance for the formulation of models. Because understanding of the biological process of carcinogenesis is limited, this question cannot be resolved unequivocally at present. However, most experimental and human observations tend to support—even if indirectly—the monocellular origin of neoplasms. Furthermore, the alternative multicellular hypothesis allows the development of models resulting in such a variety of dose-response relationships as to render the exercise of model-fitting totally meaningless.

78. All these problems were reviewed in depth by Fialkow [F3, F4, F6], Nowell [N5] and others [B60, F13, F14]. It appears from their work that the monocellular alternative is gaining increasing acceptance, except for some rare hereditary tumours in subjects with inborn predispositions (e.g., multiple neuro-fibromatosis [F5]) and other rare tumours, such as condylomata acuminata [F10]. Three main lines of evidence support the unicellular hypothesis [F3, F6, N5]:

(a) The isoenzyme pattern of glucose-6-phosphate dehydrogenase in cancerous cells derived from tumours of heterozygous women, in accordance with the hypothesis that the same X-chromosome of the homologous pair is functioning in all cells of a given neoplasm. A similar pattern was observed recently in 3-methylcholantrene-induced fibrosarcomas in $Pgk\text{-}1^a/Pgk\text{-}1^b$ mice carrying X-chromosome inactivation mosaicism for the phosphoglycerate kinase (PGK-1) gene [T17];

(b) The homogeneity of immunoglobulins produced by almost every case of myeloma;

(c) The common cytogenetic markers frequently detected in the cells of a single tumour.

This evidence is limited, indirect and compatible with the alternative hypothesis that selection of one clone from among several initially transformed cells might lead to an apparently monoclonal composition of the tumour. So far, however, this possibility has not been widely supported.

D. AUTONOMY OF TARGET CELLS FOR TUMOUR INDUCTION

79. Conceptually, even if initiation is taking place in one cell, the multi-stage nature of cancer development and possible influences of tissue and systemic origin could introduce random fluctuations into the expression of cancers in vivo. For radiation-induced cancer, therefore, such regularity and reproducibility of dose-response relationships as that seen for stochastic radiobiological phenomena in cultured cells would not be expected. Much of the information from animal experiments shows nevertheless that dose-response relationships are reasonably reproducible. Proportionality between initiation frequency and expression may therefore be assumed as a plausible hypothesis.

80. On the basis of microdosimetric considerations Rossi and Kellerer [R17], Rossi [R15, R16] and Rossi and Hall [R43] have pointed out that the observed curvilinear dose-response relationships for neutron-induced mammary tumours in rats and other tumours in mice are inconsistent with autonomous response because at low and intermediate doses there should be a direct proportionality (linearity) between dose and tumour incidence. Therefore, if the dose response is in fact non-linear, this must mean that either initiation or expression are modified by dose-dependent factors, implying a lack of "cell autonomy". If such a conclusion should generally apply, theories concerned with the response of single cells may not be relevant to dose-response relationships for cancer induction.

81. In the original experimental data of Shellabarger on Sprague-Dawley rats [S15], 14 months after an acute x-ray exposure, the incidence of all mammary tumours (adenomas plus carcinomas) per rat showed an approximately linear relationship with dose, up to 0.84 Gy, whereas 0.43 MeV neutron irradiation, with doses from 0.001 to 0.064 Gy, resulted in a tumour incidence roughly proportional to the square root of the dose [S15]. Rossi and Kellerer argued [R17] that, since cell killing would be negligible at such low neutron doses, the form of the observed relationship required the interplay of radiation effects in several cells. For mammary fibroadenomas, such an interaction leads, apparently, to a reduction of the tumour rate per unit dose even at neutron doses of a few tens of mGy.

82. Earlier data by Shellabarger et al. [S15] were later extended, with follow-up of the animals to about 1000 days [S37]. Tumours scored included fibroadenomas and adenocarcinomas, the latter malignant forms being 9-16% of the total. The data expressed as crude incidence or mortality-corrected indices, r(t,D), R(t,D), at various post-irradiation times, essentially confirmed the previous findings. A very high RBE was seen at low neutron doses for both tumour types (about 100 at 0.1 mGy) and the dose-response for the combined tumours was concave downwards for neutrons and approximately linear for x rays. There was also a significant shift of the age-specific r(t) curve in the irradiated animals (acceleration).

83. When the net R(t) values at 800 days (the latest follow-up time for all but one dose groups) were considered separately for fibroadenomas and adenocarcinomas, the following conclusions could be drawn:

(a) For all tumours combined the downward concavity of the curve after irradiation with neutrons results essentially from a low point for the fibroadenomas at 0.064 Gy. Such an effect is not seen for the adenocarcinomas, where the relation is approximately linear, although the experimental scatter precludes accurate assessments in this case;

(b) At 800 days, the departure from linearity of R(t) for the fibroadenomas is much less pronounced than at 400 days [S15] or than that for the incidence of adenocarcinoma [S37];

(c) No account was taken of cell killing in these experiments, although this may have not been negligible already at 0.064 Gy.

84. In view of their high spontaneous incidence (80% throughout the lifetime in females), the mammary tumours in Sprague-Dawley rats must be regarded as an unusual model. This view is confirmed by the facts that only a minor part of these tumours is histologically malignant [S12, S13, S14, S15, U17, V4, V5] and that the very high sensitivity of the Sprague-Dawley rat to the induction of mammary tumours is not seen in other rat strains [B43, B92, C15, S7, S11, V10].

85. In summary, the shape of the dose-response relationship reported for neutron- and x-ray-induced fibroadenomas at low doses in the mammary gland of Sprague-Dawley rats in one study is rather exceptional among all data on radiation-induced tumours. The low yield of adenomas per unit dose at 0.064 Gy, which has been interpreted to show an inhibitory influence by the neighbouring cells, may also be explained in terms of cell killing. Therefore, the observations discussed do not necessarily imply that malignant tumours arise from more than one initially transformed cell, or from interaction of several cells.

86. Other data on benign lung adenomas in RFM mice [U21, U22] may be discussed in this context. Pathogen-free animals were irradiated locally over the thorax with graded doses of fission neutrons (0.05 to 1.5 Gy) and the number of tumours in dissected lungs was counted 9 months after exposure. The effect was fully manifest at 6 months after 0.5 Gy, and intercurrent mortality was negligible. A peaked response, with a maximum around 0.25 Gy, was seen following single neutron doses. Splitting of the dose into two equal fractions, given at 24-hour or 30-day intervals, resulted in no sparing effect of fractionation. Plotting the mean number of adenomas per animal at 9 months against dose gives a slightly upward concave curve in the range of 0 to 0.25 Gy. A quadratic model fits the data very well ($P > 0.99$) but non-threshold linearity is not excluded ($P > 0.8$); also, a threshold of 0.05 Gy cannot be rejected, particularly since the gamma-ray curve suggests such a possibility. It is also possible that increasing doses of neutrons up to 0.25 Gy may have an enhancing effect, interpreted either as acceleration or promotion. Such an effect, however, is the opposite of that seen for mammary fibroadenomas in Sprague-Dawley rats. Results of other experiments with neutron induction of various tumours in BALB/c mice [U23] were also advocated as evidence that induction cannot be treated as a phenomenon related to autonomous cells. However, a correction for sterilization of initiated cells could result in approximately linear dose-response curves up to 0.2 Gy.

87. There is yet another explanation for the above data, i.e., that single-cell initiation is modified by enhancing or inhibiting dose-related effects. The nature of these effects (direct or abscopal, cellular or humoral) cannot be specified at present. Tumours requiring hormonal stimulation for their development (as in the case of the ovary) often have threshold dose-responses. In essence, therefore, none of the data discussed are incompatible with the hypothesis that tumour initiation by radiation may take place in a single cell, which from this stand-point must be considered relatively autonomous.

88. It has been pointed out [G15] that the simultaneous initiation of cancerous growth in several interacting cells would be equivalent to a multi-target event. If so, the sigmoid shape of the curve should become more pronounced with an increasing number of participating cells. There is, however, little data to support such a possibility and no known experimental system to test such hypotheses.

89. It may be concluded that if the curve is not obviously sigmoid or threshold-like upon visual inspection, the idea of a monocellular origin of the tumour may be accepted. The argument of a mono- versus a pluri-cellular theory, as well as the question of the degree of cellular autonomy in the origin of cancer, will not be finally resolved as long as the understanding of tumour pathogenesis remains unsatisfactory. As a rule, however, there appears to be no solid biological evidence against the monocellular origin of neoplasms. The assumptions that malignancy is initiated in a single cell, and that there is a reasonable proportionality between tumour induction and expression, have been incorporated—explicitly or implicitly—into most models of cancer induction by radiation. This view is explicitly accepted here as a working hypothesis, even though it is recognized that different opinions have been expressed [B83, M52, R43].

E. NUMBER OF CELLS AT RISK

90. The number of cells at risk of cancer induction in any organ is not known. When discussing this subject, most authors argue that the number of cells in which initiation takes place must be proportional to the number of cells at risk in a given tissue, and that the latter is proportional to the fraction of tissue irradiated. Most models or theories of cancer induction by radiation have accepted this assumption. It does not follow from it that tumour incidence, spontaneous or radiation-induced, is proportional to the total number of cells in any organ, or in the body of various animal

species [B49, M9], because there is no obvious correlation between body size in various species and incidence of tumours.

91. Epidemiological data on leukaemia in man, after irradiation of various fractions of the total active bone marrow, are broadly consistent with the notion that the probability of induction is proportional to the number of irradiated cells at risk, on the assumption that these are uniformly distributed throughout the marrow. Absolute annual risk coefficients derived from various studies fall within a range which is narrower than the variation of the fraction of the irradiated tissue (annex G in the 1977 UNSCEAR report [U6]). The same conclusion may be derived from experiments on cancer induction by total and partial irradiation of the mammary tissue in rats [B28, S10, S12] and by various areas of skin in mice [H11, H12, H13].

92. An important and related question is the effect on tumour incidence of a non-uniform tissue dose distribution. The extreme case is that of the so-called hot particles, i.e., particles with very high concentrations of radionuclides that are deposited in an organ such as the respiratory tract or the liver. Under such circumstances, the dose averaged over the entire organ would be much lower than that in the immediate vicinity of any such particle. Several authors addressed this question by studying carcinogenesis in the lung [I3, L35, S54]. In all cases, as expected from theoretical predictions [M9, M10], hot particles were found to be less effective than similar doses of the same radiation quality distributed in a more uniform manner.

F. POPULATION HETEROGENEITY AND SUSCEPTIBILITY TO CANCER INDUCTION

93. Baum [B16] raised the question of whether linear extrapolation of the risk from the high dose and dose-rate region of low-LET radiation to the low-dose domain is always conservative, in view of a possible difference in susceptibility to cancer induction between groups in the general population. To exemplify the situation, Baum [B16] constructed a model in which three population sub-groups, represented to 1, 10 and 89%, varied in susceptibility (expressed as D_0 values) in the ratio of 100 : 1 : 0, respectively. For each of the sub-groups he postulated a dose-response relationship of the form

$$I_f(D_0) = 1 - e^{-(D/D_{0i})} \qquad (2.1)$$

94. For the most sensitive sub-group (1%) he assumed that cancer induction might be a single-target effect ($n = 1$) with D_0 of 0.01 Gy; 10% would exhibit a lower sensitivity ($D_0 = 1$ Gy); and for the rest of the population $D_0 = \infty$. According to Baum, the composite response of the total population is dominated in the low-dose region by the highest sensitivity of the 1% sub-group. In the range from about 0.01 Gy to a few Gy, the relationship would be a curve, concave downwards, with response roughly proportional to $D^{0.5}$. The risk per unit dose above 1 Gy would be less than below 0.01 Gy.

95. It is not easy to envisage why susceptibility between groups should be reflected only by D_0, and, if so, why by a factor as large as 100. Moreover, the assumption that the bulk of the population should be totally non-susceptible to induction of malignant disease(s) lacks justification in Baum's paper [B16]. No epidemiological evidence supports this contention, even though it is known that incidence of radiation-induced cancer in man is generally low. Examples of dose-response relationships advocated by Baum to support his argument do not stand up in the face of criticism. The author presented data for acute leukaemia at Nagasaki, and for all cancers, all leukaemias, stomach, lung, and breast cancer at Hiroshima, where incidences rise with a power of dose between 0.1 and 0.8. At present, dosimetric uncertainties preclude a more detailed discussion of atomic bomb survivor data, but preliminary evaluations [K39, S46] of the dose-response relationships for leukaemia, breast cancer and total malignancies for the period up to 1978, using new dose estimates [L27], do not support the above conclusions (this information is still tentative). Therefore, Baum's hypothesis is neither satisfactory on theoretical grounds nor supported by epidemiological observations. The subject itself, however, is obviously important and warrants some exploration.

96. Progress in cancer genetics has shed some light on possible mechanisms of differential susceptibility to cancer development in individuals with various inherited traits [G12, M35]. The relevance of these phenomena to radiation-induced cancer requires attention. The relationship between genetic heterogeneity and incidence of spontaneous cancer, and cancer induced by radiation or other carcinogens, was discussed in detail in annex I of the 1982 UNSCEAR report [U24]. It is again reviewed in annex A to this report. The homozygotes for some genes (ataxia telangiectasia, Fanconi's anaemia and several others) have a significantly increased natural incidence of some forms of cancer and an enhanced sensitivity to other cellular and subcellular radiation effects. Various forms of impaired DNA repair are seen in most of these conditions. In view of their rarity, the affected subjects do not pose a public health problem, but the heterozygous carriers of these genes could also have an increased risk of developing spontaneous cancer. Calculations have shown [V6] that a few percent of individuals in the general population should carry such genes in a heterozygous state. If their capability for DNA repair should be reduced, this might result in an increased proneness to cancer development. Although it is not known at present whether these heterozygous subjects may also be more prone to radiation-induced cancer, this possibility should not be overlooked.

97. If risk coefficients at low doses were higher than those reported in most studies at about 1 Gy, then perhaps such evidence could be interpreted to suggest the presence of population groups particularly susceptible to cancer development. A higher effectiveness of low doses was claimed by Mancuso et al. [M3, K17, K32], who studied the mortality of workers employed in the Hanford works, Richland, United States, dying

with cancer from 1944, for whom death certificates and data on personal radiation dosimetry were available. This information was reviewed by several authors [A7, D14, G5, G25, H20, M30, R3, S2] who pointed to the low statistical power of the original data and to numerous other difficulties in their interpretation. From careful examination of all the evidence, it appears that these data are at present inadequate to prove or disprove that the risk of radiation-induced cancer at low doses is higher than estimated by UNSCEAR in its 1977 report [U6]. This matter will, however, be kept under review.

G. SUMMARY AND CONCLUSIONS

98. The pathogenesis of tumours, both spontaneous and radiation-induced, is at present poorly understood. The probability of cancer induction cannot therefore be derived from general principles. The data available indicate that carcinogenesis is likely to be a complex, multi-stage process. Initiation at the cellular level is followed by a long period of latency, during which numerous changes take place until the tumour becomes clinically manifest. The probability of some of these changes is very low, and during the intermediate stages numerous exogenous factors could accelerate or inhibit the development of potentially cancerous cell clones.

99. There is considerable variation between organs and tissues in the process of cancer development, presumably related to numerous endogenous factors. Among these, the hormonal and the immunological factors are known to be of importance, at least for some forms of cancer. Significant cell killing in tissues may stimulate compensatory cell proliferation and therefore increase the probability of cancer development. The ways in which, and degrees to which, radiation could modify such mechanisms, particularly in relation to dose, are not well understood. It appears likely, however, that dose thresholds such as those operating for non-stochastic effects might apply. This would imply that low or intermediate doses (below approximately 2.0 Gy of gamma rays and 0.3-0.5 Gy of neutrons) delivered acutely might have little or no modifying effect.

100. Under the circumstances described, for predictive purposes the use of simplified models of tumour induction becomes one of the possible choices, even though the degree of simplification is usually such as to exclude consideration of the above modifying factors. This important limitation of the models should be kept in mind.

101. In view of the multi-stage nature of the phenomena described, and of the small probability of occurrence of each step, the proportion of initially transformed cells giving rise to an overt tumour must be extremely small. It may be postulated that at low doses and dose rates, where the host factors mentioned above are not expected to modify primary events appreciably, there is a broad similarity of relationships between dose and tumour incidence, on the one hand, and between dose and probability of cell initiation and survival, on the other. Exogenous modifying factors (e.g., promoters and inhibitors) could alter the slope, and perhaps the shape, of the dose-response curve in some instances; in man very little is known in this respect, apart from the effects of tobacco smoke on lung cancer induction.

102. Monocellular and monoclonal hypotheses are usually assumed in models of radiation carcinogenesis. Most biological data support the notion that cancer, as a rule, starts from a single cell, but unequivocal, direct evidence to support this point is lacking, and alternative interpretations are possible. The monocellular hypothesis is critical in extrapolating the risk from high to low doses. The alternative hypothesis, that concomitant initiation or interaction of several cells is required, lacks sufficient experimental support and makes extrapolation from intermediate to low doses difficult or impossible at present. The postulate of monocellular origin of cancer must be treated, for the time being, as a working hypothesis.

103. The number of cells at risk of radiation-induced malignant transformation is usually assumed to be proportional to the fraction of an organ or tissue irradiated. The experimental evidence in favour of such an assumption is very strong, but, again, it must be regarded simply as a plausible working hypothesis. Gross non-uniformities of the tissue doses, such as those resulting from deposition of the so-called hot particles, normally result in a lower tumour incidence than for comparable doses distributed uniformly.

104. It has been proposed that sensitive sub-groups in the general population might invalidate any linear extrapolation of cancer risk to low doses of radiation, a procedure hitherto believed to provide upper values of the risk. It is known that the very rare homozygous carriers of particular genes (e.g., ataxia telangiectasia, Fanconi's anaemia) are more prone to cancer and that their cells are particularly sensitive to other effects of radiation, such as cell killing. It is also true that the healthy carriers of these same genes in the heterozygous form (a few percent of the general population) are at greater risk of developing spontaneous tumours and also have a slightly enhanced sensitivity to other radiobiological effects. Whether these same individuals may also be at a higher risk of radiation-induced cancer cannot be proved at present and this question requires further study. The epidemiological evidence in favour of the notion that higher risk coefficients per unit dose of low-LET radiation may apply at low, rather than at high, doses appears at present unconvincing.

III. DOSE-RESPONSE MODELS OF RADIATION-INDUCED CANCER

105. Although in principle a large variety of mathematical expressions and models could be fitted to experimental and epidemiological data on radiation-induced tumours, for the purpose of this annex the Committee decided to limit the analysis only to those models that appear to be supported by general knowledge of cellular and subcellular radiobiology.

A. INTRODUCTION

106. When either the crude or the actuarial incidence of various radiation-induced experimental tumours is plotted against a wide range of doses, then, for low-LET radiation, a peak incidence is normally seen at intermediate doses, followed by a decline at high doses. For high-LET particles, the essentially linear initial slope gradually decreases with dose. In some cases, it even becomes negative. The bulk of data is consistent with this generalization [U6]. Evidence in man is much less certain because only a few series cover a sufficiently wide range of doses. Nevertheless, the incidence per unit dose of bone sarcoma [M29, R18], lung carcinoma [K22, S3] and cancer of the breast [S16] decreases at very high doses. Thus, a model of radiation-induced cancer should allow for two opposing trends: a rise of probability of induction with dose and then a decline, resulting presumably either from killing of irradiated potentially malignant cells [G16, M52, R2], or, in some cases, from increased mortality rate at high doses [I5, J7]. Mathematically, this trend may be simulated by multiplying the induction dose-response function by a term describing the probability of cell (or organism) survival as a function of dose.

107. Conceptually, there are two possible approaches to the formulation of models. The first is based on radiobiological considerations, relating, by analogy, the radiation-induced cancer incidence and the influence of various parameters (dose, dose rate, fractionation) to other effects in single cells. Broad similarities have been observed in numerous cases. The alternative approach is an empirical one, aimed at approximating the data (incidence versus dose) by simple mathematical functions. In practice, the two approaches are often applied in combination.

108. There is no reason why any model might be valid for all radiation-induced malignancies: actually, a more reasonable approach would be to determine separately which model is applicable to which type of cancer, a conclusion supported by the bulk of experimental data. There are examples of radiation-induced cancer with pronounced thresholds (e.g., the thymic lymphoma of the C57BL mouse, ovarian tumours in many mouse strains). Indirect mechanisms (destruction of an overwhelming part of target cells in the thymus: killing of a large fraction of hormonally-active cells in the ovary) may explain such sigmoid relationships. Similar data are exceptional in man (see chapter V). Thus, even if threshold-type relationships cannot absolutely be excluded, the most easily induced human tumours, such as those of breast, thyroid and lung (undifferentiated small cell type), as well as leukaemia, do not indicate the existence of a threshold. Therefore, models used for these malignancies do not postulate a threshold. In principle, the models discussed below have been formulated in terms of the absolute risk, but they seem equally applicable to a relative risk increment.

B. DERIVATION AND CHARACTERISTICS OF DOSE-RESPONSE MODELS

1. The linear model

109. The simplest and oldest linear model was developed for x-ray-induced point mutations in Drosophila [G24, M46]. It was based on the postulate that each energy deposition in a cellular target carries a probability of changes in the genome (mutations) and that these may be either irreparable or the result of misrepair. Since radiation energy is transferred in discrete events, all effects should ultimately be linear with dose at low doses when only few cells absorb some energy and their number is directly proportional to dose. The probabilities of an effect assumed to be an all-or-none phenomenon in relation to each dose increment should be additive, and dose rate or fractionation would not be expected to alter the magnitude of the final effect.

110. In the course of time it became obvious that the linear model must be limited to effects showing single-hit kinetics after low- or high-LET irradiation. However, the postulated additivity of effects and the dose-rate independence does not always apply to single-hit effects [E10, H35], showing that in such cases repair processes must also operate to make an otherwise linear relationship dose-rate sensitive. It appears that when a track passing through the sensitive volume is not 100% effective, then its effects may be subject to repair. In other words, the presence of dose-protraction or dose-fractionation effects may not be incompatible with single-hit kinetics.

111. For high-LET radiation, the linearity of the initial slope, modified by phenomena of saturation or cell inactivation (killing), has been widely accepted [B20, I1, M66, U6, U7, U9, U10]. The dose response is described by the following equation:

$$I(D) = a_1 D\, e^{-\beta_1 D} \qquad (3.1)$$

If cells are sensitive to inactivation, the relationship will depart from linearity, even at low or intermediate doses, owing to cell killing. The lower the mean lethal dose ($1/\beta_1$), the more downwards concave the relationship will be. Recent experiments on neutron-induced tumours in animals (see chapter IV) suggest that this phenomenon—or others [S37, U23, U25, U26]—does in fact operate, causing departure from linearity, even at a few tens of milligray or a few tenths of a gray. This is explained by the fact that cell killing by high-LET particles is very effective with exponential non-threshold survival curves.

112. If equation (3.1) reflects the kinetics of tumour incidence as a function of the high-LET dose, extrapolation to low doses would tend to under-estimate the risk by a factor of $e^{-\beta_1 D}$. Examples and limitations of this postulate will be discussed in chapter IV, in the light of available experimental data.

113. Alternatively, the data can normally be fitted over some range of doses by an equation of the type:

$$I(D) = a_1 \sqrt{D} \qquad (3.2)$$

Such a purely descriptive model implies no linear slope at low doses, even for very radioresistant cells. This seems unlikely, however, on radiobiological grounds. In this latter model, as in any other model involving a downward concavity of the dose-response curve, dose fractionation would produce an increased

incidence of tumours if the intervals between fractions were sufficiently long for the effects of each fraction to be considered independent [R37]. By a similar mechanism, the effects at low dose rate could also be enhanced, in comparison with the high dose rate.

114. An interesting variant of the linear model is that developed by Mayneord and Clarke [M9]. They discussed dose-response curves and their relationship with time, in regard to both dose rate and latency in the appearance of tumours. This is of importance because irradiation time and latency may be comparable with the life span of an exposed individual and could, therefore, affect the manifestation of the response. Their point of departure is that irradiation confers a probability of cancer appearance in the future [B48], following a stochastic process. This probability may be estimated by integrating the response of single cells as a function of dose over the number of cells at risk. A linear relationship between the probability of malignant cell transformation and dose was assumed at low doses where cell killing is irrelevant. Because much experimental evidence from chemically- and radiation-induced tumours [B48, E3, E4, F8] pointed to an increase in latency with decreasing dose rate, this particular feature was also incorporated into the model [M9, M10].

115. The result of the analysis was that in all cases, assuming a linear relationship between each increment of dose and risk (the latter distributed in time), non-linear (concave upwards) dose-response relationships were obtained, often with an apparent threshold. This is due to the inverse relation assumed between time of tumour appearance and the dose. According to this model, therefore, in most situations a linear extrapolation of the risk from high to low doses and dose rates is likely to yield a conservative risk estimate. The dose-response relationships should tend to linearity for: (a) long observation times, compared with the median latent period; (b) very heterogeneous populations, i.e., populations with a wide distribution of the latent period after single irradiation; (c) little variation of the median tumour appearance time with the dose. In general, however, the theoretical analysis of Mayneord and Clarke [M10] does not support an overall linear relationship between dose and cumulative tumour rate over finite time intervals in populations having a standard age distribution.

116. Inverse relationships between the mean latent period (from the start of exposure to tumour diagnosis) and dose (or dose rate) are seen mostly for irradiations of long duration, for instance in dogs and mice injected with ^{226}Ra and ^{99}Sr [M33, R28, R32]; in Chinese hamsters, in which the latent period of liver tumours decreases with increasing activity of injected ^{239}Pu [B87]; in rats injected with thorotrast, which produces tumours of liver and spleen [W15]; or rats exposed over periods of weeks or months to various concentrations of radon resulting in lung carcinomas [C34]. Finally, a negative correlation of latency versus mean dose rate was seen in human dial painters with ^{226}Ra and ^{228}Ra body burdens [E3, E4, M14, P11, R18]. It is interesting to note that the inverse dose-latency relationship was much less pronounced for induction of bone sarcomas after single injections of short-lived ^{224}Ra in rats [M67]. For brief exposures such as for atomic bomb survivors, there is, at least in the younger cohorts, a suggestion that the mean induction period for leukaemia is negatively correlated with dose [L32], although the reference in question seems to compare mostly radiogenic cases with mostly naturally occurring ones. Such a relationship was not detected for breast, stomach and lung cancer in atomic bomb survivors [B17, L32, M17, K39, T12] and for breast and thyroid cancers resulting from medical irradiation [B26, S16, S38]. Moreover, of all cases showing an inverse relation of the latent period against dose, an unequivocal departure from linearity was found only for ^{90}Sr-induced bone sarcomas. The situation for human osteosarcomas induced by ^{226}Ra and ^{228}Ra is not totally clear, and the dose-response relation for leukaemia in atomic bomb survivors is still not available. In conclusion, the inverse relationship between latency and dose does not apply to many tumours. Thus, an upward concavity of the dose-response relationship as a result of this factor alone cannot be viewed as a general phenomenon.

2. The linear-quadratic model

117. For the bulk of experiments on single-cell systems, and for many end-points, the prevailing form of the dose-response curve after acute low-LET irradiation is concave upward, the response rising with a power of dose of between 1 and 2. Broadly similar shapes were also observed for tumours induced by the same radiation. This form of the response is thought to imply that for the occurrence of the final effect the interaction of two elementary effects, usually referred to as sublesions [K4], is required. Repair phenomena and dose-rate effects are usually accounted for by the interaction of these sublesions in time and space [L4, S39, S40], but other interpretations were also proposed [G29, G32]. For effects showing curvilinear responses to low-LET irradiation, linear dose-responses are frequently observed with densely-ionizing particles.

(a) The microdosimetric approach

118. Microdosimetric considerations are important because the distribution of absorbed energy divided by the mass in the volumes believed to be the primary targets of radiation action (i.e., cells or cell nuclei) is very inhomogeneous at low and intermediate doses [F7]. Thus the distribution of specific energy, z (energy absorbed divided by the mass of these volumes), may be more relevant for the analysis of the effects than the organ or tissue mean dose, D.

119. Many experiments indicate that for a number of effects the probability of occurrence, E, after low-LET radiation, rises with a power of dose close to 2. This may be accounted for by the theory of dual radiation action which assumes that the induction of two non-specified sublesions is necessary for the production of the effect (lesion). In the approximation that was first developed in detail [K4], it was assumed that the probability of sublesion interaction does not depend

on their distance within a certain volume (the site). Consequently, the probability of effect should rise in proportion to the mean of the square of the specific energy, i.e., $\overline{z^2}$, in the site. It was shown also that $\overline{z^2}$ is a function of the absorbed dose, D:

$$\overline{z^2} = \zeta D + D^2 \qquad (3.3)$$

where the ζ is a weighted average of the specific energy deposited by single events (energy depositions in the critical structures by individual charged particles). Thus, the probability of a radiobiological effect, E, should be

$$E = K(\zeta D + D^2) \qquad (3.4)$$

The quantity ζ has the dimension of dose and its value denotes the dose at which the contribution of the linear equals that of the quadratic term. For x and gamma rays, and for sites of 1 μm diameter, the value for ζ falls within the range of 0.3-0.8 Gy; for medium-energy neutrons, it is as large as 16 Gy. For smaller sites, the values of ζ are considerably larger, but the ratio of the values for neutrons and for sparsely ionizing radiation is less dependent on site size.

120. Consideration of the values of ζ for radiations with different values of LET and their comparison with biological data, indicates that intracellular distances at which sublesions can interact must be of the order of 0.1 to 1 μm [K4]. High values of ζ for neutrons and alpha particles (relative to x and gamma rays) account for a bulk of radiobiological observations. They show that the RBE of high-LET radiations varies as an inverse function of the square root of their dose and this can be understood on the basis of microdosimetric concepts. This type of dependence can hold down to doses where the response to both radiations becomes linear and the RBE reaches a plateau.

121. Suitable time functions can be inserted into the basic equation (3.4) to describe the interaction probability during the time interval between the formation of two sublesions [R12]. One of the conclusions is that the linear term for single events in equation (3.4) should be independent of dose rate. Therefore, any effect of time distribution may only result in a modification of the quadratic term. This relationship between irradiation time, T, and mean time between induction of a sublesion and its repair, τ, is reflected by a reduction factor, G, that affects the quadratic term:

$$G = 2(\tau/T)^2 (T/\tau - 1 + e^{-T/\tau}) \qquad (3.5)$$

In the presence of recovery, the curves of RBE versus absorbed dose do not change in shape, but are shifted towards higher doses by a factor depending on the dose distribution in time and the recovery time, τ. For a constant dose rate, if the exposure time is much longer than the recovery time, the yield of elementary lesions becomes simply proportional (linear) to dose.

122. The theory of dual radiation action has been applied by several authors to the interpretation of biological results, for example to cell inactivation by ionizing radiation [B62, F7]. In this model, the slope of the survival curve depends explicitly on radiation quality through the quantity ζ [K4]. The theory has also been used as a theoretical basis for the linear-quadratic model for many effects, including mutations, chromosome aberrations and initiation of oncogenic transformation. However, experiments with ultrasoft x rays [C23, G9, G10, G11] and with spatially correlated ions [B88, G31, G32, K41, R38] indicate a strong dependence of the interaction probability of the sublesions on distance, with a dominance of short-range interactions (much less than 0.1 μm) for densely-ionizing radiation. The applicable version of the theory [K5] is a model of higher complexity that is less easily tested experimentally.

123. Alternative explanations were considered for the commonly observed RBE-dose and dose-response relationships for low- and high-LET radiation. In agreement with earlier ideas of Haynes [H27], Goodhead et al. [G29, G32] put forward the notion that a number of cellular and subcellular radiation effects depend both on the production of the primary lesions and on a dose-dependent inactivation of repair mechanisms. Whereas the probability of the primary lesions is taken to increase linearly with dose, impairment of the repair system would depend on absorbed dose and specific energy. It has been postulated that the degree of impairment of repair should display a pronounced dependence upon dose and/or dose rate of low-LET radiation. For high-LET particles there would normally be no error-free repair, independently of dose. Therefore, basically linear dose-responses would be expected for induction at the cellular level of each of the various effects separately.

124. The above concepts have not been widely tested. A variety of factors have been reported that may influence the expression of potential damage, and thus change linear dose-effect relationships to curvilinear ones, and vice versa [F18, H22, L26].

(b) Characteristics of the linear-quadratic model

125. Upward concave dose-response curves that fit well the cumulative cancer incidence as a function of acute doses of low-LET radiation are in themselves no proof that cancer is actually initiated in accordance with a linear-quadratic relationship. Curvilinearity could well result from an inverse relationship between dose and latent period [M10]. However, when follow-up data show a constant latent period with dose, it may be assumed, as a working hypothesis, that the upward concavity reflects a linear-quadratic kinetics of initiation.

126. A generalized linear-quadratic dose-response relationship for radiation-induced cancer would be as follows:

$$I(D) = (a_0 + a_1 D + a_2 D^2)\, S(D) \qquad (3.6)$$

where I(D) is the incidence (in an ideal case corrected for intercurrent mortality); D is the dose; a_0 is the spontaneous incidence; a_1 and a_2 are coefficients for the linear and dose-squared terms of cancer initiation;

and S(D) is the probability of survival of transformed cells and may be written as

$$S(D) = e^{-(\beta_1 D + \beta_2 D)} \qquad (3.7)$$

In the equation (3.6), initiation may also be treated as a simplification of a more general expression, which includes some repair at low and intermediate doses and dose rates [B95].

127. To test compatibility of the model with experimental and epidemiological data, the parameters in equation (3.6) must be assigned some value. This can only be done by: (a) reasonable analogy with cellular radiobiological effects; or (b) deduction of the values from empirical studies. As to the parameters for cell survival, these are known for many cell lines (e.g., Barendsen [B5, B6, B9-B12, B45]; Goodhead et al. [C23, G9, G10]; Elkind [E2]; and others [A17, B19, B27, C1, C37, D3, D8, F2, F19, H2, H6, J6, K2, K24, L6, M16, M60, R39, S33, T18, T19, W6, W7]), but are not necessarily applicable to specific tumours.

128. The number of unknown coefficients in equations (3.6) and (3.7) is too large to permit their calculation without some constraints. One of these is that all parameters should be positive or equal to zero [C29]. However, this is often insufficient for reasonably stable estimates of β_1 and β_2, particularly when α_1 and α_2 are estimated at the same time. Attempts were made, therefore [B7, B47], to derive independently the quotient α_1/α_2, which facilitates calculations by lowering the degrees of freedom.

129. Assuming that the theory of dual radiation action [K4] applies to the initiation of cancer, there must be a subcellular structure in which the sublesions appear and an interaction distance below about 1 μm where the final lesion leading to malignant transformation is produced. Kellerer and Rossi [K4-K7, R12] did not specify the relevant structure for cell transformation, but the most likely target of radiation action appears to be the genome. In the light of this assumption, and of available evidence, it is not unexpected that models postulating a linear-quadratic relationship presuppose a direct action of radiation on DNA or make reference to phenomena involving DNA (chromosome aberrations, mutations) for derivation of the relevant parameters.

130. Barendsen [B7] selected the values for α_1 and α_2 on the basis of dose-response relationships for chromosomal aberrations in lymphocytes and the rounded values of α_1/α_2 for x and gamma rays were set at 0.5 and 1.0 Gy, respectively. On a similar principle, Abrahamson [A3] and Brown [B47] assumed that, if human radiation-induced cancers are due to mutations or chromosome aberrations in single cells, then information on the quotient α_1/α_2 could be derived from extensive data available in the literature. However, the large variability of the quotient precluded the use of numbers at their face value (e.g., mean or median). Brown showed also an inverse relationship between the DNA content per haploid genome in cells of various species and the α_1/α_2 quotient, the values extending over ranges of 10^3 and 10^4, respectively.

131. For mammalian cells, α_1/α_2 values for mutations and chromosome aberrations, as reviewed by Brown [B47], clustered around 1 Gy (geometric mean, 1.27 Gy). The values of the β_1/β_2 ratio for cell sterilization were generally much higher, with a geometric mean of 7.76 Gy. The difference is due mainly to higher values of the linear parameter for cell killing, in accordance with conclusions [B9, B11] that at low doses there must be a substantial component in cell killing that cannot be identified with the induction of chromosomal aberrations. Brown concluded that if the initial radiation lesion triggering a human cancer is of mutational or cytogenetic nature, then risk estimates derived at 1-2 Gy of low-LET high-dose-rate exposure would, as a maximum, over-estimate the cancer risk at low doses and dose rates by factors of about 2 and about 4, respectively.

132. Concerning cell survival, it has been pointed out repeatedly [B7, E2, F2, K2, M21, S17] that the low-LET survival curves can be described by various models and, among others, by functions of the "single-target" plus "multi-target-single-hit" type

$$S(D) = e^{-(D/{}_1D_0)}\,[1 - (1 - e^{-D/{}_nD_0})^n] \qquad (3.8)$$

where $S(D) = S_D/S_0$, ${}_1D_0$ and ${}_nD_0$ are mean inactivation doses for single and multiple targets, respectively, and n is the target multiplicity. Alternatively, the linear-quadratic form may be applied, as in equation (3.6).

133. Whether for each cell type there is an initial slope [β_1 in equation (3.7) and $(e^{-D/{}_1D_0})$ in equation (3.8)] is still a matter of debate, but this question is rather immaterial in the present context as both functions describe satisfactorily the experimental data for surviving fractions between 1.0 and 0.1 [B9, B11, F2, M21]. Equation (3.6) has been most commonly used in relation to the linear-quadratic model of cancer induction (see [U6, annex G] and [B7, C29, M31]). For high-LET radiation the contribution of the quadratic term is negligible.

134. As a first approximation, for low and intermediate doses, particularly of low-LET radiation, the killing term S(D) may be neglected. This could be justified under the assumption that repopulation of the target cells after irradiation has a promoting effect on the development of radiation-induced cancer roughly proportional to the degree of cell killing [P22]. If, in addition, some of the terms in equation (3.6) and (3.7) are omitted, a transition is possible from the linear-quadratic model to the pure linear or pure quadratic ones (Figure IV). As can be seen from equation (3.6), the model does not assume the presence of a threshold.

135. There are many methodological and biological factors [B10, C1, D8, H6, K24, L6], which make it difficult to select appropriate survival parameters. In particular, cells irradiated in situ might exhibit higher survival capacity than when irradiated in culture or in suspension [G14, H8, H10, M60] (however, for a contrary view, see [A17]). By using a range of survival parameters suitable to describe the most and least

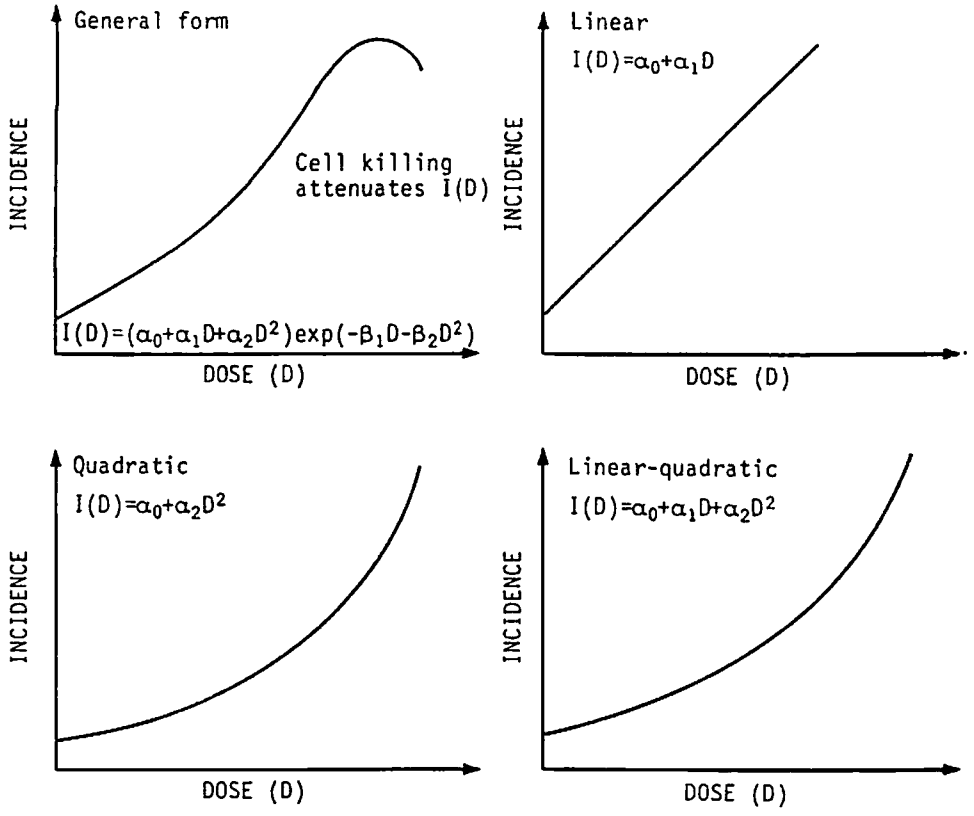


Figure IV. Various types of dose-response curves.
[C29]

sensitive cell lines, one may examine the degree to which cell killing may affect the shape of the tumour incidence data and, hence, the reliability of extrapolation from the intermediate to the low doses. This should provide some indication of the degree of over- or under-estimation of the risk, within the range of values selected for the parameters in question.

136. In an independent analysis, UNSCEAR selected two values of the α_1/α_2 quotient applying to x and gamma rays: 0.5 and 2.0 Gy. For survival, the bone marrow stem cell was selected as the most sensitive. Its survival curve is described by $\beta_1 = 4\ 10^{-1}\ Gy^{-1}$ and $\beta_2 = 8\ 10^{-2}\ Gy^{-2}$ [B6]. For the least sensitive cell, a hypothetical line was assumed with survival parameters $\beta_1 = 10^{-1}\ Gy^{-1}$ and $\beta_2 = 8\ 10^{-2}\ Gy^{-2}$ [B6]. In addition, other survival parameters for radiation-induced human leukaemia cells (Table 1 from [U17]) were used, as follows: $\beta_1 = 3\ 10^{-1}\ Gy^{-1}$, and $\beta_2 = 10^{-1}\ Gy^{-2}$. To normalize the calculated data, it was further assumed that the lifetime cumulative incidence at 3.0 Gy may be 15,000 cases per 10^6 (5000 $10^{-6}\ Gy^{-1}$). The results in terms of the yield of cases from 10^{-3} to 3 Gy for all combinations are plotted in Figure V.

137. From such an analysis, the following tentative conclusions may be drawn. First, the sensitivity to cell killing has a more pronounced effect on the shape of the dose-response relationships than the α_1/α_2 quotient. (Similar conclusions were reached by Mole [M31].) Secondly, for the cells most sensitive to killing, the

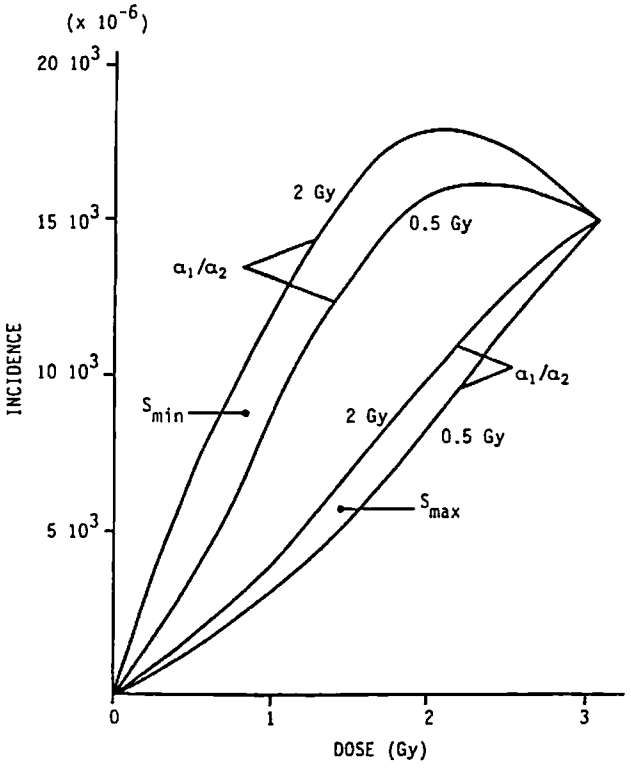


Figure V. Expected cumulative incidences of a radiation-induced cancer according to a linear-quadratic model with α_1/α_2 quotients = 0.5 and 2 Gy and cell survival functions S_{max} and S_{min} as given in paragraph 136. Incidence normalized to 15,000 cases per 10^6 at 3 Gy. For full explanation, see paragraphs 136 and 137.

relationship is concave downward, with maxima at 2-2.5 Gy. Since such curves are not observed for human cancers after low-LET irradiation, it is possible that the assumed sensitivity is too high for in vivo irradiation. This would be in accordance with the lower sensitivity of single cells irradiated in situ, which is due mostly to a wider shoulder of the survival curve [D7, G14, H8, H10, M60, S26, S27]. Thirdly, for the cells least susceptible to killing (the carcinomatous cells according to Barendsen [B6, B7]), the over-estimate of the tumour yield per unit dose from 1-2 Gy to 1-10 mGy (relative to linear extrapolation) ranges from 4.0-2.6 at $a_1/a_2 = 0.5$ Gy, to 1.6-1.3 at $a_1/a_2 = 2$ Gy, respectively. The maximum over-estimation of the risk will result from totally neglecting the cell-killing effect. In such a case, extrapolation from 2 and 1 Gy down to about 10 mGy would involve the following over-estimate:

a_1/a_2 (Gy)	*Over-estimate by a factor of:* *from* 2 Gy	*from* 1 Gy
0.50	4	3
2.00	2	1.5

The above differences for a_1/a_2 of 0.5-2 Gy could not be easily—if at all—detected between estimates derived from 1 or 2 Gy and the exceptional estimates available for doses of a few tens of mGy per single dose. The lack of statistically significant difference is therefore compatible with both the linear or the linear-quadratic model.

138. Inspection of equations (3.6) and (3.7) indicates that cell killing may alter significantly the incidence of a given cancer through interaction with the spontaneous incidence, a_0. At very high levels of the latter and with high sensitivity of the cells to sterilization, a dose-related decrease of the incidence would be expected. This in fact was seen in experiments with animals, showing a negative slope of the dose-response relationships for the so-called reticulum cell sarcoma [M19].

139. The slope of the dose-response curve in the complete linear-quadratic model will be described by a differential:

$$d/dD\ \dot{I}(D) = [(a_1 + 2a_2D) - (\beta_1 + 2\beta_2D)(a_0 + a_1D + a_2D^2)]\, e^{-(\beta_1D + \beta_2D^2)} \quad (3.9)$$

As D approaches zero this equation simplifies to:

$$d/dD\ \dot{I}(D) = a_1 + 2a_2D - \beta_1a_0 - D(\beta_1a_1 + 2\beta_2a_0) \quad (3.10)$$

To examine the interaction with dose of a_0, a_1 and β_1 and its influence on the curve at low dose, two human cancers were selected: breast carcinoma, with a high spontaneous incidence and moderate sensitivity to cell killing of initiated cells; and leukaemia, with rather low values of a_0 and high sensitivity to sterilization. The notional parameters selected were:

Breast cancer:

$a_0 = 8\ 10^{-4}\ a^{-1}$ $\qquad$ $\beta_1 = 2\ 10^{-1}\ Gy^{-1}$
$a_1 = 3.2\ 10^{-4}\ a^{-1}\ Gy^{-1}$ $\qquad$ $\beta_2 = 8\ 10^{-2}\ Gy^{-2}$
$a_2 = 3.7\ 10^{-4}\ a^{-1}\ Gy^{-2}$

Leukaemia:

$a_0 = 5\ 10^{-5}\ a^{-1}$ $\qquad$ $\beta_1 = 4\ 10^{-1}\ Gy^{-1}$
$a_1 = 1\ 10^{-4}\ a^{-1}\ Gy^{-1}$ $\qquad$ $\beta_2 = 8\ 10^{-2}\ Gy^{-2}$
$a_2 = 1\ 10^{-4}\ a^{-1}\ Gy^{-2}$

When the values of d/dD $\dot{I}$(D) were calculated at 1, 10 and 100 mGy, their ratios to the respective values of a_1 were:

	Dose (Gy) *0.001*	*0.01*	*0.1*
Leukaemia:	0.80	0.82	0.94
Breast cancer:	0.50	0.52	0.64

Thus, at very low doses interaction of cell killing, predominantly with the spontaneous incidence, would introduce some degree of over-estimation of the risk, if this interaction should be neglected in the extrapolation procedure. It appears unlikely, however, that this over-estimation might exceed another factor of 2, over that estimated in paragraph 137.

140. When extrapolation is made from intermediate or high doses of low-LET radiation, delivered at low dose rates or in small fractions (of size much below a_1/a_2), then, due to repair processes, the quadratic terms of equation (3.6) should be reduced. Under these circumstances, dose-response relationships approaching linearity would be expected in which the risk coefficient per unit dose is the same over the range of low and intermediate doses. For high-LET radiation, the contribution of the dose-squared component for most effects in single cells is negligible up to a few tens of Gy. Therefore, the model may be treated as linear, although for some effects the slope of the line may not be dose-rate independent (see III.B.1). Such observations cannot be explained solely on biophysical considerations.

141. It has been pointed out [U17] that the linear-quadratic model of cancer initiation is a simplistic concept and not a pathogenetic theory. The great complexity and the interaction of various phenomena at the cellular level preclude its acceptance as a generalized theory of cancer initiation in all tissues and under all circumstances. The dose dependence of the many modifying mechanisms operating at the tissue and systemic level is still too obscure to allow quantitative predictions over the entire range of doses. However, as discussed in chapter II, it may be postulated that the influence of modifying factors might not be very important in the range of doses up to 1-2 Gy of low-LET radiation (or their high-LET equivalent). Under these circumstances, appropriate extrapolation may be acceptable down from the dose region of 1-2 Gy of x or gamma radiation (or an equivalent dose of neutrons) to obtain risk estimates for the low-dose domain.

142. With all these reservations in mind, the linear-quadratic model has been applied to the results of selected animal tumour experiments where dose, dose rate, dose fractionation, dose protraction and LET were systematically investigated (see chapter IV). In several cases [B7, P22, U2, U3, U25, Y1] the results were in basic agreement with the model's expectations.

3. The quadratic model

143. This model is based on the assumption that for the induction of a given effect two consecutive events are necessary, or two concurrent events separated in space in such a way that their production by a single ionization track is extremely unlikely. Except for irradiation of flattened bone lining cells (see V.E.2.), this assumption is difficult to justify on microdosimetric grounds for low-LET irradiation of normal cells in situ. In tumour radiobiology, this concept may be traced back to the theory of bone sarcoma induction by β emitters [M26, M45, M47]. Proportionality to the square of the dose has been noted for various cancers [H12, H13, M26, M52, R18]: this does not exclude the presence of a linear component, but simply assumes that it may neither be demonstrated nor ruled out on statistical grounds. Therefore, if present, such a component must be relatively small.

144. Recently, Mole et al. [M52] have shown that dose-response relationships for radiation-induced acute leukaemia in CBA/H mice may be characterized by an approximately pure quadratic or linear initiation term for x rays or neutrons, respectively (see IV.B.1). On the basis of microdosimetric considerations the apparent absence of a linear term in the dose-response equation for x rays is difficult to explain when the diameter of a nucleus is of the order of few μm. The proposed hypothesis [M52] was that the interaction of two neighbouring cells is necessary for the initiation of this cancer. Initiation by neutrons is in direct proportion to dose and this was explained by the fact that a single recoil track could cross the nuclei of two neighbouring cells. However, for neutrons of maximum effectiveness (400 keV) the range of the secondary protons is less than most nuclear diameters.

145. The experimental basis of these hypotheses is still debatable, and needs further experimental testing. Moreover, the postulates are difficult to reconcile with the results of transformation experiments of cells in vitro, irradiated at low density (see chapter IV) where it is unlikely that two neighbouring cells may be crossed by a single recoil track or may interact during oncogenic transformation by x rays. Explanations other than the microdosimetric ones must be found to accommodate all these facts.

146. When fitted to the experimental data obtained at intermediate or high doses, the quadratic model will predict effects at low doses to be much less than implied by the linear or the linear-quadratic models within the usual range of α_1 and α_2 values. The influence of the time pattern of dose administration cannot be specified a priori for the quadratic model: if repair is fast and dose-rate-dependent, dose protraction or fractionation could lead to a considerable reduction of the effect, and zero effect could not be excluded.

147. The quadratic model has been used by the Committee on the Biological Effects of Ionizing Radiation (BEIR Committee) [C29] to obtain the lower boundary of likely linear-square dose responses at low doses. Three special models have recently been proposed which assume, or derive from experiments, the basic postulate of the dose-squared concept. They refer to leukaemia in CBA mice [M52], skin cancer in rats [V1] and bone sarcoma in man [M4]. They are reviewed in chapters IV and V, respectively.

C. SUMMARY AND CONCLUSIONS

148. Quantitative models of radiation-induced cancer must allow for two facts: first, that tumour incidence rises with dose at low doses; and, second, that at high doses the effect usually declines (either in absolute terms or per unit dose). This shape of the curve may be modelled by the product of two terms: an initiation term increasing as a function of dose, and a cell-survival term declining with it. The latter term can be neglected at low doses, but this simplification may lead to misinterpretations as the dose increases. There is no reason why any one model should be universally applicable to all radiation-induced types of cancer. Models should be tested in each instance by statistical criteria. In each given tumour system, they should allow for the effect of the main radiobiological variables, such as dose, dose rate, dose fractionation, radiation quality.

149. The linear model implies direct proportionality between dose and the probability of tumour induction. Absence of dose-rate and fractionation effects was thought to be an inherent feature of the linear model, because the biological lesion is assumed to result from a single-track effect. However, examples are known where this is not true, and linear dose-response relationships show shallower slopes with decreasing dose rate. There are few examples of cellular or carcinogenic effects following linear kinetics after low-LET irradiation, while the effects produced by high-LET particles often conform to these characteristics. However, there are examples where dose-rate effects for neutrons are found, in an opposite direction (enhancement) from those normally seen for low-LET exposure. The linear model may be regarded as an upper boundary for the more general linear-quadratic model when the doses at which the linear equals the dose-squared components are high or very high.

150. The model of Mayneord and Clarke assumes linearity between dose and cancer initiation at the cellular level. It also assumes a log-normal distribution of the latent periods for overt tumours and an inverse relationship of latency to dose. Solution of this model for observation times comparable to human life expectancy results in dose-response relationships which are upward concave, sometimes with apparent thresholds. The critical assumption leading to such results is the shortening of the mean latent period with dose. If this were a general rule, then extrapolation of risk from high to low doses would always lead to over-estimates. However, for some radiation-induced tumours in man (thyroid, stomach, breast, lung), the latent period is not obviously dose-dependent; also, curvilinearity is not seen in several cases where there is an inverse relation of the latent period with dose. Thus, it is impossible to generalize the notion that just for this reason curvilinear responses would normally apply.

151. When corrected for cell killing, numerous biological end-points induced by low-LET radiation in single cells show an exponential dependence on dose with exponents of between 1 and 2. On the contrary, the same end-points for high-LET radiation show essentially linear dose-responses. Consequently, the RBE is an inverse function of dose. Low-LET radiation shows pronounced influences of dose rate and fractionation, in contrast with high-LET, for which such phenomena are seldom observed or are observed to a lesser extent. Most of these facts may be accounted for by microdosimetric considerations. They predict that, as a rule, linear-quadratic dose-responses should be expected, where the relative contribution of the two terms is comparable (for low-LET). This prediction is in accordance with numerous experimental data on single cells, and so are the effects of dose rate and dose fractionation that may be deduced from the kinetics of repair of the sublesions postulated in the linear-quadratic model.

152. Recent data on ultra-soft x rays, however, do not conform to the predictions of the theory of dual radiation action in its early approximate formulation. The disagreement could be reconciled in the generalized version of the theory [B98], assuming that some parameters of the biological effect previously taken to be invariable are actually subject to some variability: or that, in case of low-LET radiation, the rate of repair depends on dose and on dose rate. Which of these two alternatives is likely to apply remains to be answered.

153. The linear-quadratic model may be characterized by the quotient of the induction constants (a_1/a_2), which varies with the radiation quality and the specific biological effect. For high-LET particles, this quotient is so high that the contribution of the dose-squared term may normally be neglected. The model then becomes linear. For low-LET radiation (considering chromosomal exchanges, mutations and induction of some malignancies) the a_1/a_2 quotient is between 0.5 and 1.5 Gy. The over-estimation of the probability of effects at about 10 mGy from single-dose data at 1-2 Gy (acutely delivered) by linear (as opposed to linear-quadratic) extrapolation would vary from 1.5 to 3.0 for an assumed reasonable set of parameters.

154. Similar over-estimations would apply to the effects of low-LET radiation delivered at low dose rates, irrespective of the total doses below the level when cell killing becomes important. This would result from the disappearance of the quadratic component of the dose-response curves owing to repair of sublesions.

155. Introducing a cell-killing term into a linear-quadratic model leads, in general, to a lesser degree of risk over-estimation at low doses. The effect of such a term may be analysed by applying a range of experimental cell-survival parameters. Since the killing effect of a given dose might be less in vivo than in vitro, the over-estimation involved in the extrapolation to low doses and dose rates would probably fall between that obtained from typical cell survival parameters in vitro and that obtained by neglecting cell killing entirely.

156. For fission neutrons and alpha particles, the a_1/a_2 quotient is of the order of several tens of Gy and the microdosimetric linear-quadratic model predicts a linear curve, relatively independent of dose rate. At doses where departure from linearity becomes substantial, a significant under-estimation of the risk must result from linear extrapolation to zero doses. Fractionation or protraction of dose may result in enhancement of the effect even at low and intermediate doses, contrary to what is seen at intermediate doses for sparsely-ionizing radiation, where the effect decreases upon fractionation and protraction. These observations, related to high-LET particles, cannot be explained on biophysical grounds.

157. Dose-response curves after low-LET irradiation have been reported for some tumours that suggest either the absence of, or a very small, linear term. In such cases, the curve approaches the purely quadratic, indicating perhaps a very low probability of interaction of lesion in two targets crossed by a single ionizing track, or the presence of highly efficient dose-dependent repair processes. Quadratic models have been proposed for leukaemia in CBA mice and cancer of the skin and bone. They predict a very pronounced reduction of the effect by lowering the dose rate or by dose fractionation. Substantial over-estimation of the risk would derive in these cases from linear extrapolation to low doses and dose rates from high or intermediate single doses.

IV. DOSE-RESPONSE RELATIONSHIPS IN EXPERIMENTAL SYSTEMS

A. PHENOMENA OBSERVED AT THE CELLULAR AND SUBCELLULAR LEVEL

158. In recent years, there has been good progress in understanding the role of oncogenes, and of related phenomena at the macromolecular level, in the causation and development of cancer. The newest data are reviewed in annex A to the present report. This progress, however, has left a considerable gap in the understanding of how these phenomena may be linked to mechanisms of radiation carcinogenesis, and what are the relevant molecular targets [G34]. From qualitative analysis of the available information it appears that a rather wide spectrum of radiation interaction with genetic material should be considered.

159. The present section, therefore, discusses dose-response relationships for radiobiological effects, at the subcellular and cellular level, that might be relevant to the induction of malignancy. Some effects, such as in vitro cell transformation, are probably closely related to in vivo carcinogenesis; the relevance of others is not yet well established, but is not implausible. Among the latter effects are mutations, because there is strong evidence of involvement of the genome in both the process of malignant transformation and of cancerous growth (see II.A). Mutational events that could be linked with carcinogenesis may include point mutations, chromosomal deletions and

translocations, as well as transposition of the genetic material [B71, B72, C32, F14, S43, S56, Y3]. It has been postulated [F21] that "tumour specific" symmetrical chromosomal translocations may be particularly relevant for two reasons: first, there are cancers whose cells consistently show aberrations of this type (e.g., chronic myelogenous leukaemia, Burkitt's lymphoma); second, this chromosomal aberration is compatible with the cell's continuous ability to divide, a pre-condition for a transformed cell to develop into a cancerous clone.

1. Mutations in germ cells

160. The frequency of point mutations as related to dose in germ cells of male and female mice, and of other species, was reviewed in depth in annex H of the 1977 UNSCEAR report [U6] and in annex I of the 1982 UNSCEAR report [U24]. The most recent findings are dealt with in annex A to this report. In summary, there is an unquestionable effect of dose rate and fractionation upon specific locus mutations induced in germ cells of male and female mice by low-LET radiation. Interpretations of these findings differ considerably. Abrahamson and Wolff [A2, A3] postulated that mutational lesions are both one- and two-track events, and tried to fit linear-quadratic equations to the data. The attempt was criticized by Russell [R24, R25, R26] who has long been advocating an alternative hypothesis, namely, that mutations themselves are single-track phenomena, and the apparent multiple-track events reflect damage and saturation of the repair processes at higher doses and dose rates. UNSCEAR reviewed both hypotheses in detail and, in the light of present evidence, accepted that of Russell as a more likely explanation.

2. Mutations in somatic cells

(a) The Tradescantia system

161. The data obtained on plant cells of the species Tradescantia are very valuable because: (a) mutations can be scored down to 3 mGy of x rays (and correspondingly lower doses of neutrons); (b) the amount of data on the effects of dose, dose rate and radiation quality is far better than for any other cellular system; (c) the effect is evidently a somatic mutation (although its molecular mechanism is not clear) and the underlying lesion is most likely chromosomal; and (d) the form of the dose-response curve is similar to that for dicentrics and deletions in mammalian T lymphocytes.

162. Dose-response relationships for somatic mutations in Tradescantia, induced by acute 250-kVp x rays, are plotted on a log-log scale in Figure VI [N2, S20, U19]. Below 0.1 Gy, the curve is linear, but then its slope increases up to 1 Gy, where a dose-squared component sets in, leading to an upward concavity of the curve. Above 1-2 Gy, the curve bends and declines, reflecting, perhaps, preferential killing of the mutated cells (the effect is scored in terms of frequency per surviving cell). The data points below

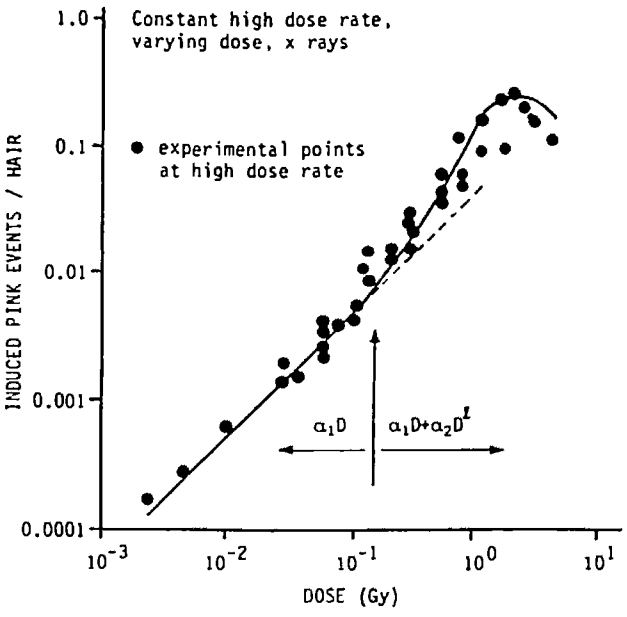


Figure VI. Dose-response curve for induced pink mutations in Tradescantia.
[B99]

1 Gy are well fitted by a non-threshold regression equation of the type $I = \alpha_1 D + \alpha_2 D^2$, where α_1 and α_2 are constants, presumably for single- and two-track events. Mean values of α_1 and α_2 deduced from three studies [S20, N2, U19] amounted to 5.1 (range 4.6-6.4) 10^{-2} Gy^{-1} and 6.5 (5.5-17.3) 10^{-2} Gy^{-2}, respectively [N1]. In terms of the linear-quadratic model, the α_1/α_2 quotient for x rays varied from 0.33 to 0.83 Gy. For gamma rays, α_1 and α_2 are 2.1 10^{-2} Gy^{-1} and 5.2 10^{-2} Gy^{-2}, respectively [N1]. Studies with monoenergetic neutrons (0.065-13.4 MeV) produced a linear dose-response up to 0.05-0.1 Gy [S19, U13] of the form $I = \alpha_1 D$. At high and intermediate doses, the RBE of neutrons versus x rays was inversely proportional to the square root of the neutron dose.

163. Reduction of the neutron dose rate had almost no effect upon the yield of mutations [N2, U13]. When the x-ray dose rate was reduced from about 1 Gy min^{-1} to 5-0.5 mGy min^{-1}, the frequency of mutations was an increasingly linear function of the dose, approaching a linear response of the form $I = \alpha_1 D$. When the dose rate of x or gamma rays was progressively lowered [M18], and a constant dose of 0.8 Gy delivered over increasing time intervals, lower mutation frequencies were observed approaching asymptotically the limiting value of the respective $\alpha_1 D$ for gamma rays. Fractionation of an x-ray dose of 0.6 Gy into two acute fractions of 0.3 Gy each [M18] produced no reduction of the mutation yield up to a 15-minute fractionation interval, but the yield declined with further spacing of the fractions up to 24 hours. Splitting an x-ray dose of 0.05 Gy into two 0.025 Gy fractions given at 5 hours from each other did not reduce the response any further [U27].

164. The influence of fractionation of two x-ray doses (0.7 and 4 Gy) was studied upon induction and repair of two types of somatic mutations (pink and colourless) in this system [W16]. The intervals between

the two fractions varied from 0.5 to 12 hours. Recovery for the two types of mutations differed, in that pink mutations showed recovery at both doses, whereas colourless events showed some recovery at lower doses, but an increased effect at higher doses. Thus, two types of mutations induced by x rays in the same system may have different dose and time kinetics.

165. In summary, the effects of dose, dose rate, fractionation and quality of radiation upon Tradescantia mutations provide, in general, a good example of the linear-quadratic model of radiation action.

(b) Mammalian somatic cells

166. In recent years, significant progress has been made in the methodology of studies of point mutations in somatic cells in culture. Enzyme deficiencies are induced by mutagenic agents, and mutant cells are screened for resistance of developing clones to substances that are toxic to normal cells, e.g., to 8-azaguanine, 6-mercaptopurine or 6-thioguanine in hypoxanthine-guanine-phosphoribosyltransferase (HG-PRT) deficient mutants. Biochemical mechanisms and methods of investigation were reviewed in detail in annex H of the 1977 UNSCEAR report [U6] and in annex I of the 1982 UNSCEAR report [U24] and are discussed again in annex A to the present report.

167. In summary, both linear and curvilinear (concave upwards) relationships have been observed for induction of HG-PRT deficiency in various cell lines by sparsely-ionizing x or gamma rays, and the character of the dose-response curve is evidently related to the genome of the cell studied and not only to the quality of radiation applied [A13, A14, B42, C10, C23, C24, E8, K16]. In cases of curvilinear dose-response relationships, after acute x or gamma irradiation there was also a pronounced reduction of the yield of mutations by dose fractionation. For densely-ionizing radiation (alpha particles, helium, boron and nitrogen ions), the dose-response relationship for induction of HG-RPT deficiency, both in human and hamster cells, was essentially linear [C20, T18]. Induction of forward mutations in Chinese hamster cells by x rays resulted in curvilinear dose-response relationships (concave upwards); moreover pronounced dose-rate effects were observed [S25].

168. Experiments on radiation-induced mutations resulting in HG-PRT deficiency show some correlation between the shape of the survival curve for low-LET radiation and the kinetics of induction of somatic mutations in the same cell lines. This observation has been generalized by Thacker et al. [T10, T9, T8], Munson and Goodhead [M36], Leenhouts and Chadwick [L3, C2] and Goodhead et al. [G29] on different radiations and cells in various stages of the cell cycle, in the sense that there is a relationship of the type $\ln S = -K.M$ where S is the cell survival (S_D/S_0), and M the frequency of induced mutations. This correlation is corroborated by other studies (e.g., [R5]). Thacker [T8] has shown that it applies to exponentially growing cells of several species (man, hamster and mouse) with the same proportionality constant K. However, the mutation frequency per lethal lesion seems higher for high-LET radiation and lower for ultrasoft x rays [G34].

169. When Thacker et al. studied the same relationship [T19], by irradiating V-79-4 hamster cells grown to plateau phase without re-feeding (most cells in the G_1 phase), they found a similar association of frequency of induced mutations with (log) survival. This was true both after high (1.7 Gy min^{-1}) and low dose rate (down to 3.4 mGy min^{-1}) gamma irradiation. There was considerable repair of sub-lethal and sub-mutational damage with decreasing dose rate. However, when the cells were held for 5 hours after irradiation, before trypsinization and seeding, the potentially lethal damage was effectively repaired, whereas that leading to mutation (HGPRT locus) remained unaffected. Goodhead et al. [G29] interpreted all this to show that the average number of mutagenic lesions in a cell is proportional to the average number of lethal lesions induced by a given radiation. However, results on repair of the potentially lethal damage show that phenomena involved in cell killing and mutation induction can be separated.

170. This conclusion remains to be confirmed. However, if the correlation were generally valid, a linear relationship between frequency of induced mutations and dose of low-LET radiation would be exceptional, because exponential cell-survival curves for x and gamma rays are also exceptional [A17, B63, C9, C21-C23, F2, K21, N8, P7, P15, S33, W6, W7], sigmoid cell survival generally being the rule [B5, B9-B12, B19, B27, B45, C1, C37, D3, D8, E2, F1, F2, F19, H2, H6, K2, K24, L6, M16, M60, S33, T18, W6, W7]. In most cases studied after neutron and alpha-particle irradiation, the survival of diploid mammalian cells is, with few exceptions [H1, C20], a simple exponential function of dose [B5, B9-B12, B29, B45, J6, K2, K3, R39, T18].

3. Chromosome aberrations

(a) Translocations in germinal cells

171. As discussed in annex H of the 1977 UNSCEAR report [U6], the frequency of chromosomal translocations induced by x and gamma rays in spermatogonia, spermatids and oocytes shows a pronounced dose-rate and dose-fractionation effect, and data can be fitted to a linear-quadratic equation. On the other hand, neutrons produce essentially linear dose-reponse relationships without any significant protraction or fractionation effect. These conclusions have been confirmed by more recent data reviewed in annex I of the 1982 UNSCEAR report [U24] and in annex A to the present report.

(b) Somatic cells

172. Studies of chromosomal aberrations in human lymphocytes have been reviewed in the past by UNSCEAR (1969 report, annex C, [U9]), and by others [B15, L13, L12, D4]. In most cases, the yield of

easily identifiable dicentric chromosomes and acentric fragments, induced in G_0 cells, was studied against the dose of various radiations. The asymmetric exchanges are not compatible with cell survival over many generations: however, the yield and kinetics of induction are accepted as representative of symmetrical chromosomal exchanges. The latter may be relevant to present considerations. The subject of dose-response relationships for induction of dicentrics has been thoroughly reviewed by Lloyd and Edwards [L36]. The review included re-calculation of the dose-response functions from original data (62 experiments) using a standardized maximum likelihood method for fitting a linear-quadratic equation. The main conclusions are:

(a) For gamma rays and high-energy electrons, the value of a_1, in the region of 2-2.5 10^{-2} dicentric per cell and gray, appears to be consistent with most observations;

(b) For x rays (180-250 kVp), a representative value of a_1 of about 5 10^{-2} dicentric per cell and gray seems to apply;

(c) The a_2 coefficients for gamma rays, x rays and electrons show less variation than the individual reported values of a_1, and they cluster within the range of 4-8 10^{-2} dicentric per cell and gray square;

(d) For fission neutrons, no significant a_2 term was observed. Typical a_1 values would be 40-90 dicentric per cell and gray. The coefficient tends to increase with lowering of the particle energy, to a peak at about 350 keV (about 160 dicentric per cell and gray);

(e) In several studies [K36, V11, Z1], the yield of chromosome aberrations in human lymphocytes was studied after doses well below 0.5 Gy of x rays. When the data on dicentrics from these studies were pooled [Z1], they fitted a linear function of dose passing through the origin, as would be expected from the values given above. The response for acentric fragments was similar, even though less regular;

(f) At neutron energies above 15 MeV, a significant value of a_2 appears;

(g) For protons with energies > 7.4 MeV, the a_1 coefficients are very similar to those for x rays. The a_2 values are rather lower than for typical low-LET radiation;

(h) For alpha particles, all dose-response relationships (excluding one study with possible methodological complications) are linear, but a_1 values scatter widely, owing probably to systematic dosimetric inaccuracies;

(i) When the value of a_1 is correlated with LET, the coefficient increases with the latter above 5 keV/μm to a maximum at about 70 keV/μm, and then falls off sharply at still higher values of the LET. The a_2 value is roughly constant for low-LET radiation, but virtually absent for high-LET particles.

173. The effects of dose rate and fractionation upon dicentric yield in lymphocytes may be summarized as follows:

(a) For low-LET radiation, the yield decreases with decreasing dose rate (or the extension of irradiation time) and with increasing fractionation intervals. This effect is attributed to the repair of interacting lesions, whose mean life appears to be about 2 hours, although some of the lesions may have a much longer life. Available experimental data and their theoretical interpretation suggest that, for very long irradiation times, the a_2 coefficient would be zero and the a_1 would remain unaffected (linear relationship);

(b) For neutrons, no effects of dose protraction or fractionation were seen.

174. The RBE of neutrons versus x or gamma rays is inversely proportional to the square root of the neutron dose. The limiting value at low dose rates may be obtained from the ratios of the relevant a_1 coefficients.

175. This was also noted when whole blood was irradiated by adding tritiated water prior to initiation of blastic transformation. Doses between 0.2 and 4 Gy β radiation were delivered over 30 minutes or 24 hours. Whereas the dose-response curve for 30-minutes exposures was practically the same as that after acute x rays, the response was close to linearity after longer exposures (the linear component remained unchanged while the quadratic one decreased by a factor of about 3 [P20]).

176. Similar relationships were obtained for dicentrics in the lymphocytes of all mammalian species studied so far (marmoset [B41], Chinese hamster [B41], rabbit [B1, B2, S5], pottoroo [S5], swine [B1, B41, L7], sheep [L7], goat [L7], mouse [B23, B41], rhesus monkey [B61], and other primates [H9, M37]). With protraction or fractionation of x- or gamma-ray doses, the linear term prevails [S4, L9]. With irradiation times exceeding 24 hours the relationships for dicentrics after exposure to gamma rays tend to approach linearity.

177. For acentric fragments, a linear-quadratic relationship is usually observed, but the results are less reproducible [B2, L13]. As these aberrations include both interstitial and terminal deletions, classified together, the relationship does not contradict linearity for single-break aberrations.

178. In conclusion, induction of chromosomal aberrations of the one- and two-break type, in somatic cells in G_0 or G_1, is in broad agreement with the linear-quadratic model for low-LET and with the linear models for high-LET particles. This agreement refers to dose and to the effects of dose rate and fractionation. For single-break aberrations, a linear model should fit the data, but methodological problems make the demonstration difficult.

4. Oncogenic transformation of cells in vitro

(a) General

179. Studies of transformation from the normal to the oncogenic state, on cells in vitro, are very relevant

to the purposes of the present annex. They allow investigation of the mechanisms of cancer initiation without interference of other factors at the tissue and systemic levels. In addition, killing and transformation may be measured in the same target cells, allowing the relative importance of the two effects to be studied at the same time. Morover, in vitro experiments are less expensive and time-consuming than studies on irradiated animals and are easier to analyse, owing to the lack of competing risks and the higher precision of measurements. On the other hand, lack of close intercellular contact and systemic regulation during culture growth is an artifact compared with the situation in situ, and could change—at least quantitatively—the reactions of cells studied. Details of cell handling, such as whether trypsinization has been applied to the cultures, or not, in the course of the experiments, may also substantially modify the results. So far, observations on cell transformation have been limited almost exclusively to fibroblasts, whereas tumours of epithelial origin prevail among radiation-induced cancers in man.

(b) Dose-response relationships

180. Transformed cells are assessed by scoring characteristic colonies recovered in a culture. This directly measures the transformation frequency per surviving cell. Most experiments are reported in this way, but, with some additional effort, information can be obtained on cell survival as a function of dose, and on the plating efficiency. The transformation yield per initial cell at risk may be calculated by correcting the transformation frequencies per surviving cell for the respective survival values and plating efficiency. This latter measure of transformation can seldom be computed from the frequencies per survivors reported in the papers, which often makes it difficult to give a precise description of the dose-response relationships. Many features of the dose-response relationships depend strongly upon the time interval between the establishment of a culture (seeding of cells) and irradiation: new and established cultures should therefore be dealt with separately.

(i) *Irradiation of freshly established cultures*

181. Borek and Hall [B33] x-irradiated early-passage golden hamster embryo cells in vitro, 24 hours after trypsinization and seeding, with doses from 0.01 to 6.0 Gy (a point at 0.003 Gy x rays was added later [B76]). A dose-response relationship per surviving cell is presented in Figure VII, showing a rise with dose up to 1 Gy, a plateau between 1.5 and 3.0 Gy, and a decline thereafter. The dose-response relationship from the same and subsequent experiments was also expressed per initial cell at risk [B29]. It is impossible to say whether a linear or an upwards concave line would be a better fit of the experimental points along the ascending portion of the curve. A linear fit was assumed by the authors themselves but a linear-quadratic fit was also attempted by Chadwick and Leenhouts [L3]. In a linear plot the line tends to pass through the origin, suggesting no threshold. Below

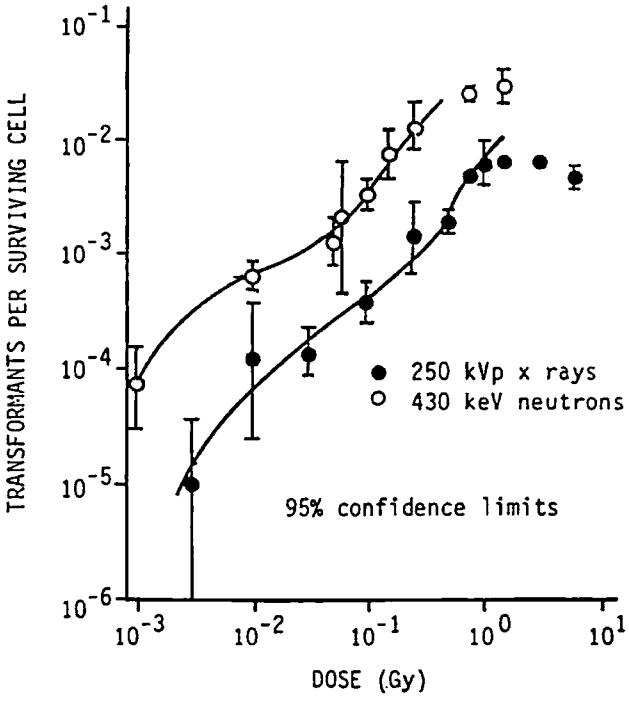


Figure VII. Dose-response curves for transformation of hamster embryo cells by neutrons and x rays. The curves were obtained by non-parametric least-squares fitting.
[B79]

0.5 Gy of x rays and down to 0.01 Gy the yield of transformants appears to rise with a power of dose < 1. The transformation frequency per Gy of x rays below 1 Gy is of the order of 10^{-2} per cell, which is several orders of magnitude greater than for any somatic mutation [U6] but almost an order of magnitude lower than the total yield of chromosomal aberrations induced by comparable doses of x rays in mammalian lymphocytes [D4]. In a comparison of 300-kVp x and ^{60}Co gamma rays [B76] the RBE of the latter varied from 0.85 at about 1 Gy to 0.5 at a few tens of mGy.

182. Borek, Hall and Rossi [B29] and Borek and Hall [B79] irradiated hamster embryo cells with monoenergetic neutrons (0.43 MeV) and compared the dose-response relationship with that for x rays. The curves representing the relationships, both per surviving cell or per initial cell at risk, were peaked in shape and roughly parallel. A fit to the neutron data similar to that for x rays, but shifted toward lower doses, was obtained (Figure VII) with no suggestion of a threshold. Below 0.1 Gy, the transformation frequency could also be interpreted as rising with a power of dose lower than unity. The RBE of neutrons, at transformation frequencies of 10^{-3} and $5\ 10^{-3}$, was about 12 and about 6, respectively. Measurable transformation was induced even by 1 mGy of neutrons. Accelerated argon ions (429 MeV per atomic mass unit) were roughly as effective as neutrons [B29].

183. Data were also obtained for cell survival [B29]. For x rays a sigmoid survival curve ($D_0 = 1.47$ Gy; $n = 6$), and for 430-keV neutrons a purely exponential curve ($D_0 = 0.5$ Gy), were reported. The RBE of neutrons varied approximately with the inverse square

root of the neutron dose, with values from about 30 at doses below 0.1 Gy to about 5 at 1.5 Gy. At doses above 2-3 Gy of x rays, cell killing was appreciable, but the decline of transformation yield per unit dose above 1 Gy of x rays and 0.25 Gy of neutrons was explained by assuming that transformed cells were preferentially killed by radiation. An alternative explanation of this phenomenon was also proposed [C7, L3].

184. The dose-response relationship for x-ray-induced transformation of C3H10T1/2 cells irradiated 24 hours after seeding was also studied [T7] and expressed per surviving cell (at cell densities below 3.8 cell cm^{-2}; 100-kV x rays, 0 to 15 Gy). The transformation frequency rose rapidly with dose, up to 4 Gy, and reached a plateau at about 15 Gy. At about 1 Gy, the transformation frequency was about 0.5 10^{-4}, roughly 2 orders of magnitude lower than for hamster embryo cells [B33]. The doses required to double the transformation yield along the ascending branch of the curves for these two types of cells were 1.0 and 0.1 Gy, respectively. The dose-response curve for C3H10T1/2 cells showed no apparent threshold and was concave upwards, the effect rising with a power of dose > 1 and close to 2.

185. In a later study, Miller et al. [M23, M41] examined, under a similar experimental protocol in the same C3H10T1/2 cells, the effect of single and split doses of 300-kVp x rays. The single-dose response curve had a complex, curvilinear shape. The transformation frequency was less than proportional to dose between 0.1 and 0.3 Gy, almost flat between 0.3 and about 1 Gy, and then rising with the square, or higher, power of dose. A plot of the data at 0.1-10 Gy on a log-log scale, per surviving cell, is given in Figure VIII. Interpretation of the shape of this dose-response relationship is very difficult, particularly in the dose range below 1 Gy.

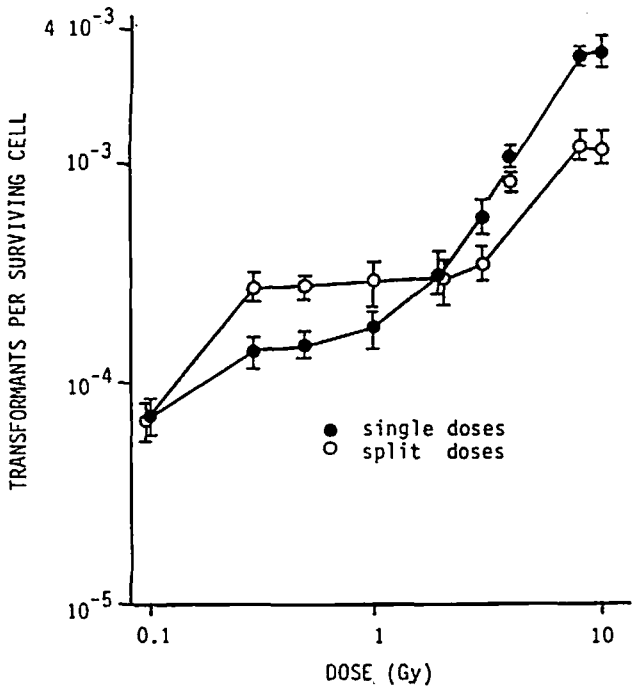


Figure VIII. Dose-response relationships for the number of transformants per surviving C3H10T1/2 cells, following single or split doses of 300-kVp x rays. In the case of split doses, the radiation was delivered in two equal exposures, separated by 5 hours.
[M23]

186. Yang, also, studied the transformation of C3H10T1/2 cells by x rays and energetic silicon ions (initial energy 320 MeV per atomic mass unit, residual range in water 4.5 cm, dose average LET = 88 keV/μm) [Y5]. This radiation was more effective than 225 kVp x rays (RBE not given). Cells kept in a highly confluent state for some time after irradiation were able to repair part of the transformation damage induced by x rays, but not that induced by accelerated silicon ions.

187. When C3H10T1/2 cells were irradiated with neutrons (35-MeV $d^+ \rightarrow$ Be), the results were as in Figure IX [B79]. The dose-response curve is shifted towards lower doses with a similar dose-independent plateau as for x rays. The RBE increased with decreasing dose and was similar for both transformation and cell killing.

188. Lloyd et al. [L15] studied transformation in C3H10T1/2 cells by irradiation with 5.6-MeV alpha particles, showing a higher effectiveness as compared with x rays (the relationship of irradiation- and seeding-time is not available). For alpha particles, the dose-response relationship is of a grossly curvilinear (concave upward) character, the effect rising with approximately the cube of the dose. When expressed per surviving cell, the maximum transformation rate was seen at about 2 Gy.

189. C3H10T1/2 cells were transformed by 100-kVp x rays, fast fission neutrons (mean energy 0.5 MeV, 8-20% gamma contribution) and cyclotron neutrons (mean energy 38 MeV, 8% gamma contribution). The dose ranges were: 1.5-11 Gy, 0.5-5 Gy, and 1.5-6 Gy, respectively [B89]. The cells were irradiated 36 hours after seeding. For fission neutrons, the response per survivor was most effective and the initial portion of the curve was only slightly concave upwards. X rays were least effective and 38-MeV neutrons produced curves very similar to those of x rays. For both radiations, the dose-response curves were grossly concave upwards at their ascending portions. A plateau of effect at high doses was reached for all radiations tested. It is worth mentioning that for each radiation the survival curves had pronounced shoulders, which were roughly proportional to the degree of curvilinearity of the dose-transformation curves. The RBE relative to x rays at the transformation frequency of 5 10^{-4} was 1.2 and 3.8 for 38-MeV and 0.5-MeV neutrons, respectively.

190. Transformation of BALB/3T3 cells by ^{238}Pu alpha particles and x rays was studied by exposure of freshly seeded single cells or confluent cell monolayers [R39]. The dose ranges were 0.5-2.5 Gy and 0.5-5 Gy for alpha particles and x rays, respectively. When calculated per surviving cell the rise of transformation frequency with dose was exponential (steeper than proportional). However, when the results were expressed as transformants per exposed cell, for alpha particles the highest yield was induced already by a dose of 0.5 Gy, with a slight decline thereafter. This

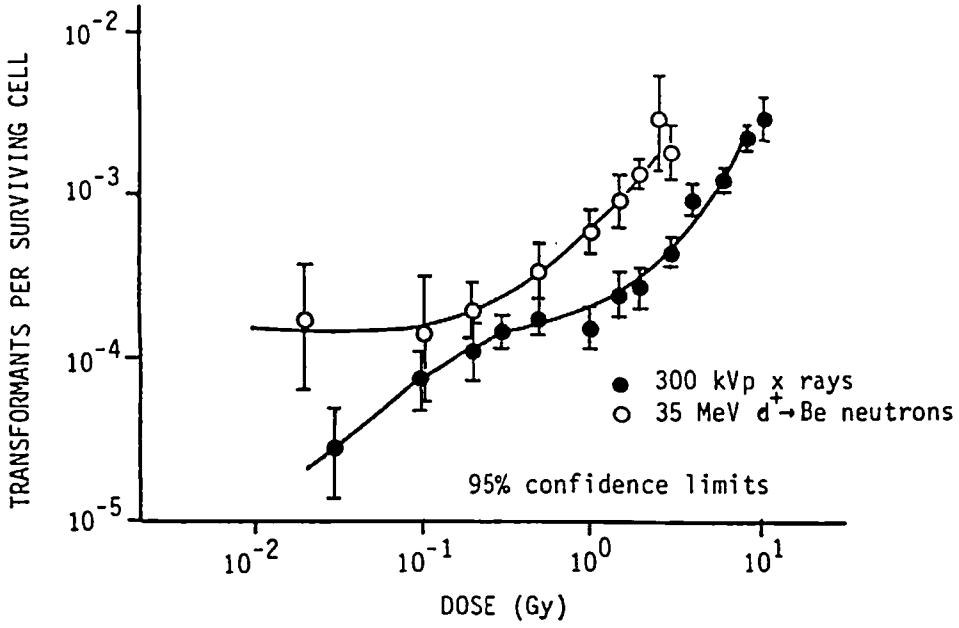


Figure IX. Pooled data obtained for the fraction of transformants per surviving C3H10T1/2 cell following irradiation with x rays or neutrons.
[B79]

may be attributed to highly efficient cell sterilization by alpha rays. A high effectiveness of the alpha particles, relative to x rays, was noted, but the precise shapes of the curves at the lower end of the dose scale cannot be established. Little studied the transformation by x rays of freshly seeded cells (20 hours prior to exposure) of BALB/3T3 mouse [L10]. Although there was some indication of an upward concave curve, the statistical uncertainty of the data does not allow precise conclusions.

191. Golden Syrian hamster embryo fibroblasts, seeded about 12 hours before, were exposed for 17 hours to varying concentrations of methyl ^{3}H-thymidine [L33]. The number of transformants per surviving cell (and mutants at HGPRI locus) showed a proportionality to the concentration of the substance. Tritiated uridine, which is not incorporated into DNA, was ineffective in inducing both oncogenic transformation and mutations.

192. BALB/3T3 embryo fibroblasts, synchronized in the S-phase, were incubated for 16 hours with the DNA precursors ^{3}H-thymidine and ^{125}I-iododeoxyuridine (^{125}I-dUrd) [L34]. The incorporation of the radionuclides into cellular DNA was proportional to concentration in the culture medium. The transformation frequency per survivor, versus concentration of activity per cell, was linear in both cases—without suggestion of a threshold—up to a frequency of about $5\ 10^{-4}$. The ratio of the initial slopes of ^{125}I-dUrd versus ^{3}H-thymidine dose-response curve was about 25. In the same experimental series, the transformation by x rays was somewhat irregular, with an approximately exponential increase of the transformation frequency with dose over the whole range of doses (0.5-6 Gy). The high effectiveness of ^{125}I-dUrd was explained by the release of a cluster of low energy Auger electrons (about 25 per decay), leading to a very high energy deposition in the vicinity of the DNA double strand.

(ii) *Late irradiation of cultures*

193. Dose-response relationships for in vitro transformation of cell line C3H10T1/2 by acutely delivered x rays (50-kVp, 0.18 mm Al filtration) and neutrons (fission, mean energy 0.85 MeV) were reported by Han and Elkind [H1]. In contrast with the experiments reviewed above, cells were irradiated 48 hours after seeding. When the transformation rate was expressed per initial cell at risk, the decline of the yield beyond the maximum had the same slope (or D_0) as for the killing of non-transformed cells, suggesting that sterilization by high doses of normal or transformed cells was similar. On linear co-ordinates (Figure X), the ascending portions of the dose-response curves (per initial cell at risk) for x rays was concave upwards (at least above 1.5-2 Gy) but details cannot be established from the graphs. For neutrons, the ascending portion of the curve appears to be close to linearity. The RBE of neutrons increased with declining doses, and the maximum attainable transformation frequency by neutrons was higher by about 50% than that for gamma rays (per initial cell at risk). In contrast with the data of Miller et al. [M23] (Figure VIII) there was a significant flattening of the yield above 4 Gy of x rays, when the data were expressed per surviving cell [H14] (see Figure XI).

194. Watanabe et al. [W18] irradiated golden hamster embryo cells 72 hours after establishing the culture. The exposures varied from 50 to 600 R at exposure rates of 5, 75 and 600 R/min. Additional exposures (1-50 R) were applied at the dose rate of 5 R/min. The

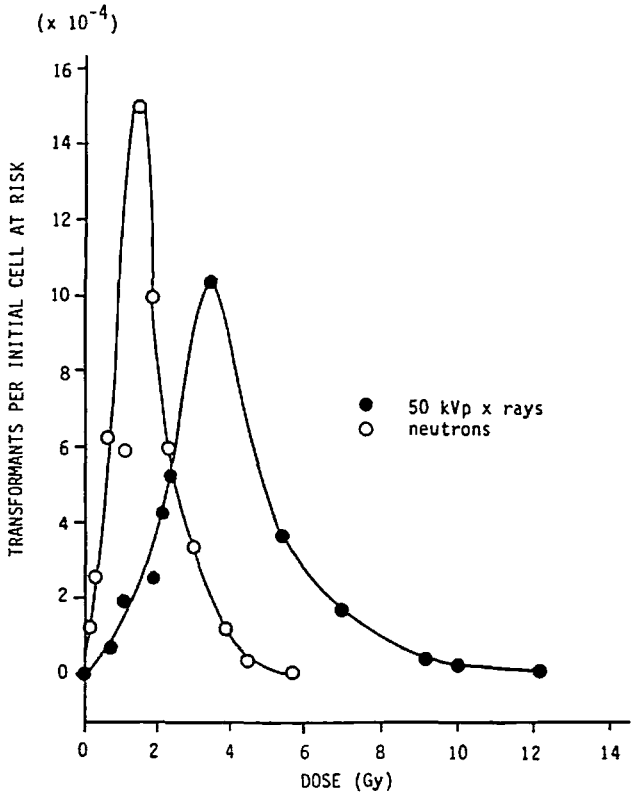


Figure X. Changes in transformation frequency of C3H10T1/2 cells after single exposures to x rays or fission-spectrum neutrons.
[H1]

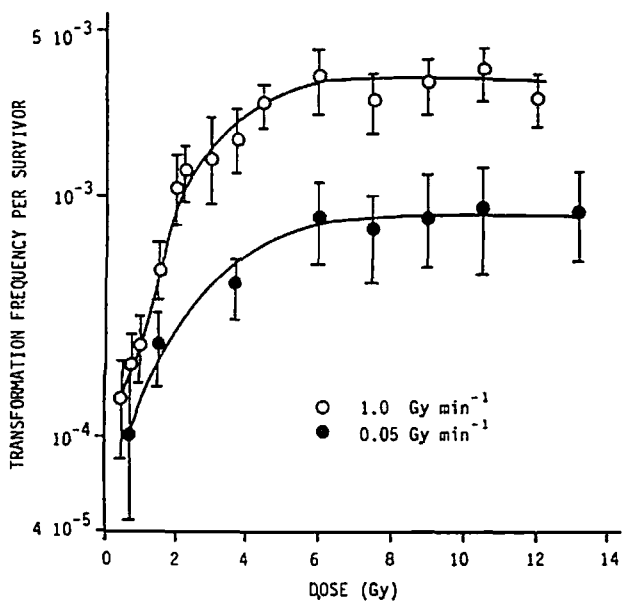


Figure XI. Frequency of neoplastic transformation of C3H10T1/2 cells expressed per surviving cell as a function of dose of gamma rays delivered at high or at low dose rate. Error bars represent the standard errors of the data pooled from various experiments.
[H14]

logarithm of transformation frequency per survivor was approximately linear up to 100 R, and had a very shallow increase from 200 R onwards (semi-plateau). From the graphical presentation of data, it appears that up to 75 R, at 5 R/min, the dose-response relationship is linear, with no suggestion of a threshold.

195. Terasima et al. [T24] studied C3H10T1/2 cells, x-irradiated (0.23 to 9.3 Gy) in the plateau phase of growth (contact inhibited). The dose response (per surviving cell) was very similar to that found by others for the same cell line. After a steep exponential increase, up to about 1.8 Gy, there was a gradually slower increase of the transformation frequency with a plateau above 6-8 Gy. Recent data on in vitro transformation of C3H10T1/2 cells by 31-MeV protons were published by Bettega et al. [B3], showing that the transformation frequency per surviving cell had a marked change in slope at about 2 Gy.

(c) Effects of dose fractionation and protraction; repair of sub-transformation and potential transformation damage

(i) *Irradiation of freshly established cultures*

196. Irradiation of cultures seeded 24 hours before exposure with two doses of 4.5 + 4.5 Gy of x rays at various intervals (zero to five hours) showed that survival of C3H10T1/2 fibroblasts nearly doubled when the interval exceeded 2 hours, with no further increase for longer intervals [T4]. For doses of 1.5, 3.0 and 8.0 Gy in two equal fractions at five-hour intervals, the transformation frequency per surviving cell remained unaltered at the lowest dose, but declined significantly ($p = 0.005$) at the two higher doses.

197. Hamster embryo cells in culture (seeded 24 hours earlier) showed a doubling of the effect after split, as opposed to single, doses of 0.5 or 0.75 Gy [B90]. At the same time, the survival of irradiated cells increased only marginally. When the experiment was extended [B64] by studying the effect on the transformation frequencies of splitting 1.5, 3 and 6 Gy of x rays, no enhancing effect of 2×0.75 Gy, as opposed to 1×1.5 Gy, was noted. Fractionation of 3 and 6 Gy led to a reduction of the total effect.

198. Miller and Hall [M23] studied dose fractionation on C3H10T1/2 fibroblasts, plated 24 hours before x-ray treatments (0.3 to 8.0 Gy). Their results confirmed the sparing effects of splitting the dose above 1.5 Gy (with a possibly incidental deviation of the points at 4 Gy) and an enhancement of transformation below that dose. The experiment was repeated [M41], and the dose range expanded to include 0.1 and 10 Gy. The results are presented in Figure VIII. In addition, a dose of 1 Gy was split into 2, 3 or 4 equal fractions [H21]. An almost proportional (2-, 3- and 4-fold) enhancement of transformation was observed. Also, when a dose of 1 Gy of ^{60}Co gamma rays was delivered at a low dose rate (over 6 hours) the effect was significantly enhanced, by a factor of about 3, by comparison with acute exposure (over 10 min) [H21]. In conclusion, using this experimental protocol, in the range 0.3-1 Gy there is an enhancement of the effect by splitting the dose into two equal fractions within 5 hours or by protracting the dose over a similar interval. At 2 Gy, there is no effect. There is a decline of the yield after fractionation at higher doses. Approximately the same trend is seen when the data are expressed per initial cell at risk.

199. Little [L10] reported dose-fractionation experiments on BALB/3T3 cells seeded 24 hours before the first exposure with essentially identical results. The fractionated doses ranged from 0.1 to 3.5 Gy, and similar observations were also made in still another study by Suzuki et al. [S44]. It may be concluded, therefore, that enhanced transformation (per survivor) below 1.5 Gy of x rays after fractionation within 5 hours is a phenomenon observable in all cell lines studied so far, irradiated in freshly established cultures. Such an effect might be deduced from the curves in Figure VIII [M23]. In fact, if an independent action of the two dose fractions is assumed, the decrease above 2 Gy, where the response rises with D^2 or with a higher exponent, is easily understood. Similarly, below 1 Gy, over the plateau, where the effect is roughly independent of dose, fractionation should increase the yield, as observed.

200. Figures VIII and IX show clearly that a linear extrapolation down from intermediate (1 Gy) and high (2-3 Gy) doses of x rays would lead to an underestimate of the real transformation frequency, particularly with respect to the effect of split doses in the low-dose region. The greatest under-estimate, by a factor of 4-6, would be encountered when the effect of single doses in the range 1-3 Gy is linearly extrapolated to predict effects of split total doses of 0.1-0.3 Gy. The relevance of this finding to tumour induction in vivo has been commented upon by several authors [B76, H21, M41].

(ii) *Late irradiation of cultures*

201. Data on fractionation were reported by Han and Elkind [H1] for x rays (0.75 Gy) and fission neutrons (3.8 Gy) on C3H10T1/2 cells exposed 48 hours after seeding. The transformation rate after doses of this magnitude was on the declining part of the curve when expressed per initial cell at risk. Fractionation of the neutron dose within 0 to 16 hours had little, if any, effect on single-dose survival and caused a slight reduction of the transformation yield, perhaps within the limits of experimental error. With x-ray fractionation times up to 5 and 10 hours, the frequency increased and then declined to the level of the non-fractionated exposure at about 16 hours. The increase was within a factor of 2 and its statistical significance uncertain. When expressed per survivor, the transformation frequency after x irradiation declined steadily to a plateau at 12-16 hours fractionation interval, reflecting essentially an expected and considerable effect upon survival of the non-transformed cells. This observation, therefore, confirmed other findings [M23, M41] that fractionation of high x-ray doses in this cell line reduces the transformation frequency when expressed per surviving cell.

202. Han and Elkind also irradiated C3H10T1/2 cells, 48 hours after plating, with ^{60}Co gamma rays at high (1.0 Gy min^{-1}) and low (0.05 Gy min^{-1}) dose rate [H14]. The range of doses varied between 0.2 and 13 Gy. The transformation frequency per survivor (Figure XI) was consistently reduced at the lower dose rate, as was cell sterilization. The reduction in transformation yield was by a factor of about 5 above 6 Gy and by a factor of about 3 at 2 Gy, and was still present at doses of 0.5 and 0.2 Gy [E9, H26].

203. Hill et al. [H30] studied the effects of gamma-ray fractionation in the same system. Throughout the dose range tested (0.25-3 Gy), fractionation of the dose into 5 daily fractions resulted in a significant reduction of transformation frequency. Up to 1.5 Gy delivered unfractionated, and up to 3 Gy fractionated regimes, the dose response could be fitted by a straight line passing though the origin (Figure XII). The yield

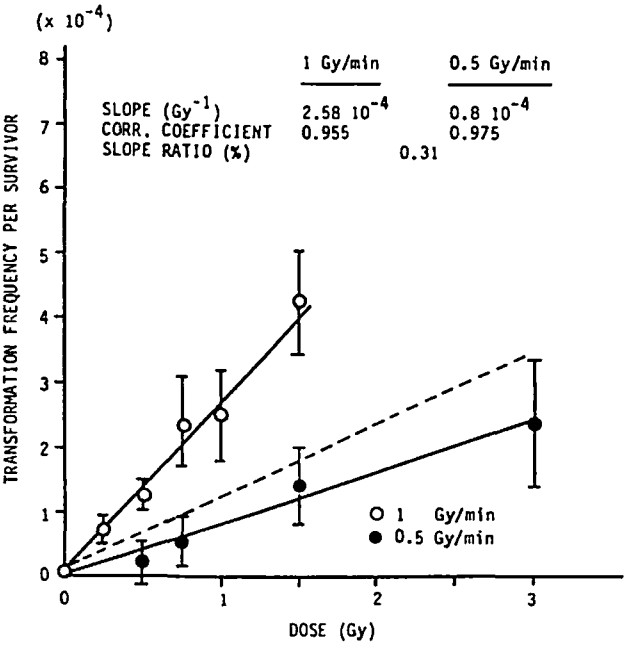


Figure XII. Transformation frequency of C3H10T1/2 cells per surviving cell against dose of gamma rays. Open circles: acute exposure at 1 Gy min^{-1}; Dashed line: continuous exposure at 1 mGy min^{-1}; Closed circles: five fractions at 0.5 Gy min^{-1}, given at 24-hour intervals.
[H30]

of transformants per unit dose was 3 times lower after fractionated than after single doses, and very similar to the dose-response curve for the lower dose-rate exposure referred to above [E9, H26]. Increasing the fractionation intervals beyond 24 hours, and reducing the dose per fraction, led to a further slight reduction of the effect. This suggested that there may be a limit beyond which further dose protraction cannot reduce the transformation frequency. Trypsinization per se, or delivery of the dose within 7 days of growth in culture, did not affect the yield of transformants per unit dose, provided they took place at least 40 hours after seeding. Confluence of the cells was excluded as a possible reason for the observed fractionation effect. These results of dose fractionation and protraction below 1.5 Gy are in striking contrast with those observed when the cells were irradiated 24 hours after seeding [H21, M23]. The difference was attributed to atypical conditions of cellular growth early after plating and to the action of radiation on para-synchronous cells [H30].

204. Watanabe et al. [W18] irradiated golden hamster embryo cells, sub-cultured 72 hours earlier, with x rays

at various exposure rates: 5, 75 and 600 R/min. Throughout the whole range of exposures tested (50-600 R), the lower dose rates produced a reduced yield of transformed cells, even within the 50-100 R range where the dose-response relationship was practically linear. At equal survival levels (which were inversely related to dose rate), the transformation frequency was higher in cells irradiated at higher than at lower dose rates. Terasima et al. [T24] studied the effect of fractionating x-ray doses (0.93, 1.86 and 3.72 Gy) in C3HT101/2 cells irradiated in the plateau phase. Equal fractions were spaced at intervals of 3, 10 and 15 hours. There was significant reduction of the yield at all doses tested, as compared with single doses, the maximum reduction being achieved already at the 3-hour interval.

205. Hill et al. [H26, H34] worked with fission-spectrum neutrons (mean energy 0.85 MeV) at various dose rates in C3H10T1/2 cells irradiated 48 hours after seeding. There was no discernible effect upon cell survival of neutrons delivered at a low rate (0.43-0.86 mGy min^{-1}) versus a high rate (0.103-0.38 Gy min^{-1}). At the same time, the low-rate neutron irradiation enhanced significantly the transformation frequency at doses below 1 Gy (by a factor of about 9 at 0.025-0.1 Gy) (Figure XIII), an effect that cannot

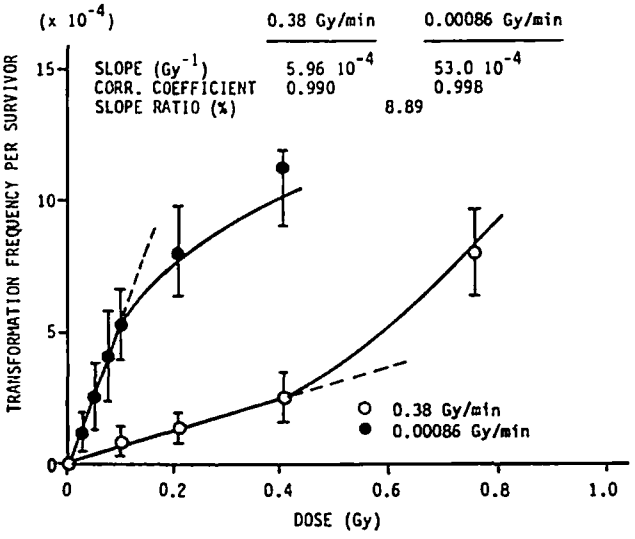


Figure XIII. Oncogenic transformation of C3H10T1/2 cells exposed to fission-spectrum neutrons at high and low dose rate. Dashed lines indicate the linear regressions fitted to the initial portions of the curves.
[H34]

be explained on biophysical grounds. Above doses of 1.5-2.0 Gy, the effect of the dose rate disappeared and dose-response relationships converged to a plateau of 5 10^{-3} transformants per surviving cell.

206. The influence of dose fractionation (5 fractions over 4 days) of fission-spectrum neutrons, delivered at a rate of 0.1 Gy min^{-1}, was studied by the same authors. Over the whole range from 0.103 to 1.12 Gy, an enhancement of effects by fractionation was observed. The ratio of linear slopes of the dose-response curves at low doses was about 8. The increased effectiveness of the low dose rate and of the fractionated neutron irradiation was explained either by the induction of more efficient error-prone repair or by facilitation of the expression of "sub-effective transformation damage", whatever this means [H37]. A recent study on transformed mammary epithelial cells transplanted in vivo to virgin female BALB/c mice suggests that the effect of fractionated neutron exposures may be analogous to chemical promotion and is due to an enhanced expression of the transformation damage [U28]. The effects of fractionation schemes applied to the cells in an asynchronous growth indicate that x and gamma irradiation—by analogy with sublethal damage—result in error-free, reparable, sub-transformation damage. The transformation damage induced by neutrons either does not undergo repair, or is subject to error-prone repair [E10, H37]; however, why the latter should be more effective at protracted or fractionated low doses is not clear.

207. Terzaghi and Little [T5] found that irradiating C3H10T1/2 cells with x rays in a density-inhibited state, and delaying plating up to 48 hours substantially increased survival rates. Delay for 2 to 4 hours caused marked increase of the transformation rate. Further delay of plating reduced the yield of transformants to very low levels after 48 hours. Terasima et al. [T24], however, did not observe any initial increase of the transformation frequency, as the potential transformation damage fell over the first 3 hours of delayed plating. The rate of potential transformation repair in C3H10T1/2 cells depended strongly on a particular batch of fetal calf serum used in the cell culture medium, both before and after release from confluence [T11]. Lack of serum was accompanied by a high degree of repair (80% over 6 hours) after keeping the irradiated cells (x rays, 3.7 Gy) in the non-proliferating state. Some batches of serum totally prevented the occurrence of repair. No repair of potential transformation could be found after irradiation with alpha particles [R39] and accelerated heavy ions [Y5].

208. When potentially lethal damage was studied by holding these cells in confluence after irradiation for varying lengths of time, a pronounced repair was observed for x rays and none for alpha particles [R39]. Equally, no repair of potential transformation damage was seen for up to 220 hours after alpha particle exposure, whereas the x-ray-induced potential damage was efficiently repaired.

209. The results of other experiments [L23] suggest that two separate processes may be involved in the recovery of damage: first, DNA repair leading to enhanced survival; and, second, a slower error-prone repair process responsible for changes in DNA and leading to mutation and transformation. It should be stressed that the frequencies of transformation reported for most in vitro experiments apply to actively proliferating cell populations and may not be representative of situations where the overwhelming majority of cells is in the resting state, as in most organs in vivo.

(d) Other factors affecting oncogenic transformation in vitro

210. Numerous factors affect the yield of in vitro oncogenic transformation. Among these, a basic role is played by both the time and the density at which cells are seeded.

211. Studies on three cell lines (hamster embryo, C3H10T1/2 mouse embryo and mouse BALB/3T3 cells), have shown [B34, K12, L10, T6] that several post-irradiation cell divisions—4 to 6, depending on the cell line studied—are necessary for expression or fixation of the transformed state. Of these, at least one must take place in the first 24 hours post-irradiation.

212. Terzaghi and Little [T7] investigated the influence of cell density on the transformation frequency per surviving cell. Above 400 viable cells per dish (about 5 cell cm^{-2}), there was a steep decline from plateau values of transformation observed at lower cell densities. The authors suggested that this effect could be the result of an incomplete expression of transformation due to early confluence, which lowers the number of cell divisions during exponential growth below that necessary for full expression of transformation [B71, B72, L26]. Han and Elkind observed, in the same cell line, a similar relationship between the density of seeded cells and the transformation rate after x-ray and neutron irradiation [H1]. Direct cellular contact cannot operate at such cell distances, but a diffusible mediator substance might prevent occurrence or growth of the transformed clones [L15].

213. Lloyd et al. [L16] experimented on co-cultivation of transformed C3H10T1/2 cells with non-transformed ones. When transformed cells were seeded at low densities, together with normal cells, at some ratios of the two cell types (1:50 to 1:500, respectively), expression of the malignant state could be completely prevented. Adding non-transformed cells in greater numbers again elicited this response. The experiment points clearly to a very complex nature of the interaction between transformed and non-transformed cells, even in vitro.

214. The data by Kennedy et al. [K26] are of importance because they throw some light on the complexity of the phenomena leading to oncogenic cell transformation in vitro and could modify substantially the current interpretation of this radiation effect. These authors studied the influence of re-suspending C3H10T1/2 cells after irradiation, once confluence was reached. When dilutions at the time of re-seeding were progressively increased, the number of originally irradiated and inoculated cells per plate decreased to very low values. In spite of that, after a constant dose of 4 Gy of x rays, the number of transformed foci per plate remained practically constant. This indicates that the number of transformed foci per plate is apparently independent of the number of cells initially irradiated. It is interesting to note that similar results were obtained when the effect of inoculum size was studied on the appearance of tumours, after in vitro irradiation of monodispersed thyroid or mammary cells injected into the fat pads of rats [G30]. These observations are in direct conflict with the expectation that—if initiation of a cell is a rare phenomenon—the probability of observing a tumour should rise in proportion to the size of the inoculum.

215. It has been suggested [K26, G30] that exposure to radiation results in some change of the cellular state in many or, after high doses, in all cells. Gould postulates that initiation is not an all-or-none phenomenon, but that its intensity rises with dose up to a saturation level, which is reached in C3H10T1/2 cells at 5-6 Gy after ^{60}Co gamma irradiation or 3 Gy of neutrons. The change is probably transmitted to the whole progeny of surviving cells. The nature of initiation—genetic or epigenetic—is unknown, but the latter would presumably be suggested by these observations. This interpretation is not easily reconciled with the demonstrated direct involvement of DNA in the carcinogenic process [B14, L33]. Only a second rare phenomenon (perhaps mutation), would lead to a phenotypically recognizable transformation at confluence of C3H10T1/2 cells. The probability of this second phenomenon should be in some proportion with the degree of initiation.

216. A report by Hall et al. [H28] challenged the hypothesis that commitment of irradiated cells to the transformed state takes place at confluence. By re-plating cultures at different times after irradiation and testing for distribution of transformed foci among the plates, the authors could show that commitment takes place within 1 week of exposure. This observation is in agreement with a study [B91] on in vitro oncogenic transformation of C3H10T1/2 cells by 7β,8α-dihydroxy,9α,10α-epoxy,7,8,9,10-tetrahydrobenzo(a)-pyrene. The results of this study showed that acquisition of the ability to form transformed foci occurred within 2 days of exposure to a carcinogen. Hall's experiments [H28] also showed that increasing the density of cells in culture probably suppressed expression of the transformed state. These results do not contradict the fact that at 4 Gy of x rays the probability of initiation per cell is close to 1, but they have been interpreted to challenge the postulated non-stochastic nature of initiation [K26].

217. The presence of thyroxin in the culture medium at a physiological concentration was shown to be a prerequisite for transformation to occur in Syrian hamster embryo and C3H10T1/2 cells [B73, G26, G27]. Thyroxin is required for protein synthesis only within a few hours of irradiation and its action can be reversed by an agent blocking protein synthesis, e.g., cycloheximide.

218. Other factors were shown to enhance transformation in culture during or after irradiation. Extensive investigations were made on a well-known promoter of in vivo carcinogenesis, the active ingredient of croton oil, 12-0-tetradecanoyl-phorbol-13 acetate (TPA). By adding TPA to the cultures within 96 hours of irradiation, Kennedy et al. [K10] showed enhancement of the x-ray transformation frequency (or its expression) in C3H10T1/2 mouse embryo cells.

The effect was particularly marked after doses of 0.5-1.0 Gy. These data indicate that promoting agents can increase the levels of x-ray-induced transformation in vitro, just as they enhance carcinogenesis in vivo. It was also shown [K27] that the most effective period of exposure to TPA is that of exponential growth. However, a delay of TPA application, e.g., addition to cultures re-seeded after confluence, did still lead to a significant enhancement of oncogenic transformation.

219. When TPA was added for six to seven weeks (at 0.1 μg/ml of medium) to cultures of C3H10T1/2 cells irradiated with graded doses of x rays (0.25-4.0 Gy), there was not only an absolute increase of transformation frequency, but also a change in the shape of the dose-response relationship, from curvilinear (upward concave) after x rays alone to linear (Figure XIV). The

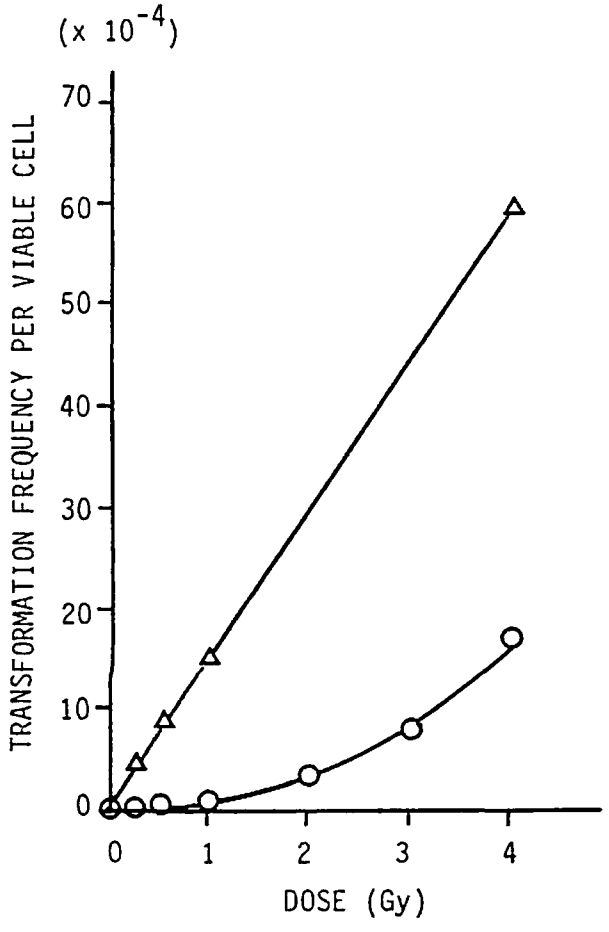


Figure XIV. Influence of post-irradiation incubation with the tumour promoter TPA on x-ray transformation of mouse C3H10T1/2 cells. ○ x-irradiation only; △ TPA (0.1 μg/ml) added for the entire period of expression.
[L26]

action of TPA was especially pronounced at doses in the low and intermediate range [L26]. A very similar effect of TPA on the shape of the dose-response curves for x-ray-induced and neutron-induced transformation of C3H10T1/2 cells was also seen in another study [H22].

220. Numerous mechanisms of action for TPA have been advocated, including inhibition of the cell-to-cell communication [H22, T15]; enhancement of chromosomal rearrangements [K28]; production of short-lived radicals [B76]; and action via mechanism of cellular differentiation [B74, S43]. Increase of cellular proliferation is a phenomenon that often accompanies promotion [F14], but it is doubtful whether it is at all necessary, or sufficient [D13, K27]. The TPA promoting effect is apparently not related to any of the known DNA repair processes [K27].

221. Enhanced transformation of various cell lines was also noted after addition to the medium of the epidermal growth factor, a natural hormone-like polypeptide [F15]; bromodeoxyuridine [R30]; high concentrations of insulin [U29]; cortisone [K30]; and interferone [B46]. The particular batch of fetal calf serum used may also have a profound influence on the transformation frequency eventually observed [T11]. A new promoter, dihydroteleocidin B, an antibiotic derivative recently discovered, has a promoting capacity per unit mass about 100 times higher than that of TPA [H31]. A synergism between x rays and a food pyrolysate product 3-amino-1-methyl-5H-pyrido-(4-3b)indol (Trp-P-2), itself a mutagen and carcinogen isolated from boiled meat and fish, has also been shown [B76] in Syrian hamster embryo cells. Hyperthermia (43°C for 60 minutes or 45°C for 15 minutes before irradiation) caused some increase of the x-ray-induced transformation frequency in C3H10T1/2 cells [C33]. The nature of most enhancing agents mentioned above suggests that the mechanisms of action are epigenetic rather than likely to cause structural changes in the genome itself.

222. There are also suppressing (inhibiting) factors. Kennedy and Little [K35] and Little [L26] described suppression by the protease inhibitors antipain and leupeptin. In other studies [B65, G28] it was shown that antipain added to cultures before irradiation enhanced the yield of transformants, while addition shortly after exposure reduced the transformation frequency, and addition 1 or 2 days later was ineffective. Inhibition of radiation-induced oncogenic transformation was also observed when inhibitors of poly(ADP-ribose) synthesis (benzamide, 3-aminobenzamide) were added to cultures of C3H10T1/2 and golden hamster embryo cells [B96].

223. An inhibition (by a factor of 3) of transformation in C3H10T1/2 cells was observed by adding, 24 hours before exposure, a non-toxic derivative of vitamin A, trimethyl-methoxy-phenyl, analogue of N-ethyl retinamide (Ro-H-1430) and other retinoids [B73]. The retinoids irreversibly suppressed oncogenic transformation when present in culture for only a few days after irradiation. Later addition of TPA to the culture remained ineffective. The retinoids may act by suppressing the carcinogen-induced progression of the neoplastic process [B76].

224. Selenium compounds [B73], actinomycin D [K31] and lymphotoxin [D19, E6, R44] also inhibit radiation-induced transformation. When superoxide dismutase was added to irradiated C3H10T1/2 cultures from irradiation to expression of transformation, the frequency of radiation-induced transformants was

greatly reduced, whether or not the drug was present during x-ray exposure [M49]. Quantitatively, the effects of oxygen and misonidazol upon oncogenic transformation and cell killing of C3H10T1/2 cells are very similar [B97].

(e) Conclusions

225. The oncogenic transformation in vitro of hamster embryo cells and several established mouse fibroblast lines by ionizing radiation shows numerous similarities in respect of dose-response relationships, effects of dose fractionation, and influence of cell density upon transformation frequency.

226. The mechanisms of transformation are still imperfectly understood and several methodological questions are not yet fully resolved. The subject has been thoroughly reviewed [B71, B76, G34, L26, Y3]. Transformation is probably a complex multi-stage phenomenon that includes initiation, progression and final expression of malignant foci. A number of promoting and suppressing factors may affect the frequency of transformation and therefore the shape of the dose-response relationships.

227. For these reasons, analysis of dose-response relationships for low- and high-LET radiation must, for the time being, remain descriptive. After single doses of x rays or neutrons, the dose-response curves have some features in common with those seen in vivo for many experimental tumours. For example, when expressed per initial cell at risk, transformation shows an initial rise of the frequency with dose, then the curve reaches a peak and the yield declines at still higher doses. The lower efficiency of gamma rays at the low, as opposed to high, dose rates in cultures established at least 40 hours before irradiation is also in accordance with most observations in vivo. The same applies to the RBE values of neutrons and alpha particles, which are definitely higher than unity and tend to decline with increasing dose, in agreement with the general understanding of cellular radiobiology [B11, K7]. Neutron dose fractionation upon oncogenic transformation in vitro produces effects that are similar to those seen recently in some—but not all—experiments in vivo. There are, however, differences, particularly when comparisons are made with cells plated shortly before irradiation. The most important is the rise of the transformation frequency with a power of dose less than 1 at intermediate doses (< 1.5 Gy). This shape of the curve may be linked with the enhancing effect of fractionation of x ray doses in the same region, a phenomenon observed in all cell lines tested so far.

228. If enhancement of transformation by fractionation applied in vivo, the complex nature of the low-LET dose-response relationship for single doses might imply an under-estimation of cancer induction when risk coefficients for man are extrapolated from the intermediate down to the lowest doses. Similarly, in the case of fractionated exposure, there might be an even greater under-estimation, owing to the enhancement produced by dose fractionation and protraction in some transformation experiments with low-LET radiation. However, in the light of present knowledge—which is still insufficient—such conclusions are premature, for the following reasons:

(a) No dose-response relationship has been observed for tumours in animals with a plateau below 1 Gy after single acute doses of x or gamma rays. It is also quite clear that no enhancement of tumour induction by fractionation or protraction of external low-LET irradiation has ever been noted at doses below 1 Gy (with one possible exception, see IV.B);

(b) The dependence of the dose-response relationships on the length of the culture period before irradiation shows that the irregular shape of the dose-response curves and the enhancement of fractionation in freshly plated cultures result from irradiation of para-synchronous cells and may therefore be considered an artifact [H37];

(c) The effects of low-LET dose fractionation and protraction on established cell cultures are in general agreement with observations related to other effects at the cellular level (induction of mutations, chromosome aberrations, cell sterilization).

B. TUMOURS IN EXPERIMENTAL ANIMALS

229. In its 1977 report [U6], UNSCEAR reviewed experimental data on radiation-induced tumours, including an examination of the dose-response relationships then available. The essential conclusions were that the peculiarities of each tumour model were such as to prevent large generalizations. There were difficulties in interpreting tumour induction curves on the basis of simple mechanisms of action, in view of the complex interplay of primary and secondary contributing factors. With few exceptions, the data came from observations at doses above 0.5 Gy. Data were insufficient to define, unambiguously, dose-effect relationships in the low and sometimes also in the intermediate dose region.

230. With the exception of the mammary tumour of the Sprague-Dawley rat, dose-incidence curves obtained at high dose rates with low-LET radiation showed a slope that increased with increasing dose, not incompatible with a linear-quadratic trend. With high-LET radiation, on the other hand, dose-effect relationships tended to be more linear and their initial slopes showed relatively little change with dose rate and fractionation. However, with low-LET radiation, a decrease in dose rate led mostly to a decrease of the oncogenic effect, following some inverse function of the exposure time. It appeared difficult to quantify this decrease because the shape of the dose-induction relationships was often altered by the change in dose rate. It was clear, however, that the sparing effect of low dose rate or fractionation was higher for low- than for high-LET radiation. Occasional departures from this general scheme were attributed to the peculiarity of the model systems tested, rather than to real exceptions of established radiobiological mechanisms.

231. The National Council on Radiation Protection and Measurements [N1] evaluated the influence of dose and its distribution in time on the induction curves for tumours, with different radiations and a wide range of dose rates. The ratio of the linear non-threshold curves fitted to the high- or to the low-dose-rate experimental points was taken to be a measure of the "dose-rate effectiveness factor" (DREF). DREF values referring to 10 different experimental tumour systems varied from 1.1 to 6.7, the majority of the values clustering between 3 and 5. This analysis led to the conclusion that in most cases the risk of low-LET radiation would be significantly overestimated if non-threshold linear extrapolation of the data for high-dose-rate were applied to low-dose-rate irradiation. Moskalev et al. [M61, M68] came to the same conclusion when reviewing the available scientific literature. New data that have become available since 1977 are reviewed below.

1. Myeloid leukaemia

232. Robinson and Upton [R7] re-analysed part of the original data on radiation effects in RF mice [U14-U16], correcting for competing risks. About 2000 male mice, irradiated with 250-kV x rays at doses between zero and 4.5 Gy, were selected. Early causes of death (myeloid leukaemia, M, and thymic lymphoma, T) or late causes (reticulum cell sarcoma, L, or others, R) were analysed separately by a non-parametric Kaplan-Meier survival function and its logarithmic transform (the cumulative force of mortality, cum. F.M.). Models were set up for treatment of these two categories, on the assumption of independence between the various causes of death. For causes M and T, there was a significant decrease of the latent period with dose up to 3 Gy. When the effect of dose on the integral tumour rate of M (which corresponds to the cum. F.M.) was studied, the form of the relationship for this cause of death peaked, with a maximum between 2 and 3 Gy and a further decline up to 4.5 Gy, depending on the age at irradiation of the animals (which was 5-6 weeks for group A and 9-10 weeks for group B) (Figure XV). The model for fitting the experimental data was such that the estimate of the ultimate value of the cum. F.M. corresponded to the number of leukaemogenic cells per animal. These were assumed to have a linear-quadratic dose dependence for induction, and linear-quadratic kinetics for killing. Following Barendsen [B7], the authors took an α_1/α_2 quotient of 0.5 Gy and a β_1/β_2 quotient of 3 Gy. The fit of the data actually produced a β_1/β_2 quotient of 2.4, which is in reasonable agreement, considering the assumptions involved. It was concluded that the data were consistent with the postulated linear-quadratic dose-response model.

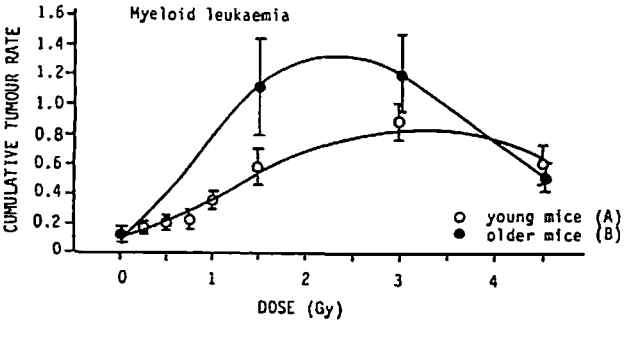


Figure XV. Final cumulative tumour rate ± standard error versus dose for myeloid leukaemia in x-irradiated RF mice. [R7]

233. Petoyan and Filyuskin [P22] tested another model on x-ray- and neutron-induced (high dose rate) leukaemia in RF mice [U16]. The basic assumptions of the model were:

(a) Initiation in the bone marrow stem cells is a two-track phenomenon, perhaps a symmetrical chromosomal translocation;

(b) The sensitivity of initiated and non-initiated stem cells to killing by radiation is the same;

(c) Most of mitotic cell death is due to asymmetric chromosomal exchanges, which have a functional dose dependence basically similar to that of the symmetrical translocations. Therefore, the shape and parameters of the dose-response functions for induction of symmetrical exchanges and cell death should be similar for a given cell line;

(d) The promoting influence of radiation is brought about through an enhancement of mitotic activity and, therefore, the degree of promotion should be inversely proportional to the post-irradiation survival of stem cells;

(e) The probability of scoring an overt malignancy during the remaining life span is a complex function of the "spontaneous" incidence of a given malignancy.

234. The parameters of the model were defined by selecting from independent sources the survival functions of bone marrow stem cells irradiated with x rays and neutrons. The model was fitted to experimental data on the incidence of leukaemia in the RF mouse [U16] by the maximum likelihood method, using a single set of two adjustable parameters; the same set was applied to x rays and neutrons. A good fit was obtained, by visual inspection, and the dose-response curve showed a slight upward concave curvilinearity and linearity of the initial ascending part of the curve for x rays and neutrons, respectively. Linear extrapolation from 1.5 Gy to the low-dose region would lead to a small over-estimate of the risk for x rays, but would be adequate for neutrons. The assumption that the dose-response functions for the initiation and cell killing are similar could be criticized on the basis of available information [B9, B11], but the postulate may be accepted as a first approximation to reality.

235. Mole et al. [M2, M52, M64-M66] studied the induction of acute myeloid leukaemia by x rays, gamma rays and fission neutrons in male CBA/H mice that have almost a zero incidence of this disease. With little intercurrent mortality from competing causes of death, this tumour model is also less sensitive to systematic bias from such causes than that on RF mice [R7].

236. Mice were exposed to one of ten doses of x rays (from 0.25 to 6 Gy, delivered at the rate of 0.5 Gy min^{-1}) and then followed until they died [M52, M64]. Median survival in all groups was very similar. There was essentially no association between latency and dose. The results were fitted to a four-term polynomial of the general form $I = (\alpha_1 D + \alpha_2 D^2) \exp -(\beta_1 D + \beta_2 D^2)$ as well as to four simplifications with three or two parameters only. All fits were acceptable in a statistical sense (P for goodness of fit = 0.34-0.44), but only two equations had all parameters positive and significantly larger than zero ($p < 0.05$). These were: $I = \alpha_1 D\, e^{-\beta_2 D^2}$ and $I = \alpha_2 D^2\, e^{-\beta_1 D}$. The former was rejected on the ground that cell survival depending solely on the square of dose is normally not found. The observed incidence could best be fitted by the latter relationship, as shown in Figure XVI. In another recent study of the induction of myeloid leukaemia in CBA male mice by whole-body x irradiation (250 kVp, HVL 1.5 mm Cu) [D3], the age-corrected incidence after doses of 1, 3, 5 and 7 Gy was essentially superimposable on the data by Mole [M52] (see Figure XVI). A purely exponential survival for haemopoetic cells is probably a simplification of reality, but survival curves for bone marrow stem cells usually show only a small shoulder at low doses. For in vivo irradiated bone marrow stem cells McCulloch and Till [M16] found $D_0 = 0.95$ Gy and n = 1.5. Mean values for 17 measurements of D_0 for spleen-colony-forming units in different mouse strains irradiated in vivo with x rays were in the range 0.95-1.61 Gy [H32]. The value of β_1 (0.7-0.11 Gy^{-1}) found by Mole [M52] is compatible with this range.

237. A contribution of a dose-linear term ($\alpha_1 D$) to the dose-response relationship in Figure XVI cannot be excluded on purely statistical grounds. The α_1/α_2 quotient estimated for the complete four parameter model was negative, but the upper 95% confidence limit was 1.29 Gy; and therefore, values of 0.3-0.5 Gy cannot be excluded as very unlikely. Moreover, when the data were tested on three models with a number of adjustable parameters greater than two, one or two of the parameters were always insignificant. From the simplified two-parameter models, one had to be chosen on the basis of additional information, and this implies a constraint a posteriori even if none had been chosen a priori. In summary, it appears that complete parameters for cell initiation and survival cannot be estimated, independently and simultaneously, solely from the data. However, when a likely shape of the survival function is assumed, the kinetics of initiation for low-LET radiation appears, in this case [M2, M52, M64], to be concave upwards with a pronounced D^2 component.

238. Induction of myeloid leukaemia in CBA/H mice was also studied after brief (0.25 Gy min^{-1}) and protracted exposure to ^{60}Co gamma rays (1.5, 3.0 and 4.5 Gy) [M65]. Protracted exposures were delivered either as daily fractions (0.25 Gy min^{-1}, 5 days per week for 4 weeks) or at a constant rate of 0.004-0.11 mGy min^{-1}. The latter two modes of exposure did not differ in their effectiveness and gave a rather constant response at 5-6% incidence for doses above zero. The shape of the dose-response curve is very similar to that observed for leukaemias induced by fractionated x-ray treatment for ankylosing spondylitis [S49]. The response after acute irradiation was higher by a factor of 2.2, 2.8 and 5 for the three doses, respectively. The most effective gamma-ray dose for leukaemia induction was higher than that of x rays.

239. Irradiation of CBA/H male mice with fission neutrons was performed at high rate (exposure times, 2-20 minutes) with 7 air-midline kerma values in the range from 0.02 through 2 Gy [M66]. The observed incidence of acute myeloid leukaemia was fitted by the equation $I(D) = (4.5 \pm 1.25)\ 10^{-1} D\ e^{-(1.01 \pm 0.28)D}$ (P = 0.25). Neither a purely linear model without correction for cell killing, nor the dose-squared model that fitted the x-ray data, could be satisfactorily interpolated to the neutron data (P for goodness of fit in either case $< 10^{-4}$).

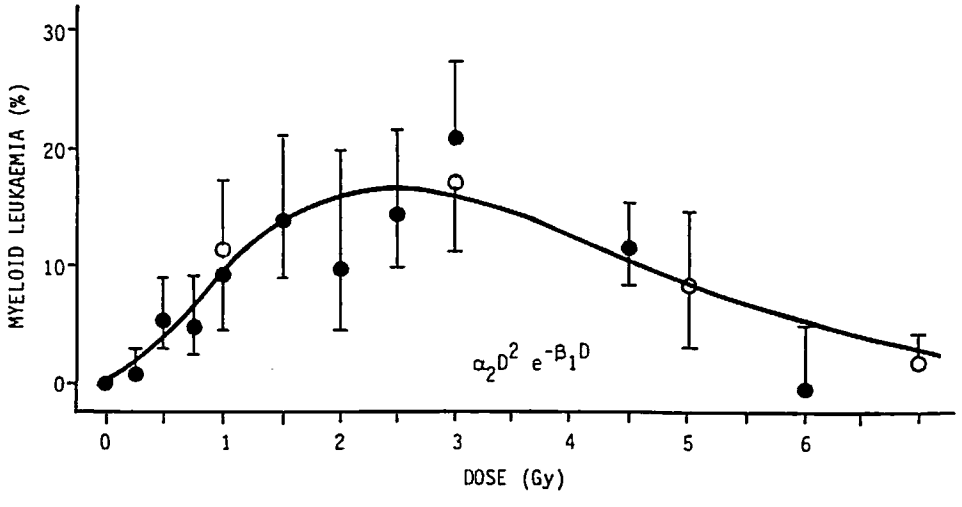


Figure XVI. Dose-response relationship for incidence of myeloid leukaemia after brief exposures of male CBA mice to 250-kVp x rays. Closed circles, data from Mole [M52]; Open circles, data from Di Majo et al. [D3].

240. In experiments by Ullrich and Storer [U20], specific-pathogen-free (SPF) RFM/Un mice of both sexes were irradiated at 10 weeks of age with ^{137}Cs gamma rays at 0.45 Gy min^{-1}, with doses ranging from 0.1 to 3 Gy. Myeloid leukaemia was less frequent in the females, in which the age-corrected incidence reached significance over the control level at 1.5 Gy. Although both a linear and a linear-quadratic model provided a satisfactory fit to the data ($P > 0.5$ and > 0.8, respectively), the dose-squared component was not significant and linearity predominated between zero and 3 Gy.

241. In male mice, the incidence was significantly higher than control, even at 0.5 Gy, and the form of the relationship was similar to that in females: it could be described either by a linear ($P > 0.5$) or a linear-quadratic model ($P > 0.35$), with a very small and non-significant dose-squared term. The ratio of the linear slopes for the two sexes indicated that males were more susceptible by a factor of about 5. Low-dose-rate (0.083 Gy per day) gamma exposure [U3] was very much less effective in inducing myeloid leukaemia in the female mice; no significant increase above controls could be reached even at 2.0 Gy. After acute and chronic neutron irradiation, the incidence of the disease was very low and did not permit any detailed study of dose-response relationships. In either case, the peak incidence was observed at 0.47 Gy, but the results were not significantly different from controls ($p > 0.05$).

2. Thymic lymphoma

242. Ullrich and Storer [U2, U3, U5, U20] studied the dose-response relationship and dose-rate effects for ^{137}Cs gamma rays and neutrons in SPF 10-week-old RFM/Un mice. The response was assessed as age-corrected incidence, standardized to the distribution of the age at death of control animals. In females, thymic lymphoma was efficiently induced by gamma rays at 0.45 Gy min^{-1}; the incidence was significantly higher than in controls in all groups receiving 0.25 Gy or more. No simple model could describe the response over the entire dose range (0.1-3 Gy). There was a steep rise in the region below 0.5 Gy, followed by a shallow rise at higher doses. Over the range of 0-0.25 Gy (three points), a dose-squared model provided an adequate fit and linearity could be rejected ($P < 0.06$). From 0.5 to 3 Gy the increase in incidence with dose was compatible with linearity.

243. In males, the significance of the difference above controls was reached only at 1 Gy. A linear model provided a satisfactory fit over the entire range of gamma-ray doses (0.1-3 Gy; $P > 0.4$). Over 0-1.5 Gy, both a linear and linear-quadratic equation (with D^2 coefficient not significant) provided a very good fit to the data ($P > 0.95$ and > 0.80, respectively). Thus, in males the dose-response relationship for acute gamma rays was predominantly linear over the entire dose range.

244. Lowering the dose rate to 0.083 Gy per day considerably decreased the incidence of thymic lymphoma in the females and changed the form of the curve from quadratic followed by linear to linear-quadratic with a negative linear component. Simple linearity could be rejected ($P < 0.001$). It is quite clear that in the RFM mouse, after low-LET exposure, there is no suggestion of the threshold-type response found by Kaplan and Brown [K33] in C57Bl mice. In these older data there was a statistically verified threshold in the dose-response relationship. As may be seen in Figure XVII (kindly provided by G. Walinder), fractionation of the dose into 1, 2, 4 or 8 fractions with one-day spacing, is without effect upon the incidence of the lymphoma. When plotted against exposure (either simple or fractionated) the incidence may be fitted by a linear function of the form $I = aD - b$ where $a = 0.112$, and $b = -21.6$ (significantly different from zero); the coefficient of correlation is very high (0.903).

245. In experiments by Maisin et al. [M62], 12-week-old male BALB/c mice were exposed to single or to fractionated doses of ^{137}Cs gamma rays (10 equal doses separated by 1 day) in the dose range from 0.25 to 6 Gy. The dose-response curve for thymic lymphoma was of a threshold type, the actuarial incidence rising above control only at 4 and 6 Gy. Single doses were more effective at 4 than at 6 Gy.

246. Other data on thymic lymphoma induction by x rays in neonatal (C57Bl/6 JNrs × WHT/HC) F_1 mice were reported [S48]. Even though the incidence in females and males at three exposure points (200, 400 and 600 R) could be fitted to a linear-quadratic equation with a negative linear term ($P > 0.80$), the data adequately fit a threshold-type response such as that presented in Figure XVII for the C57Bl mice.

247. Fast neutrons (acutely delivered doses at 0.05 and 0.25 Gy min^{-1} and chronic doses at 0.01 Gy per day, with total doses between 0.1 and 3 Gy) induced thymic lymphoma in female RFM mice [U5]. In the range 0.25-0.5 Gy, the RBE with respect to high-dose-rate ^{137}Cs gamma rays was between 3 and 4. For acute neutron exposures, the dose-response curve was concave downward. In the range 0-0.94 Gy, linearity could be rejected ($P > 0.001$) and a good fit was obtained with the square root of the dose ($P > 0.8$). Up to 0.47 Gy, a linear fit was satisfactory ($P > 0.75$). For chronic neutron exposure, a linear fit adequately described the curve over the 0-0.94 Gy range ($P > 0.8$); and the loss of effectiveness over the acute exposures amounted to about 30%. However, there was a decrease of susceptibility to thymic lymphoma upon acute exposure with increasing age, so that the lower efficiency of the low-dose-rate exposure may in part be due to this latter factor alone. The RBE of acute neutron exposure relative to gamma rays varied proportionally to the inverse square root of neutron dose.

248. Induction of thymic lymphoma was also studied in male BALB/c mice irradiated at the age of 12 weeks with d(50)Be neutrons (modal energy about 23 MeV) [M63] at doses from 0.02 to 3 Gy. The actuarial incidence of thymic lymphoma fitted the same sigmoidal threshold-type curve found for ^{137}Cs gamma rays [M62].

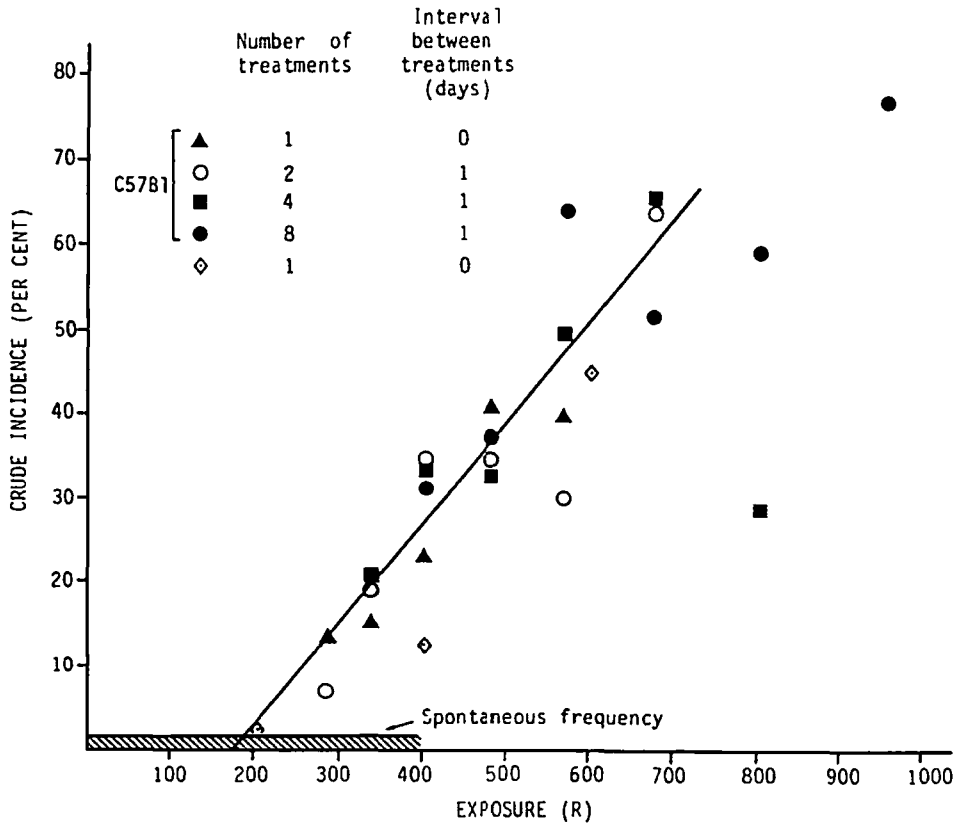


Figure XVII. Crude incidence of thymic lymphoma in C57Bl mice given single and fractionated x-ray doses at 1 day interval [K33]. Rhombard symbols represent the crude incidence of thymic lymphoma in neo-natal (C57B1/6 JNrs × WHT/Ht) F_1 mice [S48].

3. Other reticular tumours

249. The so-called mouse reticulum cell sarcoma is a group of neoplasms showing a decline of the incidence with dose after whole-body x irradiation [C19, K25, U3, U5, U20]. Ullrich and Storer [U3, U5, U20] studied the age-corrected incidence of reticulum cell sarcoma among SPF RFM/Un male and female mice irradiated with gamma rays (0.45 Gy min^{-1} or 0.083 Gy per day) and in RFM/Un female and BALB/c mice irradiated with fast neutrons (0.05, 0.25 Gy min^{-1} and 0.01 Gy per day). All treatments produced a decrease of reticulum cell sarcoma with dose, neutrons being more effective than gamma rays, and chronic exposures less effective than acute ones. The difference between acutely and chronically delivered gamma rays was more pronounced than that for neutrons. There was a clear, inverse relationship between the increase of thymic lymphoma and the decrease of reticulum cell sarcoma, suggesting some link between various radiation-induced reticular neoplasms which could greatly affect the observed dose-response curves.

250. Male mice (C57BL/Cne × C3H/Cne)F_1 hybrids received lethal whole-body irradiation (9 Gy) and were rescued from early death due to haematological failure by a homologous bone-marrow graft [C18]. In these mice, the spontaneous incidence of reticulum cell sarcoma of about 50% is reduced in irradiated survivors to a few per cent. Shielding of a part of the marrow during exposure affords a similar protection against early post-irradiation death and effectively depresses the incidence of the tumour. It was suggested that whole-body irradiation sterilizes cells from which these neoplasms originate [C18, C19] and that the D_0 for these cells is similar to that for the bone-marrow stem cells [M20].

251. Further studies [M20] showed that in vivo irradiation of the bone-marrow graft with doses of 2 and 4 Gy of x rays before transplantation into hosts given whole-body irradiation (9 Gy) provides the same protection against early death, but leads to a significantly elevated incidence of reticulum cell sarcoma in animals given irradiated marrow. The incidence expressed per number of injected marrow cells rises with dose, amounting to 1.65 10^{-8}, 1.90 10^{-8} and 2.38 10^{-8} tumours per cell irradiated with 0, 2 and 4 Gy. When related to the number of injected surviving stem cells, the incidence rose steeply from 4.3 10^{-5} through 9.7 10^{-4} and 6.4 10^{-3} at 0, 2 and 4 Gy, respectively. It is an unproved assumption that the tumours originated from these cells. If this hypothesis could be accepted, the dose-response would display a pronounced curvilinearity (concave upwards), the effect rising with a power of dose appreciably greater than 1, and even the presence of a threshold dose could not be rejected.

252. In the same animal model, studies [M19] were made on whole-body irradiated mice with shielding of one or two hind legs, from which shielding was removed for a variable fraction of irradiation time, thus exposing some of the protected marrow in situ to graded doses of x rays up to 8 Gy. The observed

incidence of reticulum cell sarcomas increased in these mice to a maximum at about 5 Gy and then declined with further increase of the dose. The final incidence of these neoplasms in all experiments with exogenous and endogenous bone-marrow protection is plotted in Figure XVIII, showing in all instances a curvilinear (upward concave) rise with x-ray dose. The form of these relationships is similar to that observed for many other radiation-induced tumours in animals irradiated in vivo.

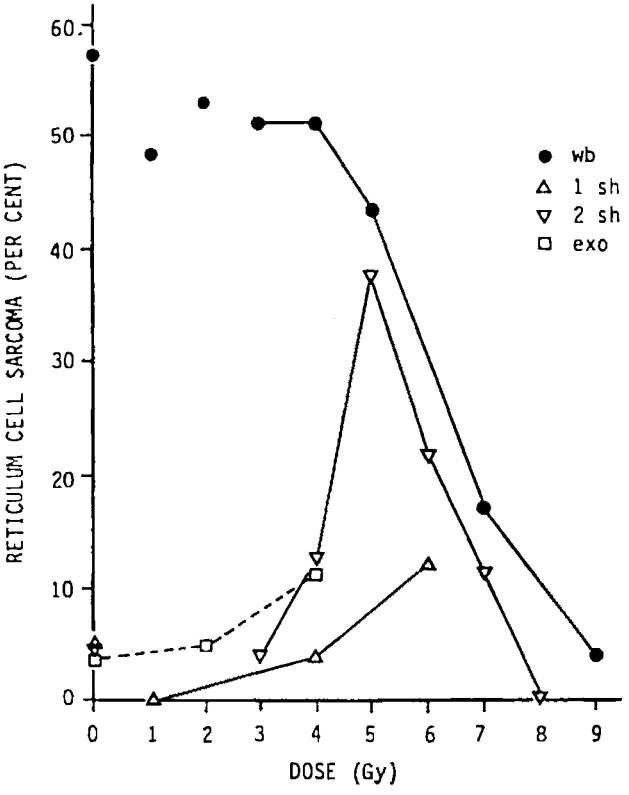


Figure XVIII. Final incidence of reticulum cell sarcoma as a function of dose under three different experimental conditions: (a) whole-body irradiation (wb); (b) shielding of one (1 sh) or two (2 sh) hind legs; (c) syngenic bone marrow transplantation (exo). [M19]

4. Tumours of the thyroid

253. An extensive study of thyroid tumour induction by 250-kVp x rays and ^{131}I in about 3000 6-week-old female Long-Evans rats was reported by Lee et al. [L29]. The study aimed at comparing the effectiveness of the two radiations delivered at different dose rates (2.8 Gy min^{-1} for x rays; the maximum dose rates for ^{131}I in individual groups were estimated at 0.17, 0.69 and 1.6 mGy min^{-1}). Local doses of x rays to the thyroid were 0.94, 4.1 and 10.6 Gy. Total doses delivered by ^{131}I were estimated at 0.8, 3.3 and 8.5 Gy. The role of pituitary irradiation in the induction of thyroid cancer was also explored by delivering doses of 4.1 Gy of x rays to the pituitary alone, or to the thyroid and the pituitary together: findings were negative in this respect.

254. Tumours included were those that appeared later than 6 months in rats dying before the age of 26 months and in animals sacrificed at 24 months. The results were given as incidence corrected for the slightly enhanced mortality of irradiated versus control rats. Data on tumour multiplicity and on tumours per animal were not presented.

255. A least square fit yielded the following functions describing the dose-response relationships (Figure XIX):

$$I(D) = 7.47\ 10^{-4}\,(D + 10)^{0.6838} \text{ for x rays}$$

$$I(D) = 1.78\ 10^{-3}\,(D + 10)^{0.5348} \text{ for } ^{131}I$$

where D is the dose given in rad (0.01 Gy). The exponents were significantly lower than unity ($p < 0.001$), indicating that the incidence of thyroid carcinomas in these rats rose with approximately the square root of the low-LET dose. Thus, there was no difference in the effectiveness of the two radiations over the observed range of doses, but a lower effectiveness of ^{131}I per unit dose (up to a factor $\simeq 3$) could not be excluded on statistical grounds [N10].

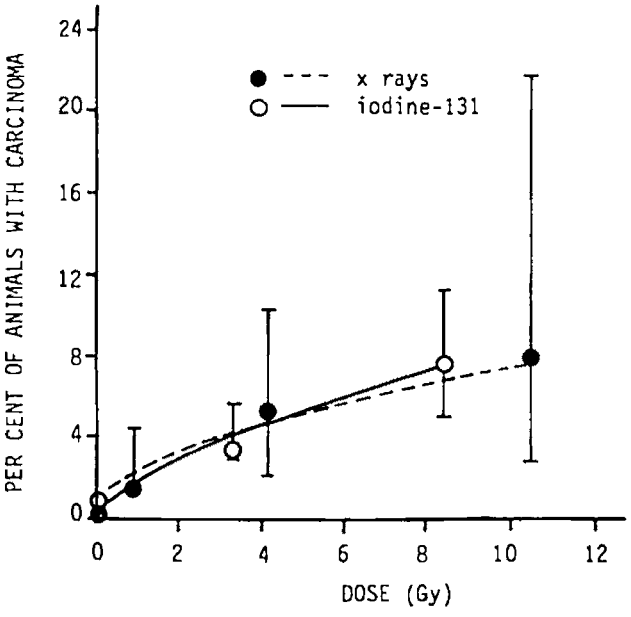


Figure XIX. Incidence of thyroid carcinoma as a function of mean thyroid dose from injected iodine-131 and localized x irradiation. Error bars are estimates of the 95% confidence limits. [L29]

256. For adenomas, the two dose-response relationships were slightly different ($p < 0.01$) and when fitted by exponential equations they assumed the following forms:

$$I(D) = 0.0245 \exp(0.00207\ D) \text{ for x rays}$$

$$I(D) = 0.0240 \exp(0.00123\ D) \text{ for } ^{131}I,$$

where D is the dose in rad (0.01 Gy). At no dose point was there a significant difference between the effect of the two radiations. However, due to the large variability of the observations, some difference in the effectiveness could not be excluded. Control incidence of medullary tumours was not affected by either radiation.

257. The downward concavity of the dose-incidence curve for carcinomas was attributed to killing of initiated cells. If an in vivo survival curve of thyroid

follicular cells with $D_q = 4.9$ Gy and $D_0 = 4.5$ Gy is assumed [D15, M51], then the dose-response curve for initiation of carcinomas or adenomas in this experiment may be expected to rise with a power of dose either close to or greater than unity. The slope of the initial portion of the dose-incidence curve for carcinomas was estimated at $1.9\ 10^{-2}\ Gy^{-1}$, which is close to the estimate for humans [S60].

258. The presence of a strong linear component in the relationships is suggested by the absence of a clear dose-rate effect, at least in young animals. This observation contradicts previous findings (reviewed in [D16, W12]) that, per unit dose, x rays are more efficient for thyroid tumour induction than ^{131}I. The study reviewed here [L29] differs from the older ones in two important aspects: first, the range of doses is below 10 Gy, and thus cell killing and other non-stochastic effects would not be expected to prevail; second, the number of animals used is large and gives the study good statistical credibility. Nevertheless, the findings refer only to one sex of one particular strain of rats. These experiments do not support the suggestion [R29] that irradiation of the pituitary gland may give rise to increased incidence of thyroid cancers in children irradiated for treatment of tinea capitis.

5. Mammary tumours

259. The age-corrected incidence of mammary adenocarcinomas was studied in SPF female BALB/c mice after high- and low-dose-rate exposure to gamma rays [U3, U25] as well as to high-dose-rate, low-dose-rate and fractionated exposures to fission neutrons [U4, U25, U26]. After acute gamma-ray exposure (doses 0.1-2 Gy) the incidence increased rapidly over the range 0-0.25 Gy, with a rather irregular plateau appearing at higher doses. The irregular response was consistent with the models $I(D) = 7.7 + 35\ D + 150\ D^2$ ($P > 0.4$) for the high dose rate and with $I(D) = 7.7 + 35\ D$ ($P > 0.4$) for the low dose rate, in accordance with the linear-quadratic model. Ramzaev et al. [R1] described a "supra-linear" response for induction of mammary adenocarcinoma in mice irradiated over ten generations through constant feeding of ^{137}Cs and ^{90}Sr.

260. Acute irradiation of BALB/c mice with fission neutrons (0.05-0.25 Gy min^{-1}) [U25] yielded a dose-response that was downward concave over the range 0-0.5 Gy (the lowest dose being 0.025 Gy) and would be poorly described by a linear model. A good fit was obtained by a model $I(D) = 7.9 + 27\ \sqrt{D}$ ($P > 0.85$). In the range 0-0.1 Gy, the response could be well fitted by a linear model $I(D) = 7.9 + 114\ D$.

261. When fission neutron exposures were split into two equal fractions delivered 24 hours and 30 days apart [U26], there was no difference with respect to the single dose-response for the 24-hour interval, but for the 30-day interval there was an increase of about 30-40% only for the highest dose tested (0.5 Gy). In the latter case, the curve was still bending over in the range 0-0.2 Gy. Protracted irradiation (0.01-0.1 Gy per day) led to a significant enhancement of the effect relative to the acute exposure, and over the whole range of doses. This was interpreted either as a promoting effect or as stimulation of progression of the growth of malignant clones. The maximum RBE of neutrons was 33; this was calculated as a ratio of the linear slope for the gamma and neutron curves (for single irradiation at low dose rates).

262. Two-month-old female, Sprague-Dawley rats were followed by Shellabarger et al. [S37] for their entire life span after single exposures to 250-kVp x rays (0.28, 0.56 and 0.85 Gy) and 430-keV neutrons (0.001, 0.004, 0.016 and 0.064 Gy). The animals were observed for appearance of adenocarcinomas and fibroadenomas. In all irradiated groups the tumour rate increased steeply with age and the effect of irradiation could be described as a forward shift in time of the spontaneous age-specific tumour rate.

263. The response was expressed separately for carcinomas and adenomas as mortality-corrected prevalence and cumulative tumour rate [R(t,D)]. The fibroadenoma and total mammary tumour responses were approximately proportional to x-ray dose over all times, while neutrons produced a downward concave relationship, rising with a power of neutron dose less than unity. The increase in R(t,D) was significant even at 1 mGy of neutrons and the forward shift of the prevalence, corrected for age-specific mortality, caused by this dose was equivalent to 35 days. The R(t,D) for fibroadenomas at 800 days was less curvilinear than at 1 year after exposure. The distribution of tumours was non-random among the animals (over-dispersion was noted relative to Poisson distribution). The response for adenocarcinomas was statistically uncertain, owing to the small number of tumours involved, but linearity is the best approximation to the dose-response relationship.

264. In this study [S37], the RBE varied roughly with the inverse square root of the neutron dose. At the highest doses studied it exceeded 10; at the lower end of the dose scale, it approached a value of 100. The implications of these observations were already discussed in chapter II.

265. In other experiments [V9], female Sprague-Dawley rats were acutely exposed whole-body to fission neutrons, or to protracted doses of 0.02, 0.06 and 0.5 Gy (over 242 hours in one month). The prevalence of mammary tumours at 10 months after exposure increased, relative to single irradiation, at all doses tested. Protraction of gamma-ray exposures (150, 300, 450 R) in a similar pattern reduced significantly the prevalence seen after corresponding single exposures. The RBE values for neutrons, measured at 20% prevalence, were 16 and 68 for acute and chronic irradiation, respectively.

266. Breast tumours (histology not specified) in young female Sprague-Dawley rats were studied [G35] after acute (over one hour) and chronic (over 10 days) x irradiation, as well as after internal irradiation by tritium, administered as tritiated water (75 and 90% of total dose delivered over 10 and 20 days, respectively). The doses of 200-kVp x rays varied from 0.29 to 2 Gy,

and those of tritium from 0.5 to 4 Gy. The competitive-risk-corrected tumour rate was calculated up to 450 days after the start of exposure and the integral values were linearly related to dose for all three irradiation modes. The effectiveness of tritium per unit dose did not differ from that for the chronic x-ray exposure. The latter produced effects similar to those of acute exposure at 0.6 Gy, but was 25-30% less effective at about 1.8 Gy.

267. X-ray-induced and neutron-induced (0.43 MeV) mammary tumours were studied in weanling, virgin female ACI rats [S52], irradiated at 88-89 days. The doses for x rays ranged from 0.17 to 3 Gy and for neutrons from 0.01 to 0.36 Gy. The animals were irradiated either 2 days after implantation of a pellet containing 5 mg of diethylstilbestrol (DES) or without prior hormonal treatment. Fibroadenomas and adenocarcinomas were diagnosed histologically and recorded separately. DES greatly increased the incidence of spontaneous and radiation-induced adenocarcinomas in this strain, which has a low spontaneous incidence of mammary neoplasms. Significant excess prevalence was detected in DES-treated rats even at the lowest neutron dose; for x rays, the significance occurred at 0.17 Gy. The RBE varied inversely with the square root of the dose and approached a value of 100 at the lowest end of the range.

268. Appearance of tumours in rats not treated with DES was followed, on the average, to about 750 days after irradiation. For x rays, the cumulative tumour rate at 600 days (for the sum or for each type of tumour separately) rose almost linearly with the dose. The same applied to adenocarcinomas after neutron irradiation, but for fibroadenomas a downward concave relationship could not be excluded. The RBE of neutrons for the sum of tumours tended to decrease with dose over the range of doses tested, but did not vary much from an average value of 10. The length of tumour-free life lost due to the sum of benign and malignant tumours was a linear function of dose, for both x rays and neutrons, and for the whole range of doses tested.

269. When non-inbred female rats were irradiated externally, with single, increasing doses of β rays from a $^{90}Sr + ^{90}Y$ source, the rise of the crude incidence of mammary carcinoma was linear with dose, up to 4 Gy [M68, M71]. These animals were also irradiated, starting at the age of 8 weeks, singly, with doses of 16 Gy (from the published text it appears likely that the doses refer to the surface of the body); daily (5 days a week) at 0.8 Gy per day for 4 weeks; or once every two weeks with 0.8 Gy over a period of 39 weeks. The observed life shortening differed significantly from the control value, but not between groups with various irradiation schemes. There was an obvious acceleration of the appearance of mammary tumours after irradiation, and the fractionated schemes were slightly less effective, although this difference could be accounted for by the fact that, on average, the fractionated exposures were delivered somewhat later in life. The crude incidence over lifetime was elevated in all irradiated groups to 100% from 40% in controls. This experiment [M71] supports the notion that fractionation of low-LET radiation has little effect upon the incidence of mammary tumours in rats.

270. Other authors reported that mammary tumours were also induced in female Sprague-Dawley and in WAG/Rij rats by x rays, and by monoenergetic 0.5-MeV and 15-MeV neutrons [B86, B92]. There was no evidence that a virus played any role in mammary carcinogenesis in these animals. The rats were 8 weeks old when irradiation was started with fractionated doses or given as single doses (absorbed doses in the glands). They were kept until their death, and the frequency of fibroadenomas and carcinomas was based on histological examination.

271. The probability of animals surviving without evidence of a tumour was calculated according to the Kaplan and Meier life-table analysis. Weibull functions were fitted to these data and showed that irradiation caused an acceleration in the appearance of fibroadenomas and carcinomas in both strains of rats. X-ray fractionation (10×0.2 Gy at one-month intervals) in WAG/Rij rats was marginally less effective, in respect of the appearance time of mammary carcinomas, than a single dose of 2 Gy. Fractionation of 0.25 Gy of neutron into 10 equal fractions at one-month intervals was also without a significant effect relative to 1×0.25 Gy.

272. When dose-response relationships were calculated from actuarial incidence data at 95 weeks of age, the results for carcinomas in WAG/Rij rats for x rays and 0.5 MeV neutrons showed such a wide scatter as to preclude unequivocal inferences about the character of dose-response relationship. For fibroadenomas (Figure XX) the response for x rays (0.25-4 Gy) was proportional to dose. The response for 0.5 and 15 MeV neutrons (0.025-0.8 or 1.6 Gy, respectively) showed a saturation effect. In Sprague Dawley rats, the actuarial incidence of fibroadenomas showed

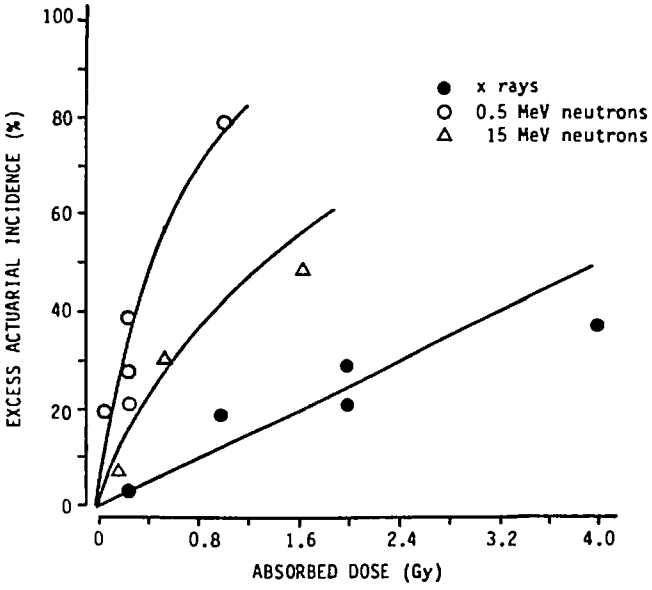


Figure XX. Actuarial incidence at 92 weeks of age of mammary adenomas in WAG/Rij rats as a function of dose for various types of radiation.
[B92]

saturation effects at high doses of all radiations. The RBE of neutrons was much lower than that observed in other studies on the same strain [S37, S52]. Carcinomas were so rare that no dose-response relationship could be established.

273. When the prevalence of mammary adenocarcinomas was studied at 10 months after x-ray exposure (200 R) in female Sprague-Dawley rats irradiated as young virgins or as pregnant, lactating or post-lactating animals [H23], no effect of the physiological state upon the incidence could be found. This result is at variance with the age-effect seen in women (see chapter V).

274. Numerous studies show that several factors may influence the development of radiation-induced mammary tumours in various strains of rats. Some of these studies were considered in annex L of the 1982 UNSCEAR report [U24]. A strong influence of genetic factors on neutron-induced mammary carcinogenesis was reported by Vogel et al. [V10]. After a single dose of 0.5 Gy from fission neutrons, the highest (56%) prevalence at 1 year after exposure was seen in Sprague-Dawley and Long-Evans females; the lowest (5%) was observed in Wistar, and an intermediate one (25-29%) in Buffalo and Fischer-344 rats. Wide variation in susceptibility to mammary tumour induction was also found by Broerse et al. [B86, B92] for Sprague-Dawley, WAG/Rij and BN/BiRij rats.

6. Lung cancer

275. Lung adenocarcinomas were induced in BALB/c female mice by gamma irradiation at 0.45 Gy min^{-1} and at 0.083 Gy per day in the dose range 0.1-2 Gy [U2, U3, U25]. After acute exposure, the age-corrected incidence could be related to dose by a linear [$I(D) = 10.9 + 11\ D$; $(P > 0.7)$] or a linear-quadratic model [$I(D) = 11.9 + 4.1\ D + 4.3\ D^2$ $(P > 0.7)$]. At low dose rate, the dose-response relationship was linear with the same slope [$I(D) = 12.5 + 4.3\ D$ $(P > 8)$] as at high dose rate in the linear-quadratic model. This model, therefore, seems to describe adequately the response in question.

276. After single acute exposure to fission neutrons (doses 0.025-2 Gy; 0.05-0.25 Gy min^{-1}), the relationship was downward concave with a maximum at 0.5 Gy [U25]. Over the range 0-0.5 Gy the data were consistent with a square-root model [$(D) = 13.6 + 29\ \sqrt{D}$ $(P > 0.7)$]. A linear model could not be rejected but was obviously unlikely. In the ranges 0-0.2 Gy, the data were fitted by a linear model [$I(D) = 14.7 + 76\ D$ $(P > 0.7)$]. When the doses were split into two equal fractions, no difference was seen for 24-hour fractionation [U26]. A slight increase of the incidences was noted for 30-day fractionation, but only at the highest dose of 0.5 Gy. For this irradiation mode the dose-response became practically linear up to 0.5 Gy.

277. Protracted neutron irradiation ($8.3\ 10^{-5}$ Gy per day and $8.3\ 10^{-6}$ Gy per day) was more effective than the high-dose-rate exposure and, as in the case of 30-day fractionation more nearly linear over the entire dose range [U26]. Higher effectiveness for 0.5 Gy at chronic and at 30-day fractionated exposure is unlikely to result from repair of sub-transformation damage, as no repair was seen for fractionation over 24 hours. The effect was attributed to repopulation of alveolar target cells. The maximum RBE of neutrons from the ratio of the linear slopes at low doses was 18.5. When derived from the square root of the dose model, it equalled $70.7/\sqrt{D_n}$.

278. Chmelevsky et al. [C34] analysed the induction of lung carcinoma in male Sprague-Dawley rats which were 90-days old at the start of an exposure to radon in equilibrium with its short-lived daughter products. The radon concentrations and the duration of daily or weekly exposure were varied. The total duration of the inhalation period was kept within one to six months. The dose was defined as a product of potential alpha energy concentration and exposure time, and expressed in working level months (WLM[c]); the range of dose covered zero to 14,000 WLM delivered at various rates.

279. Animals were studied at death for the presence and histology of lung neoplasms. In this species, lung cancer is almost never a cause of death: therefore independence between disease and death could be assumed and the data could be treated as fully censored. The prevalence of neoplasms as a function of time was estimated for each exposure group by non-parametric methods in the form of a monotonically increasing function (by a most-likelihood fit). Three models were selected for fitting prevalence to dose: a time shift, an acceleration, and a proportional hazard model. The fit of the data to all three models was equally good: none could be discarded on statistical grounds.

280. The crude and mortality-corrected incidence of lung carcinomas was calculated from the prevalence function up to 900 days. The results of the actuarial incidence are shown in Figure XXI. The initial slope (below 1000 WLM) is practically linear in both cases. When the incidence was fitted to a function of cumulative exposure E of the type $I(t;E) = K\ E^p$, the parameters obtained at t = 850 days were: $K = (3.4 \pm 1.4)\ 10^{-4}$ and $p = 0.92 \pm 0.07$. When linearity was assumed to apply over this range of exposures, the proportionality coefficient was $(2 \pm 0.5)\ 10^{-4}$ per WLM. Perhaps by accident, these values are very similar to those found for man (chapter V). At doses above $3\ 10^3$ WLM, the response flattens off. At doses above $4\ 10^3$ WLM, the exposures at high dose rate (> 1600 WLM per month) are less effective in inducing tumours than those delivered at lower rates. The data do not suggest a threshold, which, if present, would have to be much lower than 65 WLM. The character of the dose-response relationship is basically similar to that seen

[c] The concentration of potential alpha energy of short-lived radon-222 daughters is sometimes expressed in units of Working Level (WL). This level corresponds to any mixture of these daughters which, upon complete decay, will emit alpha particles with total energy of $1.3\ 10^5$ MeV per litre of air ($2.08\ 10^{-5}$ J m^{-3}). The Working Level Month (WLM) corresponds to exposure to a mean concentration of 1 WL for the reference period of 170 hours. 1 WLM = 170 WL hours = $2.2\ 10^4$ MeV h m^{-3} = $3.5\ 10^{-3}$ J h m^{-3}.

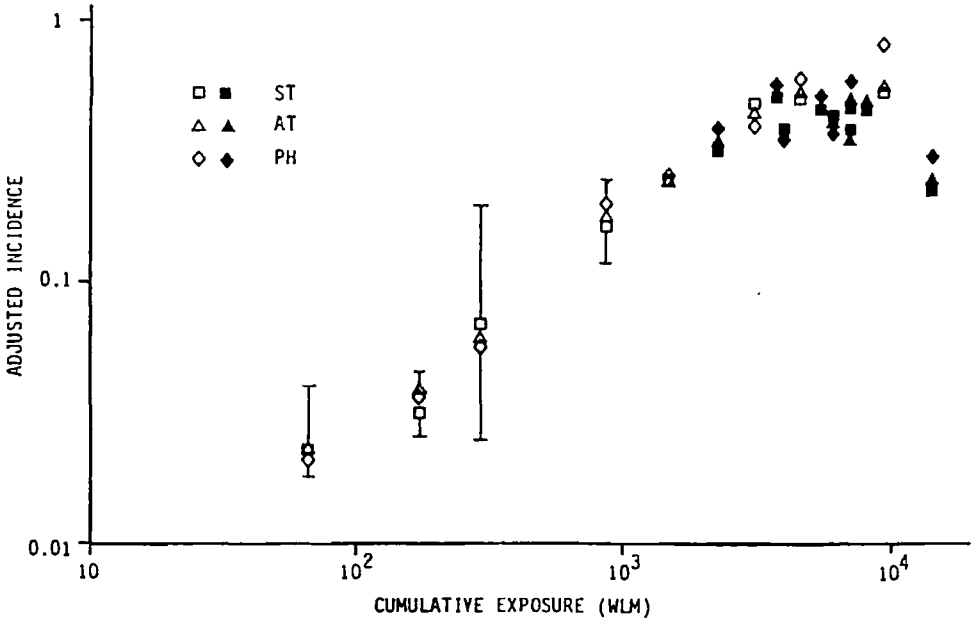


Figure XXI. Adjusted incidence of lung carcinoma in rats as a function of the cumulative exposure (WLM), calculated on the basis of three models: ST, time shift model; AT, accelerated time model; PH, proportional hazard model. Open symbols: exposure rate < 1600 WLM per month; Solid symbols: exposure rate > 1600 WLM per month.
[C34]

in uranium miners (chapter V). The loss of tumour-free life (the so-called "effect period" [U6]) was also studied in these rats as a function of cumulative exposure. Agreement between the models is less close than for the mortality-corrected incidence; however, linearity seems to prevail up to 1-2 10^3 WLM.

281. The actuarial incidence of lung carcinomas was studied [C38] in Sprague-Dawley rats, after whole-body irradiation with fission neutrons, and evaluated by methods of analysis similar to those described for radon-induced cancers [C34]. The neutron doses ranged from 0.012 to 8 Gy. The doses up to 2.3 Gy were delivered within 1 day and the higher doses were protracted over periods from 14 to 42 days to secure early survival of the animals. The time-related prevalence of pulmonary cancers was fitted to shifted-time and accelerated-time models and an actuarial incidence was calculated which did not depend upon the model chosen (Figure XXII). The dose-response relationship could be linear up to about 0.5 Gy. At higher doses, the curve does flatten, but does not decrease (actually, the absence of a decrease is due to correction for life shortening). In the low-dose range, the efficiency of neutrons versus radon in inducing pulmonary carcinomas exceeded 3 WLM/mGy. At higher doses, it was lower. Recalculation of this ratio in terms of lung doses, rather than exposures, indicates that the efficiency of neutrons, relative to alpha particles, is about 14 when expressed in terms of the bronchial dose and about 2 in terms of dose to the pulmonary parenchima [T3].

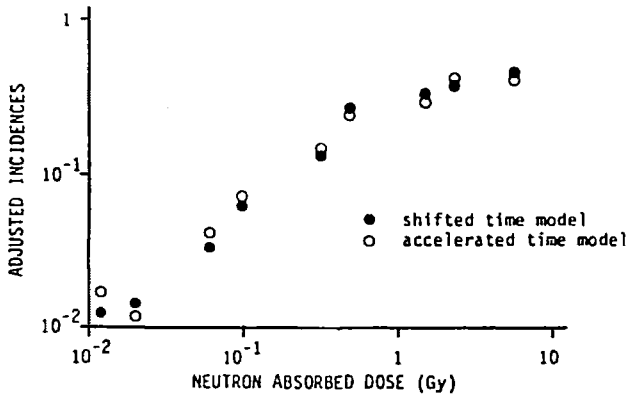


Figure XXII. Adjusted incidence of lung carcinomas in neutron-irradiated male Sprague-Dawley rats.
[C38]

282. An exhaustive review of lung cancer induction by inhalation of various radionuclides in different animal species was compiled by an ICRP Task Group and published as ICRP Publication 31 [13]. When the data from various experimental series were combined for an analysis of dose-response relationships a very wide scatter was apparent. Whereas for various alpha-emitting transuranic nuclides a linear fit to the data did not appear unreasonable, a linear dose-response relationship did not adequately describe the experimental points obtained for beta and gamma emitters. For these an upward concave dose-response relationship was typical.

7. Lung adenomas

283. Induction of benign lung adenomas in RF mice was studied [Y1] by locally-delivered, acute doses of x rays of between 2.5 and 15 Gy. The dose-response curve for tumours recorded 12 months thereafter, when plotted on a log-log scale, had a slope of 1 below 7.5 Gy and a steeper increase of the tumour yield at higher doses. In terms of a linear-quadratic model, this would imply induction of tumours by single-track kinetics in the lower portion of the curve

and two-track kinetics in the steeper region of the relationship. A split-dose experiment with fractionation intervals of 24 hours confirmed that the number of adenomas per animal was lowered by fractionation, but only above 7.5 Gy, where repair of interacting lesions would, theoretically, be expected.

284. Induction of lung adenomas by localized irradiation of the thorax with 300-kVp x rays and fast neutrons was also studied in 10-12-week-old female SPF RFM/Un mice [U21]. After 0.5 Gy of neutrons, the number of tumours per mouse at 6 months did not increase further and it was assumed that by 9 months it should have been complete. The doses of x rays ranged from 1 to 9 Gy and of neutrons from 0.05 to 1.5 Gy. The level of mortality did not influence the results substantially. For acute x irradiation, linearity could be excluded and the dose-response curve could be described by: (a) a linear-quadratic model with an initial negative linear slope ($P > 0.90$); and (b) a threshold model of the form $P(t:D) = c + a\,(D - D^*)^2$ ($P > 0.99$), where D^* is the threshold dose, estimated to be 2.47 Gy. For neutrons, the average number of adenomas per mouse rose about linearly to 0.25 Gy, peaked at 1 Gy, and then declined by a factor of about 2 toward 1.5 Gy. Over the range 0-0.25 Gy, the rise was approximately linear ($P > 0.50$). A proportionality to $\sqrt{D}$ could be rejected over this range ($P < 0.05$). Also a linear threshold model with threshold dose at about 0.07 Gy described the response within the range 0-0.25 Gy very well ($P > 0.99$). For the linear model, the RBE of neutrons increased from a value of 25 at 0.15 Gy neutrons to one of 40 at 0.01 Gy.

285. Splitting of the dose of either radiation into two equal fractions separated by 24 hours or 30 days was also tested [U22]. Under these conditions, there was a reduction in tumour yield for x-ray doses above 4.0 Gy, and the response tended to become more nearly linear. There was no difference between responses with doses split by 24 hours or 30 days. Recovery was complete by 24 hours, and amounted to 50% of the initial effect. After split neutron irradiation, no recovery could be seen. Linearity for all data combined over the range 0-0.25 Gy could not be rejected ($P > 0.8$), but better fits were obtained with a dose-squared model ($P > 0.99$) or with a model using a threshold dose at about 0.054 Gy. If it is accepted that decline of the tumour yield at high doses reflects killing of potentially transformed cells, then linearity over the range 0-0.25 Gy becomes rather improbable, as already discussed in chapter II. However, an alternative explanation of the slight upwards concave curvilinearity in the 0-0.25 Gy range could be a possible inverse relationship between latency and dose.

8. Ovarian tumours

286. Induction of ovarian tumours by x rays and neutrons was studied by Ullrich et al. [U2] using SPF RFM mice. An acute gamma-ray exposure (0.4 Gy min^{-1}) induced various types of ovarian tumours, and their age-corrected incidence increased rapidly over the dose range 0-0.5 Gy. At higher doses, there was a plateau of the response with a marginal rise of tumour incidence with increasing doses. Over the range 0-0.5 Gy linear and dose-squared non-threshold models could be rejected ($P < 0.01$) while a linear-quadratic model with a negative linear component adequately described the relationship ($P > 0.25$). Since, according to the authors, no biological meaning could be attributed to such a model, threshold models were tested and a linear one was again rejected ($P < 0.01$). However, a threshold dose-squared model (threshold estimated to be 0.12 Gy) provided a satisfactory fit ($P > 0.75$) over the dose range up to 0.5 Gy. At 0.08 Gy per day, a significant incidence was seen at 1 Gy, where it corresponded to that seen after 0.25 Gy acute exposure. Again, non-threshold linear and dose-squared models could be rejected ($P < 0.01$) as well as the threshold dose-squared one. An adequate fit was obtained for a threshold linear model with a threshold dose of 0.7 Gy and a linear-quadratic model with an initial negative linear slope (significantly negative at the 5% level).

287. After neutron irradiation [U5], the ovarian tumour incidence in RFM mice was lower at 0.01 Gy per day than at 0.05 and 0.25 Gy min^{-1} for all dose levels. The decline was attributed partly to the reduction of the dose rate and partly to an age-related decrease of susceptibility. This suggests that a true dose-rate effect was perhaps observed in this tumour system after high-LET irradiation.

288. Ullrich [U23, U25, U26] studied the age-corrected incidence of all ovarian tumours (granulosa cell tumours, luteomas, tubular adenomas) in BALB/c female mice, induced by gamma radiation and fission neutrons. High-dose-rate gamma irradiation (in the range 0.1-2 Gy) increased the incidence steeply from control levels (about 2.5%) at 0.1 Gy to 77% at 0.5 Gy, with a plateau at higher doses. As previously observed for RFM mice, the dose-response relationship was consistent with a threshold model, and the linear, dose-squared and linear-quadratic models could be rejected ($P < 0.01$). Irradiation of BALB/c mice with fission neutrons (0.025-2 Gy) led to a steep increase in the incidence of ovarian tumours from control level at 0.025 up to 76% at 0.5 Gy, with a slight decline towards 2 Gy. Over the dose range 0-0.5 Gy, a variety of dose-response models could describe the data, including the non-threshold models (linear-quadratic, dose-squared) and a threshold-type model. The linear non-threshold model could, however, be rejected ($P < 0.01$). A threshold model would be consistent with both the postulated role of non-stochastic mechanisms involved and the data for gamma radiation. Because of the apparent threshold, at low doses any estimate of RBE is meaningless. From 0.2 Gy upwards the RBE is close to unity [U25]. Splitting the neutron dose at 24-hour and 30-day intervals was ineffective, the data being practically indistinguishable from the single-dose series. At protracted exposures, the neutrons were less effective than when delivered acutely but, for instance, 0.4 Gy yielded the same result whether delivered over 4 or 40 days. This indicates that the difference with regard to acute exposure is a true dose-rate effect and not a change of susceptibility to tumour induction with age. The observation is similar to that for the RFM mouse, but no explanation is available.

289. In other experiments [Y2], mice received a series of x-ray doses over a variable time T and the animals were followed for incidence of ovarian tumours. The results were later re-analysed [K8] on the assumption that the cumulative net incidence (prevalence) is described by the equation

$$F(t) = f[\alpha_1 D + q(T)D^2] \qquad (4.1)$$

where the form of the function is left undecided and q(T) is a reduction factor for recovery of the damage with protraction of irradiation. The optimal fit to the data was obtained for an assumed exponential decay of the sublesions T = 15 h. The optimum value for α_1 for the linear term was zero, and α_1/α_2 quotients greater than 0.04 Gy in terms of the linear-quadratic model could be excluded when data were corrected for time-dependent repair using non-linear optimization. In essence, no linear component could be found, and incidence was proportional to the square of the dose over a wide dose range.

9. Pituitary gland tumours

290. In female RFM mice, pituitary tumours increased irregularly with gamma-ray dose over the range 0.05 to 3 Gy (0.45 Gy min^{-1}) and the age-corrected incidence was not significantly different from control. A linear-quadratic response adequately described the data ($P > 0.6$), but a linear response could not be excluded ($P > 0.2$) [U2]. In male mice, the effect was so slight that the dose-response could not be investigated. Lowering the dose rate (0.083 Gy per day) caused a less efficient induction of pituitary tumours in the same mice [U3]. If a linear-quadratic response was assumed at high dose rate, the linear component was very similar under both conditions and the lower dose rate eliminated the contribution of the dose-squared component. Neutrons induced a large number of pituitary tumours with an RBE greater than 5. A dose rate of 0.01 Gy per day appeared as effective as 0.05 and 0.25 Gy min^{-1} up to 0.2 Gy, but rather less effective at 0.47 and 2 Gy.

10. Harderian gland tumours

291. These tumours were induced by gamma rays in both male and female RFM mice, and the response in the two sexes was very similar. The data on age-adjusted incidence appeared to fit best a linear-quadratic model ($P > 0.25$ and > 0.99 for females and males, respectively), but linearity could be excluded only for females ($P > 0.05$). The low-dose-rate gamma irradiation substantially reduced the incidence of tumours, and a good fit ($P > 0.90$) to the equation was obtained with the same linear coefficient as for high dose rate but without a dose-squared term [U2, U3]. The same tumours showed a marked sensitivity to induction by neutrons, with an approximately linear increase in age-adjusted incidence as a function of dose up to about 0.5 Gy, with a plateau at 1 Gy and a decline at 2 Gy. No significant effect of the dose rate was observed [U5]. When the age-adjusted incidence of harderian gland tumours was studied in whole-body x-irradiated CBA mice [D3] it was found that the dose-response curve rose as a function of dose up to 3 Gy (there were, however, only 3 points) and then became flat. Correction of these data for cell killing (a survival curve was determined independently) resulted in a dose-response curve per surviving cell which rose with the square of the dose between 1 and 7 Gy.

11. Skin tumours

292. Skin cancer can be induced in experimental animals, mostly CBA mice and CD rats, by both densely- and sparsely-ionizing radiation, and relevant experiments were reviewed in the 1972 and 1977 UNSCEAR reports [U6, U7]. For both species, highly curvilinear dose-response relationships were reported for β particles and high-energy electrons [B59, H12, H13] as well as for accelerated (40 MeV) helium nuclei, which also produced a curvilinear response in CD rats [B59]. From detailed considerations of depth-dose distribution versus efficiency of cancer induction, and from the association of the latter with damage to the hair follicles, it was concluded that radiation-induced skin cancer in this latter strain is likely to originate from cells located in the follicles.

293. The induction of epidermal and dermal skin tumours was again studied in 3-month-old female CBA/CaH mice (3125 exposed, 612 controls), irradiated locally over one-third of their skin surface (mid-torso) by β particles emitted from a ^{204}Tl source [H33]. The radiation neither penetrated the abdominal wall nor reached the bone marrow. Tumorigenic doses were taken to be 75% of the nominal dose at the body surface for epidermal tumours, and 65% for dermal ones. The nominal doses ranged from 5.4 to 260 Gy, and the dose rate varied from 2 to 0.017 Gy min^{-1}. Most tumours arose well within the irradiated area and only a few at the edge. Over 70% of all tumours were dermal (fibromas and fibrosarcomas), and about 60% of the dermal and epidermal ones were malignant. It was confirmed histologically that fibromas could become malignant, and multiple tumours were noted in 12-15% of tumour-bearing mice irradiated at the highest rates. The incidence of tumours was expressed per unit area of skin. Reduction of dose rate from 1-2 to 0.11-0.22 Gy min^{-1} did not alter the incidence appreciably; at 0.05-0.08 Gy min^{-1}, the incidence of epidermal tumours was reduced at all except the highest doses (120 Gy).

294. The incidence of dermal tumours began to increase significantly with doses to the dermis of about 16 Gy and rose steeply into a plateau above 60 Gy. The incidence of epidermal tumours increased significantly and then rose steeply when the dose in the epidermis exceeded 21 Gy. The peak incidence was reached at 60 or 100-120 Gy and fell at still higher doses. At exposure rates of 0.017-0.024 Gy min^{-1}, no epidermal tumours occurred and the incidence of dermal tumours was very much reduced. At lower rates, therefore, a range of high doses was ineffective in producing skin tumours. The dose-response curve resembled those typical of non-stochastic effects, with an apparent threshold at about 10 Gy.

295. The series irradiated at the highest dose rate (1.1-2.2 Gy min^{-1}) had sufficient statistical power to distinguish between various dose-response models. The observed incidence was fitted to a series of models incorporating both initiation and cell-killing terms at various powers of dose, as well as threshold doses [P21]. From a rather elaborate analysis it was concluded that only one non-threshold model could not be discarded, and this was for induction of epidermal tumours with a very high exponent of dose (about 4) in the induction term. The incidence above apparent thresholds usually rose very steeply with dose. The authors suggested that the apparent thresholds may be due to some relatively radioresistant factor in the skin that restrains potential tumour cells, and that this factor can be overcome by very high doses, and also perhaps by aging.

296. In CD rats, the incidence of tumours over the ascending part of the curve rose roughly with the fourth power of the electron dose [B59, H12, H13] and with the square of the dose of alpha particles [B59]. However, these conclusions are only approximate, because the data were insufficient for more detailed analysis. The value of the RBE of alpha particles at about 1 tumour per animal, relative to high energy electrons, was roughly 3. The peak incidence of skin tumours always occurred at several tens of Gy of sparsely-ionizing radiation.

297. Fractionation of the electron dose [B57, B58] showed that suboncogenic damage was repaired with a half-time of about 4 hours. This observation suggested that the repair process was operating at the cellular level, as for sublethal damage. Experiments on the influence of dose fractionation were also made with 10-MeV protons [B56]: when fractions were separated by 24 hours, a reduction of the effect was interpreted as showing complete repair of recoverable damage. It was concluded, therefore, that for skin tumour in CD rats 10-MeV protons have the usual characteristics of both high- and low-LET radiation: an RBE of about 3, typical for the former, but recovery at fractionation and yield of the effect proportional to a power of dose greater than one, typical for sparsely-ionizing radiation.

298. It is difficult to say to what extent skin cancer induction in rats is an adequate model—qualitatively or quantitatively—for man. A relatively low sensitivity of human skin to cancer induction by radiation was noted in annex G of the 1977 UNSCEAR report [U6] and in the BEIR III Report [C29]. On the other hand, histogenesis of most skin cancers in rodents is different from those of the human skin [L8]. Albert, Burns and Shore [A4] suggested that radiation-induced cancers in CD rats, and in children irradiated for tinea capitis, show similarities in the distribution of the latent periods when time is normalized for both species to their mean life spans. However, the fractions of total skin surface irradiated were different in animals and in children, so that any similarity could be fortuitous.

299. On the basis of data in CD rats, Vanderlaan et al. [V1] proposed a mathematical model of skin cancer induction by ionizing radiation. The model is based on the hypothesis that radiation can initiate a cancer by converting normal cells (S_1) to potentially malignant cells by one of two routes: a reversible route involving two steps ($S_1 \rightarrow S_2 \rightarrow S_3$, the reversible stage being S_2) and an irreversible single-step process ($S_1 \rightarrow S_3$). It was assumed that the initiation process takes place in single cells but its nature was not specified. Cells in the intermediate stage S_2 can revert to the normal state S_1 at a rate λ assumed to be constant and independent of dose. The probability of developing carcinoma of the skin was assumed to be proportional to the number of irreversibly transformed cells S_3. Expression of the latter as a function of time after irradiation was obtained from solution of a pair of differential equations. The solution showed that the relationship of cumulative incidence versus dose was dominated by the dose-squared component. In this model, the relative values of the linear and squared components are not predicted by LET or any other microdosimetric consideration. From experimental observations, Vanderlaan et al. [V1] concluded that, after a dose-independent tumour-free interval, throughout the remaining life span the tumours appear at an approximately constant rate, directly proportional to the dose. However, the experimental data show a considerable scatter for all radiations used.

300. From fractionation experiments, a decrease of unrepaired damage with time was deduced, with a half-life of about 4 hours. For estimation of the dose-rate effect on the yield of tumours, a dose-rate factor DRF (the ratio of acute to protracted dose for the same yield of S_3 cells) was calculated, and it was predicted that the reduction of the carcinogenic response at low dose rate would be very pronounced. This was confirmed in fractionation experiments with 0.8-MeV electrons [A18], showing that weekly exposure to fractions of 2 Gy per week (130 Gy in 65 weeks) yielded the same incidence as a single exposure to 15 Gy.

301. In conclusion, all the data discussed above suggest that linear extrapolation of skin cancer risk from the rates observed at high acute doses to the low-dose range would greatly over-estimate the risk. To what extent these conclusions might apply to man is still, however, an open question.

12. Bone tumours (internal irradiation)

302. Although the data discussed in the following paragraphs are often referred to in terms of the average skeletal dose, it should be borne in mind that the relevant dose for the effects in question is that delivered to the bone-lining cells. The crude incidence of bone sarcoma induced by ^{239}Pu, ^{249}Cf, ^{252}Cf, ^{241}Am, and ^{226}Ra was compared in C57Bl/Do mice and albino mice [T22]; the data seemed compatible with linearity of the dose-response relationships for all radionuclides. However, the scarcity of data points for each series makes this conclusion at best tentative. It will be recalled that linearity of the dose-response was also seen earlier for bone sarcoma induction by ^{226}Ra in CF1 mice [M69].

303. The question of a practical threshold in bone sarcoma induction following internal irradiation by bone-seeking radionuclides was raised originally by Evans [E4]. This issue was addressed again by a study of Raabe et al. [R32, R40] who tested the hypothesis on the basis of results on beagle dogs. Two groups of animals were given: (a) ^{226}Ra in 8 fortnightly injections of graded activities, the median age during the injection period being about 14.5 months, to simulate the human experience with radium; and (b) ^{90}Sr by continuous feeding at various levels of ^{90}Sr/Ca ratio from mid-gestation through 540 days of extra-uterine life, to simulate the human contamination from the environment.

304. On inspection, the mortality data showed that at higher dose levels survival declined as the dose rate to the skeleton increased. The mean latent period of osteosarcomas varied inversely with the time-averaged dose rate calculated for individual animals from periodic measurements of whole-body activity (Figure XXIII). When the survival period t was plotted against the mean dose rate to the skeleton, the data could be fitted to the relationship $t = K D^{-S}$, where K and S were parameters determined by a least-squares procedure. When a log-normal distribution of times to death from osteosarcoma for a given dose rate was assumed (on the basis of empirically tested distributions), K and its geometric deviation ($\pm \sigma_g$) for radium and strontium-90 were 2500 ($\pm$ 1.24) and 8400 ($\pm$ 1.72), respectively. The corresponding values for S $\pm$ S.E. were 0.29 $\pm$ 0.01 and 0.77 $\pm$ 0.05. For 116 and 27 dogs dying with malignant bone tumours in groups given radium-226 and strontium-90, respectively, the fit to the function was good, with correlation coefficients of 0.92 and 0.95.

305. From inspection of the regression lines, it appeared that, if the relationship held down to the lowest dose rates, there must be latent periods in the low-dose range exceeding the normal life span. A practical threshold was therefore defined as the dose rate corresponding to the intersection of the regression line log(t) versus log(D) (Figure XXIII) minus three geometric standard deviations of the mean survival time t for control dogs. For dogs injected with ^{226}Ra, the threshold dose rate so defined was 0.11 mGy per day, corresponding to a lifetime dose of 0.5 Gy and a probability of about 0.7% of incurring a sarcoma towards the end of life. Corresponding values were not given for ^{90}Sr-contaminated animals but they would be expected to exceed the values for radium by one or two orders of magnitude.

306. The S values derived from dogs injected with radium were used to fit the data on latency and skeletal dose rate in women dial painters and in RFM mice. There was a high degree of correlation between the species' average life span L (years) and K values calculated for each species according to the relationship

$$K_m = [655 \pm 57 \text{ (S.E.)}] + [119 + 1 \text{ (S.E.)}] L \quad (4.2)$$

It could be concluded that a practical threshold for ^{226}Ra in man is 0.039 mGy per day and a total dose of 0.8 Gy. The relative effectiveness of ^{90}Sr and radium, in terms of doses inducing equal effects in dogs, was also estimated; it varied in some proportion to the average dose from ^{90}Sr to the skeleton. If this relation holds down to the lowest doses, a practical threshold of dose rate and cumulative dose for ^{90}Sr would be at least one or two orders of magnitude greater than those for ^{226}Ra.

307. The same methodology was applied [R40] to a study of relative effectiveness for the induction of bone sarcoma in young beagles injected with nine α-emitting bone-seeking nuclides. All nine studies showed, with relatively good precision, a three-dimensional, log-normal, response relationship represented in two dimensions by the equation $t = KD^{-S}$. S was found to be, on average, 0.29 ($\pm$ 0.01 S.E.) for all radionuclides.

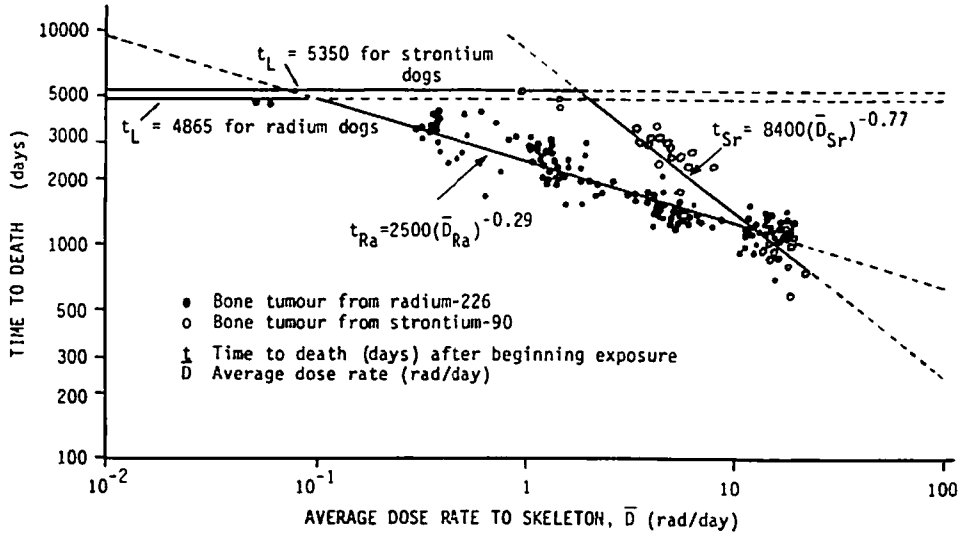


Figure XXIII. Comparison of the dose-response relationships for radium-226 and strontium-90 in beagle dogs that died of primary bone cancer. The data show the median time, t_L, of spontaneous deaths among unexposed controls and the fitted functions in irradiated animals. [R32]

A practical threshold dose or dose rate, below which bone sarcoma deaths are very unlikely, is suggested at low dose rates for all these radionuclides, just as it was reported for ^{226}Ra [R32]. Mean skeletal doses at which the defined practical threshold was reached were lower than for ^{226}Ra (0.5 Gy) by the following factors: ^{228}Ra, 3.0; ^{241}Am, 6.4; ^{249}Cf, ^{252}Cf, ^{253}Es, 6.6; ^{239}Pu, 9.0; ^{228}Th, 10.7; ^{238}Pu, 15.5. If these factors were expressed in terms of the doses to the bone-lining cells, their spread would be considerably reduced.

308. The reasoning of Raabe et al. [R32] is based on an empirical linear regression of survival times versus mean skeletal dose rate in animals dying with, or due to, malignant bone tumour. However, in the low-dose-rate groups and among the controls a majority of animals were still alive at the time when the experiments were evaluated. There is some uncertainty in the data as to the mean survival values and their distribution among control animals. The data could also change somewhat as a result of further follow-up. The derived practical thresholds must therefore be treated as tentative at best and any final assessment must be deferred. Moreover, any hypothesis regarding species-related interpolation of the risk neglects differences in susceptibility to the induction of bone sarcoma among various strains of mice and breeds of dogs. Alternative interpretations of the data were presented by Mays [M69]. However, the concept of a practical threshold for bone sarcoma is important for risk assessment, because, if extrapolation of the basic relationships is correct, there must be values of the dose and activity at which no radiation-induced life shortening occurs, and therefore the somatic component of the index of harm [16] can be taken to be zero.

309. Osteosarcoma induced by ^{239}Pu in 294 beagle dogs of both sexes was studied following single injections at ages between 400 and 800 days [W14]. The activity injected ranged up to about 0.11 MBq/kg body weight, in 7 groups of animals [M11]. Times at death due to osteosarcomas were fitted to the Weibull distribution function and described in terms of cumulative hazard or hazard rate, in both cases as a function of time after injection. The power functions of time for cumulative hazard or hazard rate corresponding to R(t,D) and r(t,D) for tumours detected at death in individual injection groups were fitted to the data by a most likelihood method. The plots on a log-log scale were virtually parallel for all groups, and therefore the proportionality constants of the lines could be analysed as a function of the injected activity of ^{239}Pu. Below 37 kBq/kg, there was a strong inverse relationship between the injected activity of plutonium and the time at which a given value of R(t,D) was reached. At the highest injection level the hazard was lower than in the preceding group, probably due to cell killing or some other non-stochastic effect. When the highest activity level (0.095 MBq/kg) was discarded, the data for R(t,D) (below 37 kBq/kg) gave an acceptable fit to a pure quadratic model ($P = 0.19$) and linearity could be rejected ($P < 0.001$). A model containing both a linear and a quadratic component did not fit the data better than the quadratic one, where R(t,D) depended also on time after injection to the power of 5.9.

310. The same data were studied in parallel [W14] by the generalized Marshall-Groer model for bone sarcoma induction [M4] (see V.E.2 for details). The solution of the model showed lack of a linear component in the relationship between effect and cumulative dose. The best fit was obtained for a quadratic relationship between dose and R(t,D) for osteosarcoma. Since many animals injected with the lower activities are still alive, a linear contribution to the dose-incidence relationship might still appear after further follow-up. When the same data [P17] were treated in terms of a non-parametric proportional hazard relative risk model, both a linear and a quadratic function could be fitted to the data and neither could be excluded. However, if—as was legitimately done by Whittemore [W14]—the data for the highest injection level are omitted, the results again support a roughly quadratic rise of the relative risk with injection level.

311. An experiment has been completed [W19] on 160 young beagle dogs, injected at the age of 17 ± 2 months with saline (controls, 44 dogs) or with increasing amounts of ^{226}Ra (8 levels from about 260 Bq to 370 kBq/kg). The average α-particle dose to the skeleton varied from 0.35 to 190 Gy. Most of the primary bone tumours were osteosarcomas. Bone sarcoma incidence was a monotonically increasing function of the dose up to 70 Gy. The dose-response fits well a linear non-threshold model over the six lowest dose ranges with a slope of 3.3% per Gy. No tumours were found in the controls or in the 0.35 Gy group, but 1 tumour over 25 dogs was found in the next group with a mean skeletal dose of 0.85 Gy. No significant change in bone tumour incidence was seen among the three highest dose levels at which the incidence exceeded 90%, and the life span was considerably shortened. There was very little, if any, life shortening at the five lowest levels up to 9.5 Gy.

13. Liver

312. Liver tumours were induced in Chinese hamsters by ^{239}Pu citrate injection, and the crude incidence for the few dose points available suggested an initial approximately linear rise up to 2.7 Gy at the time of 50% survival. At the highest dose of 14 Gy, the effectiveness per unit dose was much lower [B87].

313. The dose-response relationship of injected thorotrast was studied in female Wistar rats for the sum of liver and spleen tumours [W15]. In some of the experimental groups, the preparation was enriched with ^{230}Th in order to study the influence of the mass of injected colloidal thorium dioxide. For a constant dose rate (activity), an increase in mass by a factor of 10 proved more effective in respect of life shortening. When the crude percent incidence (I) of all benign and malignant liver tumours was plotted against the relative dose rate ($\dot{D}$), a linear dose-response relationship was observed: $I(\dot{D}) = 3.3 \pm 0.79\ \dot{D}$ with a correlation coefficient of 0.97. The I value at $\dot{D} = 0$ does not differ essentially from the observed control incidence of 2.7%.

14. Combined tumour data and indirect inferences

314. Life shortening by radiation was reviewed in depth in the 1982 UNSCEAR report [U24]. It was concluded that, in the intermediate- and low-dose region, life shortening is due essentially to a higher tumour mortality. This does not mean, of course, that dose-response relationships for both endpoints are directly comparable, because, even for the same radiation, the mean latent period of some tumours varies with dose, dose rate, age at exposure, etc. However, if life shortening is the major consideration, then comparison of results from various dosage schedules for the same radiation and in the same strain of animals could provide some indication as to what the comparative incidences and/or latent periods might be. This seems particularly interesting for neutrons, for which no human data are available.

315. Life shortening and incidence of various diseases, including leukaemias and malignant tumours, were studied in male BALB/c mice [M62] after single and fractionated doses of gamma rays split into 10 equal fractions delivered at intervals of 1 day. The doses ranged from 0.25 to 6 Gy. The causes of death were ascertained by autopsy and histological examination, and actuarial incidences were calculated, with correction for competing risks. In general, single exposures were more effective than fractionated ones with regard to life shortening. Over the whole range of doses, the incidence of all leukaemias and cancers combined appeared significantly higher after fractionation. However, the dose-responses were very flat and included more than 70% of spontaneous cancers. For all carcinomas and sarcomas, except lung carcinomas (for which the spontaneous incidence in BALB/c males is very high), a higher effectiveness of fractionated doses was seen only after doses above 1 Gy.

316. These observations must be taken with some caution, due to the very high spontaneous tumour incidence; to the lack of statistically significant differences between incidences of individual tumours after two modes of irradiation; to the generally flat dose-response relationships; and to the fact that, as shown by Storer [S53], this strain has a number of significant associations between various tumours. Finally, the effect of single and fractionated gamma-ray doses upon life span was opposite to that seen for combined cancer incidence, showing, perhaps, that in this case a specific combination of induction and acceleration of some tumours could have played a significant role.

317. Whereas incidence of all carcinomas and sarcomas combined (except lung carcinomas) showed a negative trend after single doses of gamma rays on the same strain [M63], an almost linear increase was seen after single doses of d(50)-Be neutrons in the range from 0.02 through 3 Gy.

318. Life shortening of B6CF1 mice was studied by single, fractionated (short- and long-term), and lifelong exposures to gamma rays and fission (0.85 MeV) neutrons [T20, T21, T25]. When survival data were compared for doses given in 24 weekly fractions or as single exposures, the effectiveness of gamma radiation was consistently decreased by fractionation. However, for neutrons the same fractionation scheme increased the effect throughout the whole range of doses, down to 0.05 Gy. It was argued, therefore, that neutron fractionation in the intermediate- and high-dose range led to an increased incidence of tumours, or their earlier appearance, or both.

319. Thompson et al. [T26] recently published new additional data on life shortening induced by single exposures of B6CF1 female mice to fission neutrons in doses down to 0.01 Gy. They concluded that the assumption of a response proportional to $D_n^{0.5}$ grossly overestimated the life shortening induced by 0.01-0.03 Gy of neutrons and that the data up to 0.1 Gy of neutrons were best fitted by a linear dose-response relationship. The limiting value for the RBE fission neutrons compared with gamma rays was in the region of 12 to 16, depending upon the method used to analyse the data. No consideration was given in any of these publications to RBE values at low doses for fast neutrons as compared with the standard reference radiation, i.e., x rays of about 200 kVp.

320. In another experiment [S57], life shortening was studied in female BALB/c mice exposed to single doses of fission neutrons (mean energy 1.3 MeV) or given into two equal fractions at either 1- or 30-day intervals (whole-body doses from 0.02 to 2 Gy). Protracted exposures from a ^{252}Cf source were also used at rates from 1 to 100 mGy per day (total 0.025 to 0.4 Gy). Life span was considerably shortened between zero and 0.5 Gy for both single and fractionated exposures, and then a plateau ensued. The data were fitted by a linear and a square-root model. Both models adequately described the results below 0.4-0.5 Gy for single, fractionated and protracted exposures, with the exception of a 30-day protraction scheme where the square-root model could be rejected and the linear one still provided a good fit. In contrast with the observations in $B6CF_1$ mice, no increase in effectiveness on life shortening was observed for fractionation and protracted exposures to neutrons below 0.5 Gy. Only at 0.5 and 2.0 Gy was a significantly increased effect of fractionated doses observed.

321. Storer and Mitchell [S62] analysed published data from the Oak Ridge and Argonne laboratories on the shape of the dose-response curves for life shortening induced by single exposures to fission neutrons at doses from 0.025 to 0.2 Gy and by fractionated exposures resulting in total doses up to 0.8 Gy. The response was found to be proportional to $D_n^{0.9}$ to $D_n^{1.0}$, and not to the function $D_n^{0.5}$, which does provide a reasonable description of the dose-response curve at higher neutron doses. The limiting RBE of fission neutrons compared to gamma rays was found to be 18-29 if the response were proportional to $D_n^{0.9}$ and to be 13-22 in the equally likely event that the response were proportional to $D_n^{1.0}$. The range of RBE in both cases was determined by the strain and sex of the mice. Thus, the most recent publications [S62, T26] suggest that a linear dose-response model rather than a square-root model is appropriate at low neutron doses.

C. SUMMARY AND CONCLUSIONS

322. On the assumption that cancer is initiated by lesions in the genome of a single and relatively autonomous cell, the kinetics of induction of point mutations and chromosomal aberrations, mostly symmetrical translocations, could perhaps throw some light on the form of the dose-response relationship for cancer initiation. Studies of cell transformation in vitro could also provide some information in this respect. These end-points cannot, however, provide insight into other factors affecting tumour development at the tissue and systemic level: thus, the relevant conclusions must be regarded as over-simplifications of the real situation.

323. The dose-response relationship for point mutations induced by low-LET radiation in mouse male and female mouse germ cells appears to be curvilinear (upward concave). It also appears to be greatly dependent on dose fractionation and protraction as a result, at least in part, of repair of primary damage at the cellular level. At very low dose rates, linearity and independence of dose rate have been observed. For high-LET radiation the usual form of the curve is linear for all dose rates; fractionation and protraction effects are marginal or absent. Under these conditions, linear extrapolation from high and intermediate doses delivered at high dose rates, down to low doses and dose rates, would over-estimate the mutation rate by sparsely-ionizing radiation. For high-LET radiation, a linear extrapolation provides an adequate estimate of the risk.

324. The induction of somatic mutations in the stamen hair of the plant Tradescantia was studied over a wide range of doses, dose rates and radiation qualities. This system provides direct and extensive information at very low doses of x and gamma rays and of neutrons. The relevant dose-response relationships fit very well a linear-quadratic model for low-LET radiation and a linear model for neutrons.

325. Data on various other types of somatic mutations are also available in several established and early-passage mammalian cell lines. For x- or gamma-ray doses delivered acutely, the observed dose-response relationships are mostly curvilinear, with pronounced fractionation effects in the few instances tested. Exceptions showing linear responses (e.g., human fibroblasts) are also found, showing that the shape of the curves depends on the biological characteristics of the cells. High-LET particles induce mutations in a linear proportion to dose. Sub-mutational damage is readily reparable after low-LET radiation but not after high-LET particles. Studies in several cell lines show a simple inverse relationship between the induction of somatic mutations by low-LET radiation and the logarithm of cell survival. This must imply that linearity of the observed response is accompanied by simple exponential cell survival. Since for low-LET radiation this is an exceptional finding in mammalian cells, the inverse relationship between survival and mutation must, as a rule, imply an upward concave dose-response for induction of somatic mutations, similar to that described for Tradescantia.

326. For low-LET radiation, data on chromosomal exchanges in germinal and somatic cells are, almost without exception, in agreement with a linear-quadratic model, both in respect of dose and of time-dose relationships. For terminal deletions, linearity would, in theory, be expected for all types and dose rates of radiation, but curvilinearity is often seen in some cells (e.g., lymphocytes). This is attributed to the difficulty in distinguishing between terminal and interstitial deletions that have linear and quadratic relationships, respectively, with resulting curvilinearity of the response for both types combined. For high-LET radiation the response is linear and practically unaffected by dose protraction or fractionation.

327. Much work has been done over the last few years on radiation-induced oncogenic transformation in vitro of several established and some early-passage mammalian cells. Numerous factors affect the observed transformation frequency. These include: cell density at irradiation and post-irradiation; cell-cycle stage; time between seeding and exposure; phase of growth at exposure; mitotic delay; and promoting and inhibiting agents. The experimental model appears to be much more complex than originally envisaged for cells in culture, and cell-to-cell influences are found to be present.

328. Cells irradiated with a wide range of doses and types of radiation show dose-response curves that have some features in common with those reported for tumour induction in animals. These are: an initial rise of the transformation frequency with dose up to a maximum and an ensuing decline or plateau; a higher transformation efficiency by high-LET radiation; and a decline of the transformation yield by low, as opposed to high, dose rate of gamma rays in cells irradiated in culture 40 hours or later after seeding. An enhancement of the oncogenic transformation in vitro by a reduction of dose rate of fission neutrons at low and intermediate doses is similar to that which has been described in some, but not all, experiments on tumour induction (or life shortening) in animals.

329. However, several features of the single-cell studies are at variance with animal studies. These are mostly for cells irradiated shortly after seeding: a shallow rise of the transformation rate over the range of intermediate doses, with a power of dose less than unity; an enhancing effect of low dose rate and dose fractionation for low-LET radiation for a fractionation interval of about 5 hours at doses below 1.5 to 2.0 Gy, with reduced transformation at higher total doses. These results most probably indicate a non-homogeneous sensitivity to transformation of the irradiated cells, due to the non-random distribution of cell-cycle stages in freshly seeded cells. If so, they would not be representative of most situations in vivo.

330. The above results were sometimes interpreted to imply that linear extrapolation to zero dose from the transformation frequency at high doses could lead to an under-estimation of the effect at doses below 0.5 Gy, particularly for fractionated and protracted exposures. For the time being, however, while taking note of the complexities referred to above and of the

enhancing effect of fractionation, UNSCEAR does not encourage a direct projection of the in vitro data to the situation in vivo, particularly when irradiation is performed early after seeding. Further analysis of various culture conditions, and a better understanding of the mechanisms of initiation, oncogenic transformation and progression in vitro, is required for meaningful extrapolations to tumour induction in vivo. It appears likely that results obtained from asynchronous cell cultures (i.e., those irradiated later than about 40 hours after seeding) and those irradiated in density-inhibited state may more adequately represent the situation in vivo.

331. New dose-response relationships for a variety of tumours generally support the conclusions reached in the 1977 UNSCEAR report, the most important being the specificity of the response for each tumour-host system. The new experiments enlarge the data base, particularly at the lower end of the dose scale, down to 150 mGy of gamma rays and to a few tens of mGy for neutrons. They justify more specific statements than hitherto possible about the form of some dose-induction relationships.

332. For sparsely-ionizing radiation, most curves are upward concave and may be fitted by linear-quadratic or quadratic (leukaemia in CBA/H mice) models, but in some cases approximate linearity may apply. This is so with mammary fibroadenoma and carcinoma in Sprague-Dawley, adenomas in WAG/Rij and carcinomas in AC rats, thymic lymphoma in RFM mice, and lung adenocarcinoma in BALB/c mice. Thymic lymphomas in most mouse strains and tumours with a pronounced hormonal dependence (e.g., ovarian tumours), show curves with pronounced thresholds. They may reflect the role of non-stochastic mechanisms in the development of these tumours, such as the need to inactivate a large proportion of hormonally-active cells in the ovary, or to kill a large proportion of cells in the thymus.

333. The incidence of the so-called reticulum cell sarcoma after whole-body irradiation usually declines with increasing dose in several mouse strains. Animals protected from early radiation death, by either bone-marrow transplantation or partial marrow shielding, show a very low incidence of this neoplasia. It has been suggested that by relating the number of induced tumours in these animals to the number of irradiated marrow stem cells at risk (assumed to be the targets for tumour induction) it may be possible to estimate in vivo the incidence of tumours per cell at risk. The x-ray dose-response curves obtained under these assumptions are curvilinear (upward concave).

334. Induction of skin cancer in rats and mice by local low-LET irradiation requires high doses. The dose-response relationships are therefore grossly curvilinear (upwards concave) and apparent or real thresholds cannot be excluded. Fractionation and protraction of doses greatly reduces the carcinogenic action of radiation in the skin of rodents.

335. Dose-rate studies with sparsely-ionizing radiation almost invariably show a decreased incidence with decreasing dose rate. In some instances (lung adenoma in RFM and BALB/c mice and harderian or pituitary tumours in RFM female mice), lowering the dose rate results in a more nearly linear dose-response relationship in which the dose-squared component is substantially reduced or abolished.

336. For neutrons, the ascending slopes of the dose-response curves are closer to linearity than for gamma rays. However, in some cases (lung adenoma in RFM mice), curvilinearity is suggested at low doses, even though linearity cannot be excluded. Factors such as a dose-related latency may perhaps contribute to this curvilinearity. In other cases, neutron-induced tumours rising with a power of dose less than unity have been confirmed at low doses. The downward concave shape may be accounted for by killing of potentially neoplastic cells.

337. For most tumours, either no effect, or an enhancement of the tumour yield by a lower neutron dose-rate or fractionation, has been documented. At low and intermediate neutron doses, such effects are less pronounced than for x rays. At high doses, an enhancement of tumour incidence by fractionation or protraction is often observed, but the overall picture is not as simple as cellular data might imply. Factors operating at the tissue level, or perhaps systemic influences, could modify the final tumour appearance to some extent.

338. Pulmonary carcinomas induced by low doses of inhaled radon and of neutron irradiation show an essentially linear non-threshold relationship with cumulative exposure or dose, respectively. High exposure rates of radon daughters at high total exposures are, however, less efficient than low rates. For neutrons also, the effectiveness per unit dose decreases at high doses. These observations are in line with results of epidemiological studies in miners exposed to radon daughter products.

339. Analyses of the latent period of bone sarcoma after incorporation of ^{226}Ra and ^{90}Sr in dogs and mice show an inverse relationship between mean latent period and mean dose rate to the skeleton. According to these observations, there may be a practical threshold for these tumours. Under these circumstances a linear extrapolation of the incidence rate and of the length of life lost per induced bone sarcoma down to zero, from values recorded at high doses, would surely overestimate the risk at low doses. This also applies to tumours induced by β-emitting bone seekers.

340. Studies of bone sarcoma induced by alpha-emitting bone-seeking radionuclides, particularly ^{226}Ra, support a linear activity-response relationship for crude incidence. However, for ^{239}Pu, more refined statistical analyses of data from dogs injected with this nuclide, and observed for longer times, have shown that a purely linear dose-response relationship between integral tumour rate (cumulative hazard) and administered activity is highly unlikely. The same seems to apply to the relationship between dose rate to cells at risk and tumour rate (hazard rate). The appearance of a linear component in the curves cannot be excluded

in the follow-up of animals that are still alive but at present the dose-squared component is dominating.

341. The most recent data on radiation-induced life shortening in mice suggest that a linear dose-response model applies at low neutron doses, while at intermediate and high doses the response follows a square-root function of the dose. Fractionation and protraction of the neutron dose increases the effect of life shortening in some experiments, but not in others; fractionation of low-LET radiation reduces the effect. To the extent that life span shortening in irradiated mice can be attributed to the induction of new tumours, these conclusions may also be applicable to radiation carcinogenesis.

V. DOSE-RESPONSE RELATIONSHIPS FOR TUMOURS IN MAN

342. Data on the incidence of radiation-induced human cancer, at different levels of dose, may be tested for consistency with various models in two ways: directly or indirectly.

343. Indirect inferences may be drawn from limited comparisons in the few instances where risk coefficents (F_{TA} or $\dot{F}_{TA}$) are available at two ends of the scale: high and low doses (total or per fraction). Risk coefficient which are not substantially different under such circumstances will be taken to be consistent with a linear-quadratic or a linear model, because in most cases the variability of data precludes a clear distinction between the two models. Theoretically, for a dose-squared model, an appreciable difference would be expected between F_{TA} or $\dot{F}_{TA}$ at low and intermediate doses, but examples of this kind have not been found for the types of cancers reviewed.

344. In direct studies, attempts may be made to fit various models to the epidemiological data over a wide range of doses. There are often shortcomings to these data (dosimetric uncertainties, a narrow range of doses, pre-selection of groups, ill-defined controls, possible influence of confounding variables, errors of sampling) and consistency with a model rarely, if ever, excludes a fit to alternative models. Thus, consistency of a set of data with a given model should not be taken as evidence that only that model provides an adequate description.

345. Much information on dose-response relationships for radiation-induced malignancies (e.g., leukaemia, cancer of the breast) has been derived in the past from the follow-up of atomic bomb survivors at Hiroshima and Nagasaki. These cohorts represent the statistically most powerful set of data available for dose-response studies, because of the great number of person-years at risk, the wide range of doses, and the relative lack of selection of the samples.

346. The dose-response data in these groups were based on the so-called T65 dosimetry. Since 1980 this dosimetry has been under revision [K34, L27, L30, R4, R6] and a new dosimetry system (DS86) is being installed at the Radiation Effects Research Foundation in Hiroshima as of March 1986. Preliminary estimates based on somewhat more detailed analyses and the current state of knowledge (for a preliminary review see [B77]) differ substantially from those of T65 dosimetry. It appears now that the gamma-ray component had been under-estimated in Hiroshima by a factor of 1.5 to more than 2, and the neutron component had been over-estimated by a factor of about 10 in Hiroshima and of about 2.5 in Nagasaki. As a result, much of the information based on T65 dosimetry will have to be re-assessed upon completion of the ongoing dosimetric revision and will be reviewed by UNSCEAR in the future. However, there is no question as to the qualitative validity of the previously accumulated information about the effects of age and sex upon the incidence of various neoplasms in atomic bomb survivors. The same applies to the clinical and pathological forms of diseases and to the distribution of their latent periods, which are discussed here.

A. LEUKAEMIA

1. Direct studies

(a) Leukaemia in atomic bomb survivors

347. From the information collected in the Life Span Study Sample it appears that the age at time of irradiation had a pronounced effect on the magnitude of the risk when expressed in absolute and relative terms. The effects of sex differences were also discussed in the 1977 UNSCEAR report [U6]. The age-adjusted leukaemia mortality rates reveal that the risk of leukaemia (all types) in males is significantly higher than in females. For both cities combined, the male : female ratio is 1.36, 2.86 and 1.56 for the TD65 kerma categories of 0-0.09, 0.1-0.99 and >1 Gy, respectively. The distribution of cases in time varied with the type of leukaemia and with age, as shown schematically in Figure XXIV [O1].

(b) Leukaemia in x-ray treated spondylitics

348. Smith and Doll [S49] studied mortality through 1970 in 14,111 ankylosing spondilitis patients given a single course of irradiation during the period 1935-1954. Of these patients, 98.5% were traced to their death, to the date of emigration from the United Kingdom, to the closing date of follow-up (1 January 1970) or to the end of a year after a second treatment, whichever was the earliest. The average period of follow-up of those with one course of treatment was 16.2 years. Causes of death were obtained from death certificates.

349. The number of expected deaths in the cohorts were calculated from age- and sex-specific mortality rates for England and Wales in the respective calendar five-year intervals. An analysis of mortality revealed that the number of deaths was 66% more than

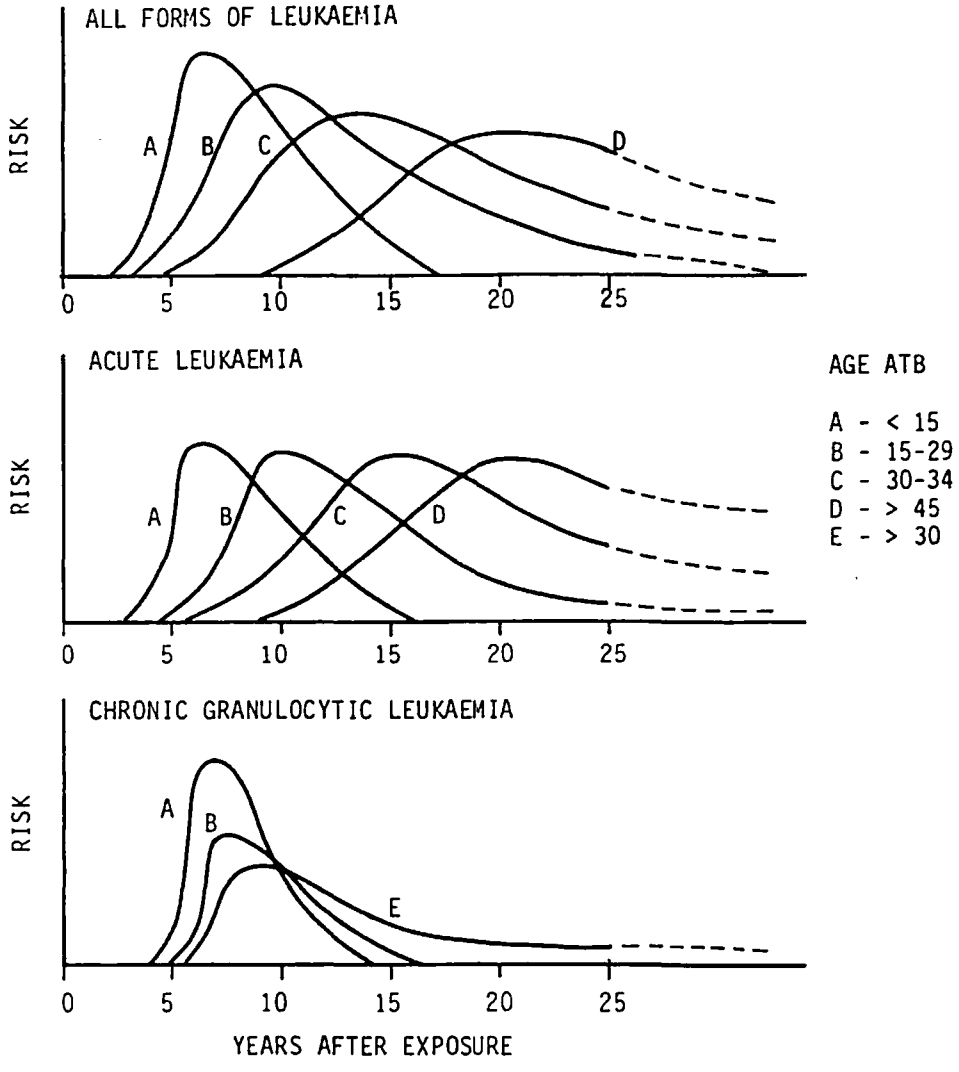


Figure XXIV. Schematic model of the influence of age at the time of the bombing (ATB) and calendar time on the leukaemogenic effect of radiation (heavily exposed survivors).
[O1]

expected in the patients (1759 versus 1062 expected). The total excess of leukaemia, as well as that for neoplasms, was highly significant ($p < 0.001$), and did not differ among males and females (the latter made up only one-sixth of the population).

350. The only malignancies for which the dose-response relationship has been studied were leukaemias. The excess death rate was high, the overall observed/expected (O/E) ratio being 4.79 (3.06 and 5.10 in women and men, respectively). The time trends were characteristic, with the death rate rising even at 2 years after the first irradiation, peaking at 3 to 5 years, and declining to the control level more than 20 years after treatment. Chronic lymphatic leukaemia was apparently not increased by the treatment. The relative risk of leukaemia (O/E ratios) was equally increased in all age groups (age at first treatment). The excess risk coefficient per 10^5 person-years rose from 251, in those younger than 25 years, to 1366 in patients treated at more than 55 years of age. In this instance the radiation-induced leukaemia incidence increased temporarily in proportion to the age-specific spontaneous incidence (at age of exposure), as represented schematically in Figure II, c and d.

351. As the distribution of local absorbed and mean doses to the bone marrow among all patients is unknown, it had to be reconstructed through an extensive phantom study in all patients who died with leukaemia and in a sample of all followed-up patients. The doses ranged from 0.5 to 7 Gy, with a rather uniform distribution of frequency, involving 90% of cases below 5 Gy. The proportion of cases above 6.5 Gy did not exceed 2%. The mean marrow dose was 2.49 Gy.

352. The excess leukaemia mortality rate, plotted versus the mean dose to the marrow is very erratic, and a zero response (independence of mortality rate on dose) may not be excluded on purely statistical grounds. However, due to the time characteristics of the mortality, and to the fact that no increase of leukaemia mortality was seen in non-irradiated spondylitics [R33], the non-zero effect at zero dose was discarded as very unlikely. Three models, a linear, a linear with cell killing, and a quadratic with cell killing were fitted to the data by the method of maximum likelihood. Such a method is not formally correct for the last model because simple averaging of organ doses when a large fraction of marrow was unexposed,

must lead to erroneous results when a dose-squared dependence of initiation of the cells is assumed. The first model could be discarded ($P < 0.03$), and the fit obtained for the second was satisfactory ($P = 0.28$).

353. The coefficient of the linear slope in the second model gave a risk coefficient in accordance with most other estimates of leukaemia risk. However, owing to the erratic character of the dose-response, this value must be taken with caution. The cell-killing term cannot be taken in its usual meaning of mean lethal dose, because absorbed doses to the irradiated fraction of the marrow were 2.5 times higher than the mean. Moreover, the fractionated treatment allowed sub-lethal repair and cellular repopulation to occur.

2. Indirect evidence

354. The risk of leukaemia was studied in radiologists exposed to x and gamma rays either at low dose rates or at higher rates, but in small fractions, accumulated over decades [M7, S8]. The risk was significantly elevated. The records of mortality of the 1920-1927 cohort followed for 50 years showed excesses of 390 and 170 deaths per 10^6 person-years at risk due to leukaemia and to aplastic anaemia, respectively. Calculation of risk per unit dose to the marrow is affected by great uncertainty about the doses accumulated. The diagnoses are also very uncertain. The BEIR Committee [B20] estimated the likely average value to be about 6 Gy, with a resulting annual risk coefficient of 70 leukaemia deaths per 10^6 Gy^{-1} a^{-1}. This value is not significantly different from estimates for low dose and dose rate derived by UNSCEAR in annex G of its 1977 report [U6] from studies on other acutely-irradiated groups (spondylitics, females irradiated for induction of menopause, or other benign conditions) given doses and/or fractions above 1 Gy. If the above estimates of dose were in error in either direction by a factor of 2-3, the derived risk would still appear similar to that deduced from studies on acute irradiation, and therefore consistent with the linear or linear-quadratic model of induction of leukaemia.

355. In conclusion, therefore, it may be assumed, on the basis of the present fragmentary information, that the dose-response relationship for leukaemia after acute low-LET irradiation is likely to follow a linear-quadratic model.

B. CANCER OF THE BREAST

356. The female breast is one of the most sensitive organs for cancer induction by ionizing radiation [B20, I1, M28, U6]. The data reviewed in annex G of the 1977 UNSCEAR report [U6] have been given either in terms of mortality or morbidity, but the latter category will preferentially be discussed here. Epidemiological data relate to three categories of exposure: atomic bomb explosions, therapeutic irradiation for benign conditions (e.g., mastitis), and tuberculosis patients undergoing multiple fluoroscopies for pneumothorax or pneumoperitoneum. Since the 1977 UNSCEAR report [U6] new information has become available [T12, T23] and several attempts have been made to fit cancer induction models to the relevant epidemiological observations [B24, B25, L1, L22].

357. Dosimetric estimates were retrospective in all studies. The uncertainties were particularly great in the Nova Scotia Fluoroscopy Study [M39, M40], where subjective judgement made assessment of the likely confidence limits unfeasible [B20, B25]. This study, therefore, should not be used for discussion of consistency with dose-response models. The Swedish radiotherapy study [B4] is also limited by the absence of an appropriate control group and by a possible association between fibroadenomatosis or chronic mastitis and increased cancer risk. The following discussion, therefore, is based principally on studies of three series: atomic bomb survivors (tentative), the Massachusetts fluoroscopy study, and the Rochester mastitis patients.

358. Several factors could affect the results of such studies, if not appropriately accounted for. These would mostly be age at irradiation, age at manifestation of the effect, length of the latent period, duration of the period at risk, and relationship between latency and dose.

359. Age at exposure is a major determinant of the breast cancer risk. The three studies cited provide strong evidence of cancer induction in females exposed below age 30, with girls of 10-19 years having the greatest absolute risk. The coefficient of the relative risk increment was already highest in the lowest age bracket (0-9 years) at the time of the bombing, but the absolute attributable risk coefficient for this age was lower by a factor of 2 when compared with that for the next age bracket, i.e., 10-19 years. The absolute and relative risk coefficients for ages 20-39 years remain approximately constant [T23]. The fluoroscopy data are scarce for ages 40-49 years, and absent for older ages at irradiation. The atomic bomb survivors showed no significantly elevated cancer incidence when exposed at ages higher than 40. On the other hand, the Swedish radiotherapy data [B4] imply a radiation risk at all age groups, including 40-49 and greater than 50 years, but statistically the estimates at older ages are uncertain. The possibility that concomitant ovary irradiation in atomic bomb survivors at, or close to, menopause might have been responsible for this protective effect (due to sterilization) was suggested by Boice et al. [B25] and Kato and Schull [K39], but this explanation must remain hypothetical. It has more recently been suggested [T23] that differences in the distribution of the risk at ages above 40 parallel the age-specific incidence of mammary cancer in the various countries (Japan, United States of America, Sweden). Taken together, the data show that the risk is highest when the hormonal action affecting the gland is most intense [T23]. It should be mentioned, however, that the follow-up of the younger age cohorts is still incomplete.

360. The increased incidence becomes manifest in all groups at ages above 30 and particularly at the ages of highest natural incidence rate of the disease. This

observation calls for the use of age-corrected incidences in the exposed and control groups. The so-called minimum latent period can be estimated approximately from all observations [B25], but pitfalls of such estimates have been discussed in chapter I. In the Massachusetts, Nova Scotia and Canadian fluoroscopy series, no excess of breast cancer could be seen for the first 10 years after exposure. In atomic bomb survivors, and in the Swedish radiotherapy patients, the increased risk—particularly in those irradiated at ages above 30 years—could be seen even at 5-9 years after irradiation. Thus, it appears that in younger women (under 30 years) the minimum latent period is perhaps close to 10-15 years, and still longer in irradiated children, whereas in the older women it may be shorter (about 5 years). This observation is important for the selection of a period at risk in calculations of the excess incidence. All studies [B26, S16, T12, T23] show a continuing excess cancer incidence up to follow-up times of 30-45 years in women older than 30 years at exposure. There is, as yet, no indication of a decreasing risk even at the longest follow-up of 45 years. There also appears to be no relationship of latency to dose [L32].

1. Radiotherapy for mastitis

361. The Rochester study on women treated for mastitis [S16] was reviewed in detail in annex G of the 1977 UNSCEAR report [U6]. Only those aspects dealing with the shape of the dose-response relationship are discussed here. By dividing the irradiated group into five dose sub-groups, a dose-response relationship was obtained which was controlled for age and for interval since entry into the study, by means of the Mantel combination χ^2 technique, and by test of linear and quadratic trend. The interval at risk for the irradiated group was from 10 to 34 years after exposure. In a first analysis, the average dose to both breasts was used as the independent variable: the data are presented in Figure XXV. The difference between controls and irradiated women was significant ($p = 0.01$) and the linear trend χ^2 test for association with dose was highly significant ($P = 0.0006$). The incidence increased linearly up to about 4 Gy, and then dropped at higher doses. No significant quadratic trend with a coefficient greater than zero occurred. The second analysis was based on doses to single breasts. The relative risk for the period 10-34 years after irradiation was highly significant ($P < 0.0001$), and amounted to 3.3 when controlled for age and interval since entry into the study. The results in terms of relative risk are presented in Table 1, together with results of the first analysis. Significance was obtained for the linear gradient ($P < 0.0001$) and for a quadratic effect with a negative coefficient ($P = 0.0003$). The latter reflects a decreased carcinogenic effect above 4 Gy, owing perhaps to cell killing or other influences.

362. The possible effects of fractionating the dose were analysed within a range of total doses below 3.5 Gy. The analysis compared breasts receiving one or two treatments (mean dose = 1.9 Gy) with three or more treatments (mostly 3-4, mean dose = 2.86 Gy).

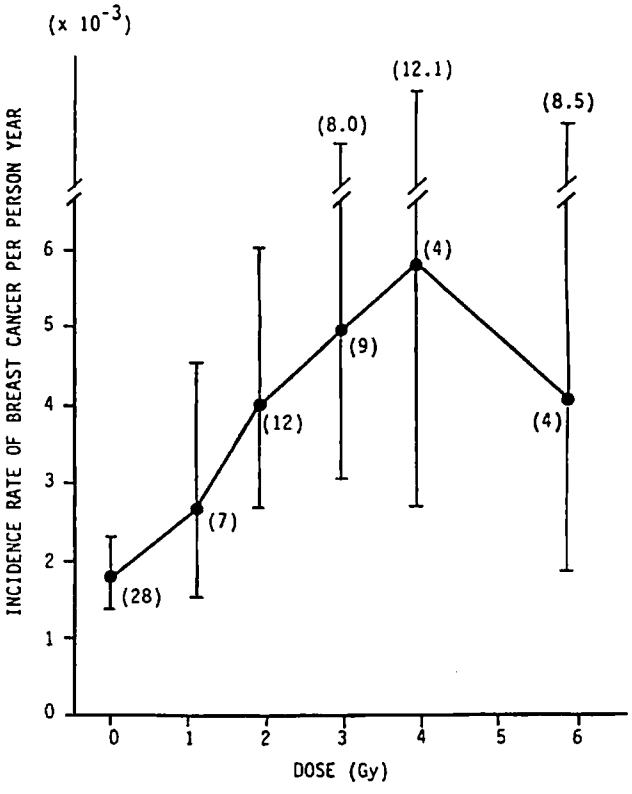


Figure XXV. Breast cancer incidence rate as a function of the average dose to both breasts in mastitis patients for the interval 10-34 years after irradiation. Error bars represent 80% confidence intervals. Numbers in parentheses are breast cancer cases in each dose group.
[S16]

Single, non-irradiated breasts served as controls. For a risk interval of 10-34 years post-irradiation, the adjusted coefficient of the absolute (attributable) risk of breast cancer was 910 10^{-6} Gy^{-1} a^{-1} per breast in the 1-2 fraction group, as compared with 1120 10^{-6} Gy^{-1} a^{-1} per breast in the 3-4 fraction group. Thus, fractionation did not appear to reduce the carcinogenic effect, although the validity of the comparison is limited by the difference between mean doses in the two subgroups.

363. The annual absolute risk coefficient during the period, using the average dose to both breasts, and age- and interval-adjusted incidence rates (irradiated adjusted to controls), was calculated as 830 10^{-6} Gy^{-1} a^{-1}. For irradiation of a single breast, the age- and interval-adjusted estimate of the coefficient amounted to 496 10^{-6} Gy^{-1} a^{-1}. If this figure is doubled for the two breasts, it is consistent with the average for two breasts given above.

2. Pneumotherapy patients

364. The Nova Scotia series on breast cancer induction by repeated fluoroscopies [M1, M39, M40] showed that repeated low doses of diagnostic x rays, when delivered to the gland in sufficient amounts, led to an increased risk of tumours. The doses were

estimated retrospectively, but the margin of uncertainty was so large [B20, B25] that detailed discussion of the likely shape of the dose-response relationship is difficult. However, the fact that the risk estimate was similar to that derived from other studies suggests additivity of the effect and thus approximate linearity of the dose-response relationships.

365. A follow-up study of Boice and Manson [B26] on female tuberculosis patients has been discussed already in annex G of the 1977 UNSCEAR report [U6]. The methodology of estimating the radiation dose to the breasts was described in detail in a separate report [B24] and warrants some discussion because it is critical for the assessment of the dose-response relationship. The data on the number of fluoroscopies were abstracted from the medical records and checked by interview. It was estimated that 63% of the patients faced the physician during the fluoroscopic examination, 16% faced the x-ray tube, 21% had variable positions, and 12% reported being rotated during examination.

366. Out of the 15 former tuberculosis physicians interviewed, 29% reported that they examined their patients with breasts directed to the x ray tube. Sixty-nine per cent conducted the fluoroscopy with the beam-shutters wide open and 81% always scanned the opposite lung. The average time of examination was given as 15 s (3 to 60); 70-80 kVp and 5 mA were the usual parameters of x-ray machines employed; and 1 mm Al filtration was added in 1948.

367. Exposure measurements were made on three representative types of fluoroscopy units, and exposure rates were determined at the fluoroscope panel. Half-value layers for a range of tube voltages and added filtrations were also checked. The exposure measurements were translated into average conditions before and after 1948. Based on these data, estimates were made of absorbed dose in the breast, by means of a Monte Carlo radiation transport method in relation to an anthropomorphic phantom. The shape of the breast was geometrically simulated, separately for an adult and for an adolescent breast. A typical elementary composition of the gland was assumed. The absorbed dose in the breast per 1 R skin exposure (free in air) was calculated for selected exposure conditions: 2 beam qualities, 2 patient orientations, 2 breast sizes and 4 field sizes. These calculations were approximately in agreement with TL dosimetry in a phantom.

368. Cumulative breast doses of all fluoroscoped patients were calculated from all the above information (medical records, physician interviews, patient contacts, exposure measurements and absorbed dose calculations). Females under 17 years of age were assigned doses for the adolescent breasts and the older ones doses for adult breasts. Individual orientations could not be determined and it was assumed that 25% of all examinations were performed in the antero-posterior position, and both breasts were assumed to be in the unshuttered beam 81% of the time while fluoroscoping a unilateral lung collapse, and 19% of exposure time was assigned to the ipsi-lateral breast. Average doses were computed by adding the dose received by the directly exposed breast and the scatter dose received by the opposite breast, and dividing by 2. In a few cases of bilateral lung collapse, both breasts were assumed to be in the beam for 100% of the time.

369. Uncertainties affecting dose estimates based on so many variables, sometimes estimated from memory of 20 to 45 years previously, must be affected by considerable errors and should therefore be taken with great caution. It is very difficult to say whether average breast doses calculated by Boice et al. [B24, B26] are representative of the the real situation and what might be the systematic errors involved. However, the shape of the dose-response relationship should perhaps not be affected by a systematic over- or under-estimate of the real dose.

370. For the exposed women, the onset of the period of risk for breast cancer development was assumed to be the date of the first fluoroscopic examination, and, for the non-irradiated controls, the date of admission to the sanatorium. Expected breast cancer cases were determined with the use of the age- and calendar-specific incidence rate for the neighbouring state of Connecticut, where a cancer registry has been in existence since 1935. The number of expected breast cancers in the exposed group was calculated by multiplying the age- and calendar-specific women years (WY) at risk by the corresponding incidence rates in Connecticut. Standard morbidity ratios and absolute risk coefficients were calculated. The end of the period at risk was regarded as: the date of cancer diagnosis; or the date of death from another cause; or 1 July 1975 for those found alive; or the last date at which the woman was known to be alive, for those lost from the follow-up.

371. The number of breast cancers found among the irradiated women was 41, as against 23.3 expected (excess significant: $p = 0.0006$). Among the controls, 15 cancers were found, against 14.1 expected. The observed/expected ratios were, correspondingly, 1.76 and 1.06. The absolute excess risk increased with increasing numbers of fluoroscopies up to 100-149: a decrease after a greater number was suggested. Nevertheless, a linear increase could not be excluded [χ^2 (trend) = 4.1, $P = 0.04$; χ^2 (departure from linearity) = 6.9, $P = 0.14$].

372. When the incidence rate was calculated as a function of the average dose to the breast, the results were as shown in Figure XXVI. The average dose to the breast per examination was estimated to be 0.015 Gy, and the mean cumulative dose to the breast amounted to 1.5 Gy [B24]. No decrease in the excess incidence per unit dose was apparent at doses above 4 Gy (the highest average was 5.74 Gy) and the dose-response was consistent with linearity down to the lowest dose group (0.32 Gy average) [χ^2 (trend) = 9.4, $P = 0.220$; χ^2 (departure from linearity) = 1.6, $P = 0.8$]. Some differences between the relationships for dose and for number of fluoroscopies resulted from fluoroscopic examinations in different positions of the patients, in different periods, at various ages and for different sizes of the breast.

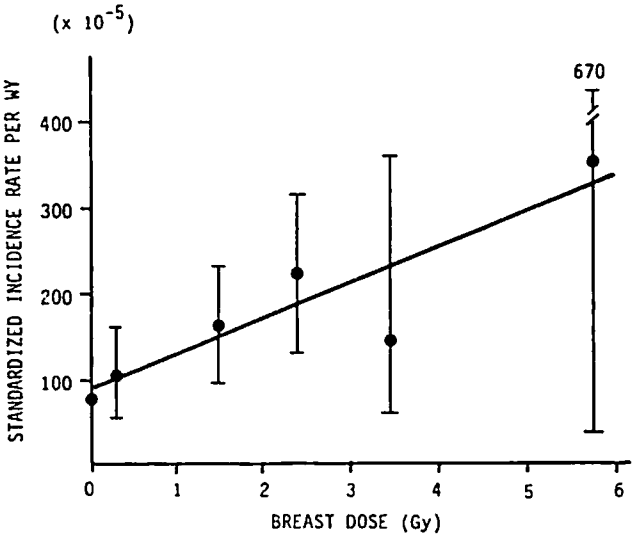


Figure XXVI. Standardized incidence rate of breast cancer in fluoroscoped pneumothorax patients per 100,000 women-years (WY) at risk, as a function of estimated cumulative breast doses. Error bars represent 80% confidence limits. [B24]

373. The breast cancer risk appeared after 15 years, and the excess risk was present for at least 40 years after initial exposure. The average age at cancer diagnosis was 48.4 years (the greatest risk appeared among women aged 40-49 years at diagnosis) and the mean latent period from exposure to diagnosis was 24.4 years. The radiation risk coefficient derived from subjects of this study living 10 or more years after the first exposure was 620 excess cases per 10^6 women-year and Gy (280-1070 are the 90% Poisson confidence limits).

374. In 1980 Land et al. [L22] reported a comparative study fitting the same set of models to mammary cancer incidence data from 3 main studies: atomic bomb survivors, Rochester mastitis and Massachusetts fluoroscopy series. They assumed that the level of breast cancer response to irradiation may depend on age at exposure. To avoid confounding of dose and age, the dose-specific data were age-standardized using the overall age distribution of each series as an internal standard. It was assumed that the shape of the dose-response curve was not dependent on age. Linear, linear-quadratic and quadratic models, with or without a cell-killing term, were fitted to the data. The linear component was omitted from the killing term as it did not improve the statistical fit, but increased the statistical uncertainty in other parameters. This procedure is, however, biologically implausible. Another constraint was that no parameters should be negative.

375. The model assumed that the control incidence rate, a_0, was equally affected by presumptive cell sterilization, implying that all transformed or potentially transformed cells from which cancers would later develop were already present at the time of exposure. This unproved assumption requires that latent periods for spontaneous and radiation-induced breast cancers should be the same, or longer for the former, and is in fact supported by the apparent lack of dependence of the latent period on dose, as shown by Land et al. [L32].

376. The results of the above fits are presented in Tables 2 and 3, according to the notation in equations (3.6) and (3.7). For the Massachusetts series, parametric constraints reduced the linear + killing model to linear, and the linear-quadratic + killing model to linear-quadratic. For the Rochester series, the linear-quadratic model was reduced to linear. For the mastitis series, accounting for cell killing improved the fit significantly (Table 3). Better results were obtained in this respect when single-breast data were used from the mastitis series, where the linear + killing model gave a substantially improved fit ($P = 0.27$) over the linear model ($P = 0.012$). This suggests that cell killing at 4-14 Gy may be a real effect in unfractionated or relatively unfractionated exposures. The quadratic and quadratic + killing models did not fit the age-standardized data as well as did the models with the linear term $a_1 D$. The results show that low-dose risk estimates for breast cancer induction should be based on models with a pronounced linear term. The values for the a_1 term are very close in the series, particularly when differences in age distribution are considered.

377. When age-standardized percentage incidences were plotted in exposed and unexposed women of the three cohorts against time after irradiation, in no group was there evidence of an acceleration of breast cancer expression with dose. This result emphasizes two points: that expression of radiation-induced breast cancer may be influenced by the same physiological factors that affect the normal age-specific incidence rate of this tumour; and that an inverse relationship between dose and latency is highly unlikely for this neoplasm (see also [K39 and L32]).

C. TUMOURS OF THE THYROID

1. Direct studies

378. In their most recent published report, Shore et al. [S60] updated the follow-up to 1977 and reinvestigated several aspects of thyroid cancer induction by x rays in a series of subjects irradiated in childhood for alleged thymus enlargement [H18, H19, S38]. The subjects studied included 2856 irradiated and 5053 controls; 2652 and 4823, respectively, were followed for five or more years after the treatment (on the average, for 30 years).

379. Irradiation was performed with x-ray machines operating at various parameters of voltage and filtrations that were probably not very critical for assessment of the dose to the thyroid (in all cases, the skin dose was very close to the absorbed dose in the gland). The important factor was whether the gland was inside or outside the primary beam. Individual dose estimates were made on this basis, with other corrections. For 241 subjects, such estimate proved impossible, and they were excluded from studies involving analyses with dose.

380. Siblings of the irradiated subjects were the primary control, but comparisons were made also with cancer rates in upstate New York. The subjects were located by various means, and a questionnaire

was used to identify health problems, including tumours. Responses were obtained from 88% of the subjects. Only medically verified neoplasms were used in further considerations, and pathology reports were obtained for all cancers and about three-fourths of the nodules (which were benign). From the total person-years, five years were subtracted in each subject as the likely shortest latent period.

381. There were only small differences in some parameters characterizing the two groups. A large excess of thyroid cancer ($P < 0.0001$) was diagnosed in the irradiated groups (30 cases of various histological forms), and only 1 case in the controls (1.43 expected). The relative risk for the carcinomas, adjusted for sex, ethnicity and post-irradiation interval, was 49.1 (90% confidence limits 10.7-225) ($p < 0.0001$) when related to controls, or 44.6 (32.1-60.6) when related to the rate in the general population. There was also an excess of adenomas: 59 among irradiated against 8 among the controls (adjusted RR = 15 (90% confidence limits 8.1-27.7) ($p < 0.0001$). A separate comparison of cases with matched controls yielded similar odd ratios and p values for cancer as given above, but a somewhat lower estimate of relative risk for adenomas.

382. Doses in the thyroid ranged from 0.05 to 11 Gy, with a weighted average of 1.38 Gy and 62% of individual doses below 0.5 Gy. An absolute risk analysis of the dose-response relation (Figure XXVII)

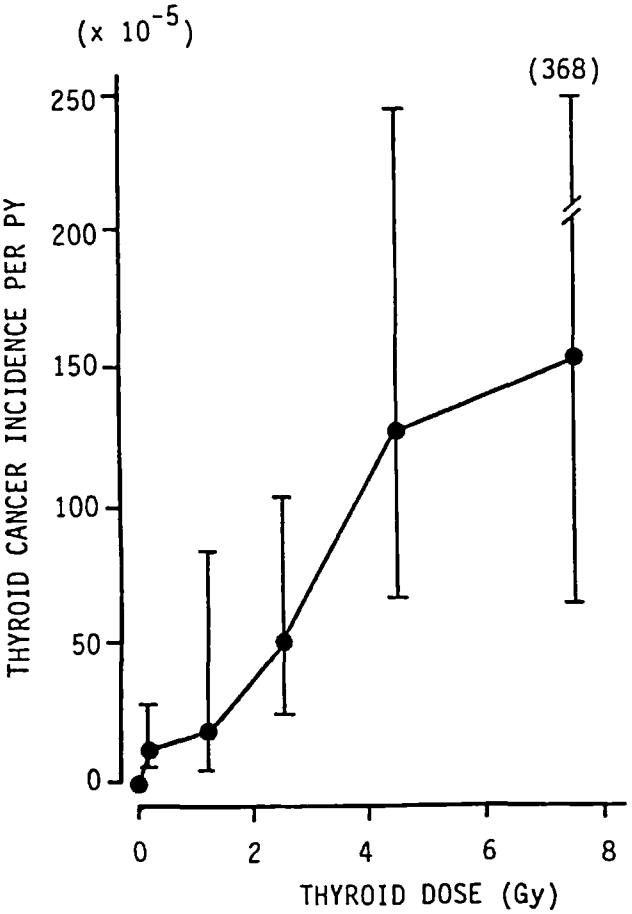


Figure XXVII. Thyroid cancer incidence per person year (PY) as a function of the radiation dose in the thyroid. Rates adjusted for sex, ethnicity and interval after irradiation. Error bars represent 90% confidence limits.
[S60]

was undertaken with 6 and 12 dose categories, controlling for sex, ethnicity, and interval since irradiation. A linear regression (Mantel regression coefficient) yielded a coefficient of 3.46 (± 0.82 S.E.) $10^{-4}\ Gy^{-1}\ a^{-1}$ ($P < 0.0001$) (5.25 and 2.05 for females and males, separately). Fitting the data to a linear-quadratic model, by iteratively weighted least square regression analysis, resulted in a highly significant linear term ($P < 0.0001$) and a non-significant dose-squared term ($P > 0.4$). When the so-called ridge regression analysis was applied, the linear term retained its predictive power, but the quadratic term was even farther removed from significance. The Cox regression analysis used for calculation of RR-model coefficients yielded for cancer a strong linear component ($P < 0.00001$) and an insignificant quadratic one ($P = 0.08$). The value of the relative increment coefficient was 0.0058% of the control frequency per Gy.

383. For adenomas, the risk expressed in absolute terms yielded a linear dose-response with a coefficient of 5.7 (± 1.2 S.E.) $10^{-4}\ Gy^{-1}\ a^{-1}$ (7.7 for males and 3.6 for females) significant at $P < 0.00001$. In a linear-quadratic fit, the linear coefficient was 3.8 (± 1.4) $10^{-4}\ Gy^{-1}\ a^{-1}$; that for the quadratic term was negative, -0.04 (± 0.004) $10^{-4}\ Gy^{-2}\ a^{-1}$, and the relationship was downward concave. A strong linear component ($P < 0.00001$) and a significant quadratic component ($P < 0.01$) with a negative coefficient, were obtained for the risk expressed in relative terms. A simple linear regression yielded a relative increment coefficient of 0.0044% of the control frequency per Gy.

384. Of 2358 subjects with doses below 6 Gy, 51% were irradiated once, 39% twice and in 10% of cases the dose was split into 3 to 11 fractions. No influence of the dose per fraction, number of fractions and interval between fractions was found for carcinomas or adenomas. Tumour appearance as a function of time seemed to decrease slightly beyond 25 years post-irradiation, but still after 40 years there were excess tumours. The data were not a good fit to the relative risk projection model, but an adequate fit was obtained to the absolute risk model. The latent periods of thyroid carcinomas and adenomas did not show any relationship with the dose.

385. In conclusion, these data, derived from a cohort irradiated in infancy, show a dose-response relationship with a strong contribution of the linear terms, lack of demonstrable dose-squared terms, and lack of dose-fractionation effects. A paradox was also noted, in that irradiation seemed to multiply the sex-specific "spontaneous" risk, while, at the same time, the results fitted an absolute, but not a relative, risk projection model.

2. Indirect evidence

386. Among the studies on thyroid cancer reviewed in annex G of the 1977 UNSCEAR report [U6] none seems to qualify for the derivation of the dose-response relationship or for testing of various models. However, when the risk coefficients for irradiated

children are considered (see Table 10 in annex G of the same report) they seem to fall within a rather close range, although the average estimates of dose for each group vary from 0.065 to about 10 Gy. This would suggest a dose-response relationship close to linearity, a suggestion that must be taken with caution owing to the great uncertainties in retrospective dose estimates in all studies, and to the genetic, demographic and geographic differences between the series.

387. Modan [M25], and later Ron and Modan [R29, R45], followed up children irradiated for tinea capitis in their childhood. The last paper in the series [R45] summarizes the results for the follow-up period 1950-1978. All individuals were irradiated between 1948 and 1960 at an average age of 7. The majority (96%) were treated between 1 and 15 years, and over 50% between 3 and 8 years. Only 6% were irradiated more than once.

388. The final cohort study included 10,842 irradiated persons (IS) and 10,842 non-irradiated tinea-free subjects matched for age, sex, country of origin and year of immigration to Israel (PC). A second control group was composed of 5400 siblings (SC), non-irradiated and tinea-free. All groups were equally divided by sex. By the end of 1978, the three groups had accumulated 244,909, 245,435 and 121,854 person-years at risk, respectively. The average follow-up interval was 22.8 years. The dose to the thyroid was estimated to range from 0.043 to 0.16 Gy, with a mean of 0.096 Gy.

389. The following numbers of cancers were found in the three groups: IS, 29; PC, 6; SC, 2. They were ascertained from the Israel Cancer Registry with an efficiency of recovery of about 80%. The relative risk of thyroid cancer, estimated by using the Mantel-Haenszel method for cumulative data, amounted for the whole group to 5.4 (95% confidence interval 2.7-10.8). The absolute risk may be estimated betweeen 12 and 14 $10^{-4}\,Gy^{-1}\,a^{-1}$, depending upon the efficiency of detection assumed (100 or 80%, respectively). There was a clear influence of sex upon the incidence, the relative risk and absolute risk ratios females:males being 1.2 and 3.8, respectively. Subjects in the age bracket 0-5 years were twice as sensitive as those in the 9-15 years group. A significant ethnic difference was also seen because the children of Moroccan and Tunisian origin (contributing about one-half of the total) had an absolute risk twice as high, and a relative risk 6-9 times higher than the rest of the cohort.

390. The $\dot{F}_{TA}$ from this study is about 3-4 times higher than that derived by Shore et al. [S60] for a cohort with an average dose of 1.38 Gy. This however, does not indicate that the risk is truly higher at the lower dose of about 0.1 Gy, because the tinea capitis sample is composed entirely of people of Jewish origin. From the results of Shore et al. [S38], it follows that this factor alone could account for a two-fold difference, and the contribution of individuals of Moroccan and Tunisian origin may have added another factor of 2. Any systematic bias in dose estimates due to inadvertent movements of children during irradiation would have resulted in higher, and not lower, doses to the thyroid.

391. In summary, therefore, a similar value of $\dot{F}_{TA}$ for thyroid cancers in a cohort of children who received a thyroid dose of about 0.1 Gy, and in another cohort with doses ranging from 0.17 to 7.5 Gy, strongly supports the conclusion that the dose-response relationship for thyroid cancer may be essentially linear. Concurrent irradiation of the hypophysis with higher doses (of the order of 0.5 Gy) has been suggested as a possible explanation for this unique observation. However, only an increased secretion of thyroid stimulating hormone (TSH) would be expected to enhance the risk of thyroid carcinoma, while irradiation of the hypophysis would be expected to result in a decreased secretion. Data from an experiment aiming at answering this question are also in conflict with the explanation referred to above [L29]. A smaller group of 2213 children [S36] irradiated to induce epilation did not produce an excess of thyroid cancer. However, because of the low statistical power of the study, this result is consistent with reported values of $\dot{F}_{TA}$.

392. Holm [H17] published a retrospective study on patients given ^{131}I for diagnosis of thyroid diseases in the Stockholm area in 1952-1965. The population consisted of 10,133 persons, of average age 44 years, followed for an average period of 18 years after administration of the nuclide. Of these, 95% received ^{131}I when 20 years or older (2086 males and 8047 females). The diagnostic tests were administered for suspected thyroid tumour (32%); hyperthyroidism (44%); hypothyroidism (16%); or other reasons (8%). Thus, from the viewpoint of thyroid physiology and/or pathology, the population studied was a selected one. Persons with cancers diagnosed within 5 years of administration of ^{131}I were excluded from the study as were those given any therapeutic irradiation of the thorax, head and neck.

393. The mean activity administered was 2.2 MBq, and doses to the thyroid were calculated on the basis of a measured retention of about 40% at 24 hours after administration. The assumed mean effective half-life of ^{131}I was 7 days and the mass of the thyroid was estimated in a representative sample (about 10%) of the population under study from scintigraphic measurements and palpation. In persons above 20 years, the mean weight of the thyroid was 50 ± 33 (S.D.) g, and in those below 20, 10 ± 5 g. The resulting mean doses were 0.58 and 1.59 Gy. The population average (adjusted for age) was 0.62 Gy.

394. The expected number of thyroid carcinomas was computed from country-average age, sex and calendar-year specific rates derived from the Swedish Cancer Registry statistics. The assumed period at risk was the period of follow-up since administration of ^{131}I minus 5 or minus 10 years. In the first case, the number of expected cancers was 8.3, in the second 5.9. The Swedish Cancer Registry was searched for names and identity code numbers of all the patients enrolled in the study. Nine cancer diagnoses among them were identified and 8 confirmed. Thus, there was no excess cancer among the subjects given diagnostic amounts of ^{131}I.

395. Holm et al. [H17] compared the number of cancers diagnosed with estimated numbers calculated from UNSCEAR risk coefficients of 5000-15,000 cases 10^{-6} Gy^{-1} [U6] (derived predominantly from surveys on children) or from Hiroshima and Nagasaki surveys [U6] of 1400 10^{-6} Gy^{-1}. In the first case, the number of expected cancers would be 47-124, which is obviously very different from the observed 9 cases. For the second alternative, the authors quote a figure of 19 cases, which they claim to be not significantly different from the 9 cancers diagnosed.

396. However, when the lack of the excess incidence in that study was compared [N10] with the expectation in adults, taking the risk for adults to be one-half that in children [S60], to account for the age-related lower sensitivity, the difference appeared statistically significant on two tests applied. This would suggest that the effectiveness of ^{131}I for induction of thyroid carcinomas is lower, at least by a factor of 2. The question whether this is a true dose-rate effect, and to what extent other factors play a role, cannot be answered at present.

397. Several factors, separately or in combination, could be responsible for the difference between the predicted and the observed numbers of cancers. First, the linearity of the dose-response relationship in Figure XXVII may be more apparent than real, because the positive dose-squared term for initiation and the negative term for cell killing may compensate each other. Secondly, the subjects are a selected unhealthy population, with a high percentage of thyroid involvement, to whom specific rates of thyroid cancer induction, valid in the general population, may not apply. Thirdly, the treatment given after the diagnosis (surgery, thyroid hormones) could have suppressed the risk. This appears rather unlikely, as more than half the patients were not given any treatment and the nine with diagnosed cancers were treated with hormones (2 cases) and surgery (4 cases), which did not prevent the manifestation of tumours. Fourthly, a non-uniformity of dose distribution from ^{131}I in pathologically enlarged glands could be another confounding factor. Fifth, it cannot be excluded that risk coefficients are being compared for populations which may differ in their average iodine uptake and hence in activity of the thyroid and hypophysis (TSH stimulation). Finally, other dietary or environment-related factors could further confound the comparison.

398. In summary, two studies on humans [R45, S60] argue persuasively that the contribution of the linear term is very strong in the dose-response relationship for induction of carcinomas of the thyroid. This is also the conclusion to be drawn from the experiments on rats by Lee et al. [L29] discussed in chapter IV. If this conclusion were true, a dose-rate effect, should not be expected. However, the results of Holm's study [H17] are not consistent with this picture. Further investigations in this field are certainly called for.

D. CANCER OF THE RESPIRATORY TRACT

399. Induction of lung cancer has been discussed repeatedly in many UNSCEAR reports [U6, U7, U9-U12, U24] and risk estimates were given based on various groups' findings ([U6], annex G). Most of the data on lung cancer induced by external irradiation appeared unsuitable for analysis of the dose-response relation. The most numerous group, the atomic bomb survivors, is still affected by uncertainties in organ dosimetry. As a result, there are large statistical uncertainties in excess rates in various exposure categories ([U6], annex G).

400. The most interesting case for a discussion of the shape of dose-response relationships is the prolonged exposure of miners to radon and its daughter products. The difficulties in this case are:

(a) The long period of exposure, often at a variable rate. Exposures toward the end of the follow-up period are increasingly less effective, in view of the long latent period of these tumours;

(b) Possible changes in susceptibility with age, which is itself a variable correlated with the length of the exposure;

(c) Possible interaction of radon and its daughters with other factors, particularly smoking habits of miners [A8, A16, W17];

(d) The dosimetry, which is based either on measured concentration of potential alpha-energy in the air (WL)[d] or on estimates of radon concentrations, on the assumption of some degree of radon-daughter product equilibrium. Translation of these quantities into an absorbed dose in the cells at risk (basal layers of bronchial epithelium) is uncertain, but a recent ICRP review [I4] gives, for mining conditions, a range of about 3 to 8 mGy per WLM. The use of cumulative WLM as an indirect measure proportional to dose is probably adequate for discussions of the derived dose-response relationships.

1. The risk expressed in absolute terms

401. In Newfoundland, a group of 2120 fluorspar miners were exposed to an accumulated mean exposure to radon of about 550 WLM. They were followed for about 25 years and those who accumulated more than 1 WLM had a relative risk of cancer of the respiratory tract of 5.58 (95% C.L. 4.54-6.72). The absolute annual excess risk coefficient amounted to 6 (4.6-7.5) cases per 10^6 PY per WLM. The excess lung cancer incidence rose roughly in proportion to the exposure [M5].

402. Several studies were published on the epidemiology of cancer of the respiratory tract among uranium miners in the United States. The 1977 UNSCEAR report [U6] reviewed those by Archer et al. [A8] and by Lundin [L18]. To sum up the situation, the study by Archer [A8] referred to 3366 white and 780 non-white miners who had worked one or more months in underground uranium mining before 1 January 1964. Mortality analysis was terminated on 30 September 1968, and only 1% of people

[d] See footnote *c*.

enrolled were lost from the survey. The death certificates of those deceased before the closing date were obtained. There was a substantial excess of deaths (437 observed versus 276.6 expected) among which there were 70 cancers of the respiratory system against 11.7 expected ($p < 0.01$). The diagnoses were ascertained using all sources of evidence (clinical findings, x rays, autopsy, histology, biopsy, cytology, sputum analysis). Numerous cancers occurred after 1968, or were evaluated as probable ones. These were not used in the assessment of risk or for characterization of the dose-response relationship [B20].

403. The exposure was assessed by radon daughter measurements (nearly 43,000 from 1951 through 1968 in approximately 2500 mines). Measurements taken in a mine over yearly periods were averaged, but, in many instances, exposure over a number of years could only be estimated approximately, particularly in the early years of highest exposure. In addition, a fraction of miners had a history of hard-rock mining, before the work in uranium mines, which also required approximate assessment. Cumulative radon daughter exposure values were calculated with the above approximations for each miner and for each month of his employment.

404. Person-months of risk of dying by single calendar year, for 5-year age groups, and for each time interval after the start of underground uranium mining, were calculated by a modified life table technique. These values were related to cumulative radon daughter exposure in WLM. Individuals who were lost to follow-up were considered to be alive throughout these analyses. A miner often contributed person-months to more than one exposure category if during the course of employment he passed from one category to the next. The expected number of deaths was calculated by applying the specific rates for age, race, calendar year and cause of death for white United States males to the appropriate number of person-years at risk.

405. The number of expected and observed cancers of the respiratory tract as a function of cumulative exposure in WLM during the whole period of observation was converted to incidence rate by BEIR [B20], weighing the incidence in each group of white miners by its inverse variance. The fit was as shown in Figure XXVIII. Consistency with linearity is evident and the slope is about 3 10^{-6} person-year WLM^{-1} for the whole range of exposure.

406. There were confounding variables, like cigarette smoking, metropolitan versus non-metropolitan residence, possible mis-classification of miners into exposure categories, and dependence of WLM calculations on quality of the work histories, which could have distorted the data to some extent. It is difficult to see what their combined effect could have been. However, the authors suggest that the influence of these variables should not basically alter the trend of the dose-response relationship. Also, the excess of cancer cases even in the 120-359 WLM category is beyond doubt.

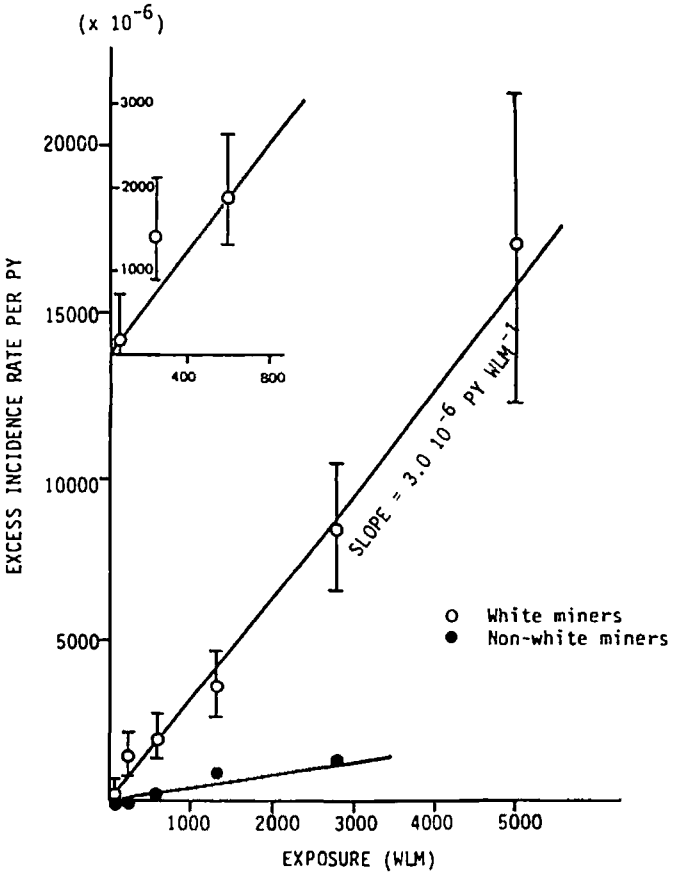


Figure XXVIII. Dose-response relationships for lung cancer in uranium miners in the United States. Error bars include 90% range based on Poisson statistics. Modified from [B20].

407. The mortality study of the uranium miners from the United States was extended to September 1974 [A16] with essentially the same methodology as in a previous study [A8]. Lung cancer rates were calculated for eight exposure categories and for the time after starting uranium mining. The total number of person-years at risk was 62,556; the average period of work in uranium mines was 9 years; the mean accumulated exposure was 820 WLM; and the average follow-up period was 19 years. The incidence rate increased approximately linearly up to 480 WLM, then the slope of the response decreased to give a lower risk per WLM, a feature possibly related to cell killing, which was also seen in the series from Czechoslovakia [S3]. Miners exposed to higher rates were usually followed for longer times, and most miners were middle-aged when they entered the occupation. Cigarette smoking, and constitutional factors such as stature and eye pigmentation were found to be correlated with the effect. Stature was thought to be correlated to lung volume in the sense that, for the same work at comparable oxygen consumption, a smaller lung volume means enhanced ventilation rate and higher lung doses. More recently, uranium miners from the United States have been followed through 1977 [W13], but the data, as reported, do not provide new information, as all uranium miners examined by the United States Public Health Service medical survey team were already considered in the study by Archer et al. [A16].

408. The data from the United States miners were tested by Myers and Stewart [M43] for their fit to various dose-response functions. The fit was made to an equation of the form $\dot{I}_{TA}(WLM) = a + bE^j$ where $\dot{I}_{TA}$ is the annual net incidence rate (10^{-6} a^{-1}) and E the cumulative exposure in WLM. The j exponent was fixed at 1.0, 0.5 and 0.25, and maximum likelihood estimates were obtained in each case for a and b. Allowing all parameters to produce a maximum likelihood estimate led to a preferred value of j not significantly different from unity and to a positive value of a, indicating that an excess cancer of the lung may obtain even in the absence of radon exposure. A linear fit to the data was found to be the best, with $b = 3.5\ 10^{-6}\ WLM^{-1}\ a^{-1}$.

409. The latent period from the start of the exposure to diagnosis was examined as a function of the age at the start [A16]. It declined from about 45 years to about 10 years in those who started mining at 20 or 60 years, respectively. Smokers usually had a shorter induction time (see annex L of the 1982 UNSCEAR report [U24] for a discussion of the influence of tobacco smoke). There was also a shorter latent period associated with higher exposure rates, which appeared to contribute to shortening more than cumulative exposure.

410. Sevc, Kunz and Placek [S3] reported on lung cancer incidence among uranium miners in Czechoslovakia. The number of miners was not specified, but the group was similar in the number of people to that studied by Lundin et al. [L18, L19] in the United States, which consisted of 3366 workers. According to [I5], the study was based on about 60,000 person-years at risk, and a follow-up in the range of 21-26 years, 10 years of average working period in the mines and a mean cumulated exposure of 310 WLM. Fifty-six per cent of these miners started uranium mining between 1948 and 1952 inclusive (group A), the rest between 1953 and 1957 inclusive (group B). Miners were also subdivided into 3 age groups at the start of exposure: $<$ 29 years (45%), 30-39 years (28%), and $>$ 40 years (27%). The age structure in groups A and B was very similar. Each age group was subdivided into eight exposure sub-groups, the exposures being expressed as WLM. The numbers in each sub-group were approximately equal. Exposure estimates were based on about 120,000 radon concentration measurements made since 1948. Estimates of potential alpha energy concentration were made from radon measurements by choosing average values of equilibrium between radon and its decay products, typical for given ventilation conditions and practices (which were available from records) and radon daughter measurements which were introduced in 1960. Attempts were made to estimate the variability of dose measurements. The rates of exposure accumulation in the three age groups were comparable.

411. In each sub-group of miners (belonging to each exposure category and age group), the expected rate of lung cancer was calculated by year from the beginning of exposure up to 31 December 1973, on the basis of age- and calendar-specific lung cancer mortality rates for Czechoslovakia. A statistically significant excess (at 5% level) started to appear in the 100-149 WLM category.[e] The presumption of linearity for the dose-response relationship in group A (start of the exposure 1948-1952, follow-up 21-26 years) could not be rejected at the 5% level of significance.

412. The same data [S3] were fitted by Myers and Stewart [M43] to quasi-threshold functions of probit and logistic response on the logarithm of cumulative WLM. When results were tested by means of χ^2 distribution for significance of deviations from these assumed functions, the χ^2 values were tenable at P = 0.98-0.99. However, the quasi-threshold was less than 3 WLM. Thus, the mathematical analysis, using maximum likelihood as the criterion, does not provide any reason to reject linearity, for which the χ^2 test gives a P value of 0.82.

413. Cumulative exposure E (WLM) and lung cancer incidence (I_{TA}) in group A were also fitted by Jacobi [J4] to a function of the form $I_{TA} = a\ E\ e^{-kE}$. A better fit was obtained than that resulting from assumption of linearity throughout the whole range of exposures. The most likely estimates of a and k were 320 excess cases 10^{-6} WLM^{-1} and 6 10^{-4} WLM^{-1}, respectively.

414. The excess cumulative cancer incidence in the various age groups shows that for the older age group the incidence was significantly elevated (5% level) at 100 WLM or more. For the two younger groups, this significance was reached at exposures above 150 WLM. The risk per unit exposure (WLM) increased with age, with some irregularity of response in miners who were older than 40 at the beginning of the exposure. In the younger age groups, linearity, with different slopes, could not be rejected at the 5% level of significance. The differences in incidence between the groups disappeared above 300 WLM.

415. Cigarette smoking did not appear to be a confounding variable because it was not dependent on exposure categories, although it was correlated with age. From random sampling, the frequency of smoking was similar to that in the country for which specific mortality rates were used for computation of the expected numbers of cancers. Also, hard-rock mining was not a complicating factor in assessment of the exposure.

416. In another paper, Kunz et al. [K22] studied the excess lung cancer incidence in miners in Czechoslovakia over the period 1948-1975 and related their findings to different time distributions of exposure. The previously mentioned group A composed of miners who started work between 1948 and 1952 was followed for 26 years on average. The cohort was divided into five exposure categories and also, according to duration of exposure, as short (4.0-7.9; mean 5.6 years), intermediate (8.0-11.9; mean 9.5) and long ($>$ 12; mean 14). The same group was also divided alternatively, according to exposure rate, into group II with nearly constant accumulation rate; group I for which the earlier rates of exposure were higher than

[e] More recently, it has been reported [S51] that the excess is already significant at an average exposure of 72 ± 2 WLM.

later ones; and group III where the rate of accumulation increased with time and reached highest values in recent years.

417. The additional lung cancer incidence for the group as a whole, when related to duration of exposure and its cumulated values, is shown in Figure XXIX. For the group as a whole, a linear exposure-

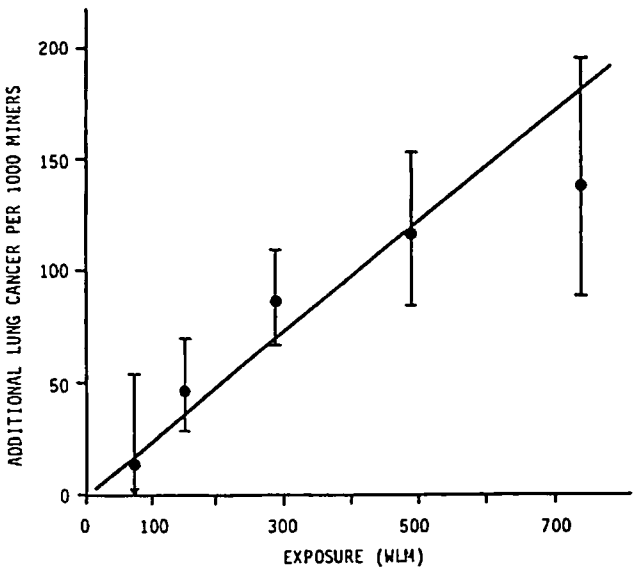


Figure XXIX. Relationship between additional lung cancer frequency and cumulated exposure in all uranium miners from Czechoslovakia. Error bars represent 95% confidence limits. [K22]

response relationship cannot be rejected, but there is some suggestion of saturation at the highest values of WLM. When divided into three groups in relation to the duration of exposure, the two groups with shorter exposure showed saturation very clearly. The early exposure rates in both groups with shorter duration of exposure at which a significant deviation from linearity occurs corresponds to about 50 WLM a^{-1}. The lower incidence resulted from a diminished excess of small-cell undifferentiated cancer. The groups with uniform and decreasing rate of accumulation showed linearity of the response, whereas that with the increasing rate showed a breakdown of the response in the highest exposure category (> 400 WLM). This decrease of the incidence was also due to diminished occurrence of small-cell undifferentiated cancer. A similar influence of exposure rate to radon daughters upon lung cancer incidence was observed in experiments on rats by Chmelevsky et al. [C34] (already discussed in chapter IV).

418. Since all Czechoslovak miners started exposure in 1948-1952, those accumulating their exposure over a shorter period did not have a shorter follow-up, and therefore the lower incidence in the two groups of 9.5 and 5.6 years of mean exposure duration cannot result from the shorter time available for manifestation of the effect (truncation due to long latency and short follow-up). A more likely explanation would be a killing effect on the transformed cells, which becomes manifest at an exposure rate of about 50 WLM per year. However, a shorter survival of miners at high exposures was also suggested [J7]. Thus, lung cancer induction by alpha-particles of radon daughter products can be described by equation (3.1), with the proviso that the proportionality constant of the cell-killing term is dose-rate dependent. The slopes of the exposure-response relationships for different times of accumulation in the low-dose region were very similar. The effect of exposure rate cannot be easily separated from the effects of time course in groups that differ in respect of the rate of accumulation of WLM. Both the exposure rate and latency effects may play a role in the decreased incidence for the 400 WLM category of group III.

419. Horacek and Sevc [H25] studied the relationships between incidence (per 10^3, I_{TA}) of various histological forms of respiratory cancer in uranium miners from Czechoslovakia and the exposure (E, in WLM). For all miners, a function of the type $I_{TA} = 0.16\ E$ gave a good fit to the data, and absence of a threshold could not be excluded. For epidermoid-type lung cancer, the relationship was different, and a regression line of the form $I_{TA} = aE + c = 0.15\ E - 11.2$ could be fitted up to 700 WLM (c was significantly different from zero). Thus, the analysis suggests the presence of a threshold of about 75 WLM. There was also a small excess—unrelated to exposure—of other histological types of lung cancer the statistical significance of which cannot be assessed from the report [H25].

420. It is interesting to note that basically the same picture was obtained for the miners whose exposure began at ages less than 40 years. For those above 40 years, the relationship for epidermoid-type lung cancer was again linear with threshold ($I_{TA} = 0.13\ E - 21.7$), suggesting a threshold of a similar magnitude, but a steeper linear rise of incidence with exposure up to 700 WLM. For small undifferentiated cancer, the excess at about 60 WLM was already close to 60 10^{-3} cases and rose much less steeply to 80 10^{-3} cases at about 300 WLM, with a decline to about 40 10^{-3} cases at about 500 WLM. Other histological types also showed an increased incidence to about 40 10^{-3} cases at 300 WLM, with a decline to very low levels at 500 WLM; however, the form of the ascending branch of the curve cannot be derived from the report.

421. The relationships of these findings to smoking could not be studied, due to lack of relevant information. The reasons why the two main histological types of pulmonary cancer should have different forms of the dose-response relationship (presence or lack of threshold) and different age dependence, are unknown. However, there is a causal link between development of epidermoid lung cancer and metaplastic changes in the bronchial epithelium [S58, S61]. The intensity with which noxious factors (e.g., tobacco smoke, radon exposure) act upon exposed individuals is probably related to the speed with which metaplasia develops. Therefore, at lower exposure rates, development of metaplasia and epidermoid cancer may simply be delayed. The percentage of the small undifferentiated and epidermoid cancers varied strongly with numerous factors, such as calendar time, age at diagnosis, and length of exposure. The epidermoid cancers usually appeared later, and at higher exposures, than the oat-cell undifferentiated carcinomas. All

these circumstances call for great caution in accepting a threshold-type relation for epidermoid lung cancer in uranium miners, particularly because the analysis of a similar type of cancers induced in rats exposed to radon decay products [C34] (see IV.B.6) did not suggest any threshold above a few WLM. A detailed study of the latent periods for the two types of cancer could give some insight into the problem.

422. By far the largest study on the mortality of miners, including that from lung cancer, was recently reported by Müller et al. [M70] from Ontario, Canada. Out of several groups of miners engaged in mining various minerals, excess of lung cancer mortality was found in three: uranium miners, gold miners, and those mining a mixed assortment of minerals. The dose-response study described below refers only to uranium miners, for whom radon daughters in the air could be envisaged as the sole causative factor. The group included all full- and part-time underground uranium miners with mining experience of one month or more. They were followed from 1 January 1955 through 31 December 1981. The cohort numbered 15,984 men, with an average follow-up of 15 years, average duration of exposure of 2 years, mean accumulated exposure of 60 WLM, and a total of 241,942 person-years at risk. The exposures to ^{222}Rn daughters were calculated in WLM from area monitoring and occupancy data from 1955 through 1967 and, starting in 1968, from personal exposure records. For each miner, upper and lower best estimates were derived, called "special" and "standard WLM", respectively. It was postulated that the most likely true exposure would fall within these boundaries.

423. Deaths among cohort members due to respiratory cancers were identified via the Canadian Mortality Data Base, utilizing death certificates. The expected number of deaths was calculated using age and calendar mortality rates for the male population of Ontario. Smoking habits were not taken into account, but, according to the authors, there were good reasons to suppose that the miners did not differ in this respect from the reference population. Among the uranium miners there was a highly significant excess of cancers of the respiratory tract (121 observed against 70.5 expected; $P < 10^{-9}$).

424. When the absolute attributable risk was calculated in 6 exposure groups according to a linear model, the intercept did not differ significantly from zero, irrespective of whether a zero, 5- or 10-year lag in exposure against effect was assumed. The slopes of I_{TA} as a function of WLM varied between 2.0-2.8 10^{-6} WLM^{-1} for "special" WLMs and 4.8-7.2 10^{-6} WLM^{-1} for the "standard" WLMs (at 3 different lag intervals). The slopes were significant at $P < 0.001$. An example of a dose-response relationship is presented in Figure XXX. In terms of the absolute attributable risk, the slope was significantly greater, by a factor of about 6, for those who lived to age 55 or more than for those who died at younger ages. Thus, all dose-response relationships were well described by a non-threshold linear function. A single relative risk model described the relationship for all attained ages (see paragraph 428).

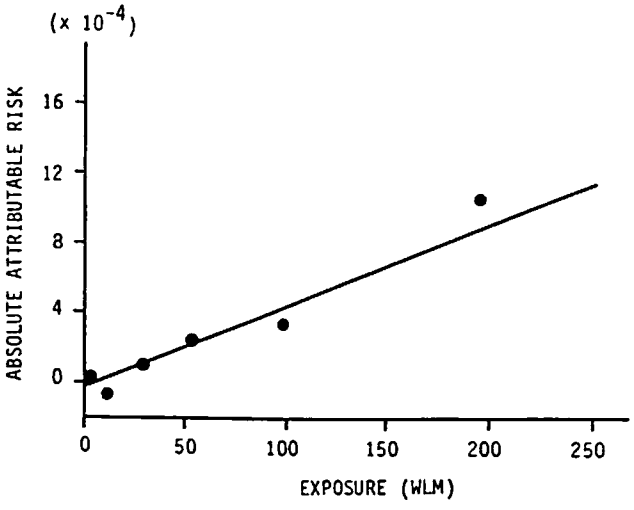


Figure XXX. Dose-exposure relationships for lung cancer incidence in uranium miners from Ontario, Canada, who had no prior exposure in gold mines. Exposure is expressed in WLM "standard" units.
[M70]

425. Preliminary data were reported from Sweden on lung cancer induction in iron-ore miners exposed to relatively low levels of radon daughters. A typical rate of exposure is 2 to 6 WLM per year of underground work, presumably rather constant over the last 60 years [R35, R36]. The group consists of 1435 miners born between 1880 and 1919, known to be alive on 1 January 1920. The mortality analysis dealt with the cohort alive on 1 January 1951 (1294 men) and covered the period through 31 December 1976.

426. The analysis [R36] is almost a life-long follow-up. Details and accuracy of exposure evaluation are not known. The estimates of exposure ranged from 2 to 300 WLM, the average being about 90 WLM. Detailed histories of smoking were available for each miner, and the expected numbers of lung cancers were calculated from the calendar- and age-specific cancer rates for smokers and non-smokers in Sweden. The interesting feature of this study is the very long latent period, with a minimum of 20-29 years after the start of mining and a mean of about 40 years.

427. From this series, only limited data have been published [R41] concerning the dose-response relationship. The earlier report [R36] states that "... the preliminary data show a reasonable dose-response relationship over the range of cumulative exposure from 2 to 300 Working Level Months (WLM). The significant point is that in the lowest dose range we do get a significant excess of lung cancer at about 25 WLM. So we have some indication that at these low doses and dose rates there is a significant lung cancer risk as the linear dose-response would have predicted."

2. The risk expressed in relative terms

428. The lung cancer risk of Canadian uranium miners was also expressed in terms of a relative increment versus exposure. The intercept of the

function was not significantly different from zero for all assumed exposure-risk intervals (0.5 and 10 years). The slopes for relative risk versus exposure varied from 0.51 to 0.54, and the coefficient for increment of spontaneous risk per WLM assumed a single value of 1.3%. The slope was significant at $P < 0.001$. Thus, a non-threshold linear model, with a constant slope for all attained ages, was adequately described in the data.

429. Lung cancer mortality of the uranium miners in the United States was re-appraised [W17] using Cox's proportional hazard model for mortality rates. The analysis was based on 194 lung cancer deaths recorded through 31 December 1977 in the cohort of 3362 white and 780 non-white miners in the Colorado plateau, who worked at least 2 months underground. The data on exposure were the same as used by Waxweiler [W13]. Smoking histories were used to estimate the total number of cigarettes smoked until the exposure cut-off (1968).

430. When considered in terms of the relative risk (RR), various specific models were tested which treated the exposure to ^{222}Rn decay product and smoking as additive or synergistic factors. The best fit to the data by the maximum likelihood method was obtained by a synergistic model of the form:

$$RR = (1 + a\ WLM)(1 + b\ packs) \qquad (5.1)$$

where WLM and packs are accumulated exposure to ^{222}Rn daughters and estimated total number of cigarette packages smoked up to 10 years before the miners' current age, respectively. The fit yielded $a = 0.31\ 10^{-2}$ WLM^{-1} and $b = 0.51\ 10^{3}$ pack^{-1} and was significantly improved over that obtained when exposure to ^{222}Rn decay products was taken alone. Several additive models could be rejected. For exposure to ^{222}Rn decay products alone the dose-response model is a non-threshold linear one.

431. An ICRP Task Group [I5] re-calculated the lung cancer risk among United States, Czechoslovak and Canadian miners in terms of the relative risk. The ratios of the coefficient for the linear slope of the exposure-response relationships, i.e., the relative increment of spontaneous lung cancer risk per unit of exposure are as follows: United States, 0.5-1.0; Czechoslovakia, 1.0-2.0 and Canada 0.5-1.3 per cent per WLM. These values are much closer to each other than the respective values of the coefficient $\dot{F}_{TA}$ (in terms of the absolute attributable risk) of 3-8, 10-25 and 4-10 10^{-6} WLM per year. The relative risk per WLM also becomes slightly less at high accumulated exposures.

432. Data on induction of lung cancer are practically limited to prolonged exposure to alpha particles emitted by short-lived radionuclides attached to dust particles or as free ions in air passage ways (trachea, bronchi). Moreover, the available data refer to miners among whom a majority are tobacco smokers. The latter factor may act synergistically with radiation in inducing bronchial neoplasms ([U24], annex L). There were also other factors in the working environment of miners whose co-carcinogenic or promoting effects upon lung cancer induction could not be completely discarded. Attempts at dissociating these from radon decay products and tobacco effects have been so far unsuccessful. Whatever the limitations of the five studies discussed, they imply basic agreement with expectations of the linear non-threshold model, irrespective of whether the risk is expressed in absolute or relative terms.

E. BONE SARCOMA

433. The available information on induction of bone sarcoma by bone-seeking radionuclides has already been reviewed by UNSCEAR ([U6], annex G), which also discussed many experiments performed on animals ([U6], annex I). Relevant new information on animals is discussed in chapter IV of the present annex.

1. Direct studies

434. A group of dial painters who acquired various amounts of ^{226}Ra and ^{228}Ra has now been followed for more than five decades [E3, E4, R18-R20, R34] and has provided knowledge of average doses to bone and to endosteal tissue, in which the cells at risk are thought to be located. Average doses from radium isotopes in man can be calculated with reasonable accuracy for groups of subjects who acquired their body burdens 50 or 60 years ago [R18-R20]; however, the precision of individual estimates is difficult to appraise.

435. The ^{226}Ra and ^{228}Ra body burdens were measured in most of the individuals (in some of them on numerous occasions) and the initial skeletal uptake was estimated using Norris' [N7] empirical retention function for radium in man. The average skeletal doses of alpha radiation from both isotopes of radium and their daughter products were computed by integrating the retention function from the mid-point of exposure to the end of follow-up, and dividing the released energy by the average skeletal mass.

436. A large group of these subjects (dial painters) has been followed for more than 45 years and the estimated cumulative incidence should be very close to the complete life-long effect of the radionuclides. It is still uncertain whether the group might be selected for dose, i.e., whether or not the subjects with symptoms are grouped preferentially in higher dose categories where skeletal effects (including bone-sarcoma) occur more frequently [M29].

437. Rowland et al. [R34, R46] analysed the dose-response relationships for bone sarcoma in this population. Female dial painters were selected from the total group and were followed until 31 December 1979. Among 1468 individuals with a measured body content of radium, 42 bone sarcomas were found, whereas 0.4 were expected on age- and time-specific rates for white females in the United States. However, among all recognized sarcoma cases, the body burdens were not measured in about one-third of cases [R46]. Excess of sinus and mastoid carcinomas was also reported and they were thought to arise from irradiation of the lining epithelium by ^{222}Rn and decay products accumulating in the cavities. Their number

was too small and dosimetry too uncertain for any reasonable discussion of dose-response relationships.

438. The numbers of cases per person-year at risk were calculated as a function of the systemic intake of radium (activity of ^{226}Ra + 2.5 activity of ^{228}Ra; it had been shown [R18] that for induction of osteosarcomas in man ^{228}Ra is 2.5 times more effective per unit activity than ^{226}Ra). All cases with systemic intakes greater than about 10 kBq were used for the fit. The breakdown of cases into 14 intake groups was made in such a way that 3 strata covered each order of magnitude (Figure XXXI) from about 10 kBq up to about 1 GBq. Mean intakes were calculated either as simple weighted means or as roots of mean weighted squares. The former was used when linear, and the latter when quadratic, functions were fitted to the independent variable. Values of 0.7 10^{-5} and 1.75 10^{-5} were taken as expected (control) incidence rates for the two modes of treatment mentioned above.

439. Various forms of general initial activity (A)-incidence-rate expression $\dot{I}_{TA} = (a_0 + a_1A + a_2A^2)e^{-\beta_1 A}$ were fitted to the data and tested by χ^2 statistics for goodness of fit. Fitting of 13 data points was carried out by a general weighted least-squares procedure. A quadratic initiation + killing expression gives the best fit (P = 0.73). Arbitrary selection of a positive a_1 still gave an acceptable fit (P = 0.05) of a_1 = 1.3 10^{-5}. The parameters of the equation $\dot{I}_{TA} = (a_0 + a_2A^2)\, e^{-\beta_1 A}$ are: $a_2 = (7.0 \pm 0.6)\ 10^{-8}$ and $\beta_1 = (1.1 \pm 0.1)\ 10^{-3}$, where A is the initial systemic intake of activity.

440. The pure quadratic and linear-quadratic functions give a similar response at higher intakes, but differ markedly in the region of about 4 MBq intake. To change the response from quadratic to linear while retaining a good fit, three additional sarcomas would have to appear in the years to come in the low-dose region where no sarcoma has yet been seen. This, the authors judge as quite improbable (although the activity distribution among unmeasured sarcoma cases is not known). Arbitrary changes of intake ranges did not alter the fact that dose-squared plus killing functions always gave the best fit to the data; only in isolated categorizations of the intake could a linear fit not be discarded.

441. When the dependence between radium intake and time of sarcoma appearance was examined, an inverse relationship was found between intake and maximum or mean (but not minimum) induction period. The numbers of observed and predicted bone sarcomas as a function of time after intake were in good agreement, suggesting that the risk is rather constant over 65 years after intake. No bone sarcoma has been observed among the 1680 measured cases (all categories) with intakes of less than about 2 MBq. The conclusion is, therefore, that the life-span probability of bone sarcoma induction below this level of intake must be very small. The authors calculated that after an intake of about 40 kBq ^{226}Ra over one year, the corresponding lifetime risk of bone sarcoma was 5 10^{-14} and 1.3 10^{-5} per year, for the quadratic and linear-quadratic dose-response functions, respectively.

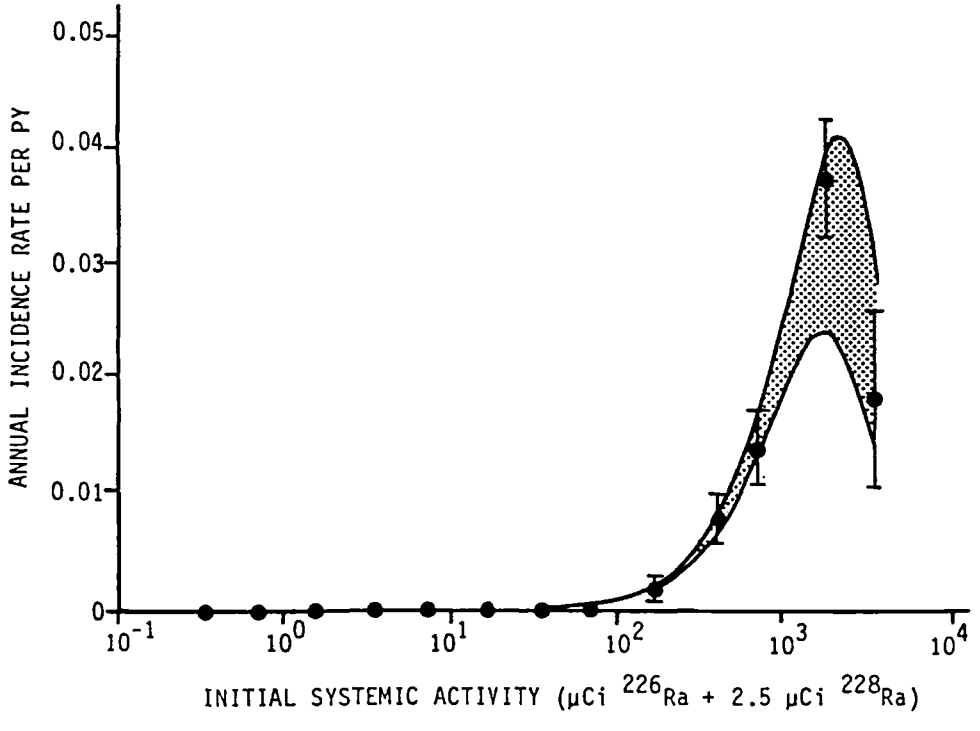


Figure XXXI. A semi-logarithmic plot of bone sarcoma incidence rate as a function of systemic intake for female dial painters employed before 1950, showing a dose-squared exponential fit. The shaded band indicates the range covered by the fitted function when the coefficients are allowed to vary by ± 1 S.D. Error bars represent the binomial standard errors of the observed incidences. [R34]

442. Schlenker [S50], assumed a binomial distribution to calculate the probability of observing a number of bone sarcomas greater than predicted by the relationship $\dot{I}_{TA} = (a_0 + a_2A^2) - \exp \beta_1 A$ in the zero range, i.e., for the activity A below about 4 MBq where no tumours were actually seen. For the dose-response curve itself, the probability was 50%. For pairs of curves delineating the 68% and 95% confidence limits (Figure XXXII) there is a corresponding chance that the true number of tumours lies between the two predictions. The curves enveloping the 95% confidence interval span a factor of 90 and their widest distance gives a feeling for the uncertainty in the estimated dose-response relationship at low activities of radium systemic uptake.

443. Because of the inverse relationship between activity and latent period, it might be expected that the upward concavity of the dose-response curve would result from the choice of the variable (rate per year) and would vanish when expressed as cumulative incidence. In annex H of the 1972 UNSCEAR report ([U7], Figure IX), the results of the follow-up through 1969, expressed in this way, showed a downwards concave dose-response relationship. In 1972, Mays and Lloyd [M11] investigated the dose-response relationship for all United States subjects containing radium in their bodies, thus continuing the combined MIT and the Argonne series updated to May 1971. In all, 762 individuals below 200 Gy average skeletal dose were included, 48 of whom developed bone sarcomas. The dose-incidence relationship had a linear trend with a slope of 0.46% per Gy. However, the probability of seeing the deficit of cases below 10 Gy as observed, on the basis of the regression analysis, was less than 0.1. Mole [M29] plotted, as a function of dose, the cumulative incidence of bone sarcoma per 10^3 individuals for the group of dial painters who started work before 1930 [M27] and who were followed through 1972 [A10]. He assumed equal effectiveness of doses from both radium isotopes, as quoted in [A10]. Functions of incidence I_{TA} against dose (D) in Gy, of the form $I_{TA} = a_2D^2e^{-\beta_1 D}$ and $I_{TA} = a_1De^{-\beta_1 D}$ gave fits of comparable goodness (P = 0.26 and 0.45, respectively). The fit to a linear equation is

$$I_{TA}(D) = (111 \pm 22)10^{-4}\, D\, e^{-(8.5 \pm 2.2)10^{-3}D} \qquad (5.2)$$

characteristic of the linear model for high-LET radiation, which could be used for interpretation of the data on incidence. The slope gives the risk of bone sarcoma from the absorbed dose from radium alpha-radiation. Very low values of β_1 cannot be interpreted in terms of a very high lethal dose to the transformed cells for a variety of reasons, including the long duration of exposure with possible repopulation of the irradiated cell pool.

444. Schlenker [S50] approached the same problem theoretically by calculating the life-time probability I_{TA} of bone sarcoma, corrected for the presence of competing risks, expressed as a function of time-average tumour rate from $^{226}Ra + {}^{228}Ra$ derived from Rowland's equation referred to above [R18]. Thus,

$$I_{TA} = \int_A^{100} da\, \dot{I}_{TA}\, e^{-\int_A^a (I_{TA} + \dot{S}_a)\, da} \qquad (5.3)$$

where A is the age at exposure; a is the age in years; $\dot{I}_{TA}$ is the time average tumour rate, equal to zero

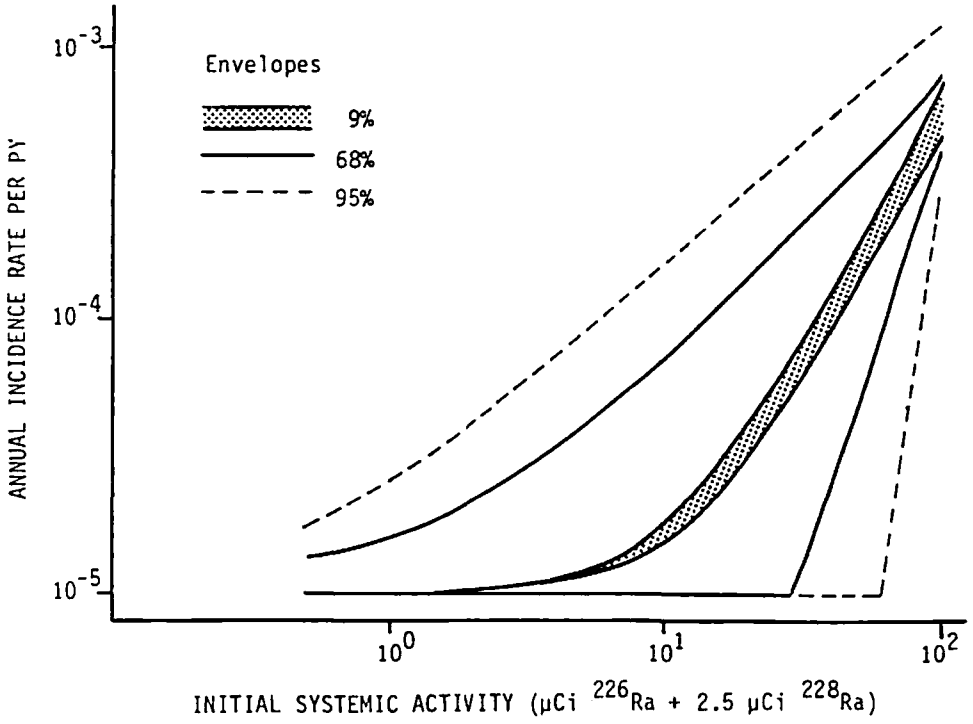


Figure XXXII. Plot of bone sarcoma incidence rate in female dial painters, as a function of the initial intake of radium. Three pairs of curves denote probabilities that the true number of bone sarcomas, in the region of intake where no tumours were observed, falls within the calculated envelopes [S50]. The shaded area covers two standard deviations on either side of the dose-response curve $\dot{I}_{TA} = (a_0 + a_2A^2)\, e^{-\beta_1 A}$, as calculated from the standard errors of the parameters [R34].

until a five-year latent period has passed and constant thereafter; and $\dot{S}_a$ is the death rate from all other causes as a function of age.

445. For single ^{226}Ra intakes at ages 20, 45 and 70 years, the results are presented in Figure XXXIII,

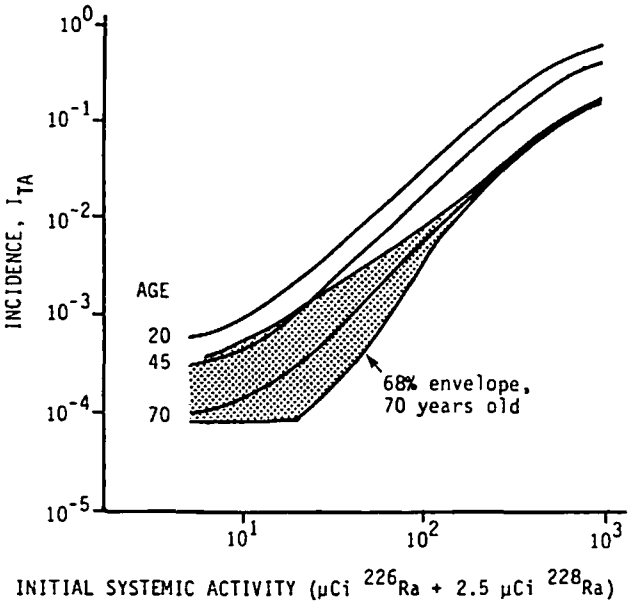


Figure XXXIII. Predicted life-time incidence of bone sarcoma in the presence of competing risks, as a function of a single intake of ^{226,228}Ra.
[S50]

together with 68% confidence limit envelopes for a 70-year-old. For other ages, the envelopes are very similar. It is quite obvious that an approximately linear dose-response for cumulative incidence I_{TA} against intake of activity into the blood might be the prevailing trend over the range from about 200 kBq to about 8 MBq. This conclusion, of course, excludes neither the possibility of a "practical threshold" nor the absence of a life-shortening effect such as that referred to above, nor that a dose-squared relationship may be fitted into the envelopes.

446. The linear trend of bone sarcoma incidence (I_{TA}) against alpha-ray dose in the human skeleton is in accordance with the bulk of the evidence from animal experiments, as reviewed in chapter IV. However, more refined analyses of bone sarcoma integral tumour rates, induced in beagles by ^{239}Pu injections, support a dose-squared dependence of the rate [P17, W14]. For radionuclides emitting low-LET particles like ^{90}Sr, an upwards concave dose-response relationship was invariably observed [M12-M14].

447. Several thousand patients in the Federal Republic of Germany were given repeated intravenous injections of ^{224}Ra in the course of therapy for tuberculosis and ankylosing spondylitis. In contrast with ^{226}Ra, ^{224}Ra, with its short half-life of 3.64 days, decays on the surface of bone where it becomes deposited early after injection due to rapid ionic exchange. The fraction of the mean dose to the skeleton delivered by ^{224}Ra to the target cells is much higher than that for ^{226}Ra. The effectiveness of the mean skeletal dose is therefore about 7 times higher for ^{224}Ra. The patients were of both sexes and included adults as well as juveniles. The most recent report on these patients through 1980 [M57] includes 218 juveniles and 680 adults. Bone sarcomas had appeared in 35 patients injected as juveniles and in 18 adults. The follow-up times ranged from 0 to 36 years; deaths accounted for most of the short follow-up times, whereas 582 patients were followed for more than 19 years and 78% were still alive in 1980. The mean skeletal doses from α-particles were estimated to be 10.98 and 2.05 Gy in juvenile and adult, respectively; the corresponding injection spans averaged 11 and 6 months. Virtually all bone sarcomas are ascribed to radiation, as only 0.2 cases would be expected, based on general population rates.

448. The shortest appearance times were 3.5 and 5 years in juvenile and adult patients, respectively; the corresponding average values were 10.4 ± 5.1 and 11.6 ± 5.2 years, and were not significantly different. The time distribution was similar to that for leukaemias in atomic bomb survivors, as described for those exposed within 1500 m of ground zero by Bizzozero et al. [B82] for which the average appearance time was 9 years. The peak of bone sarcoma appearance was 6-8 years. No additional cases were discovered since the previous report in 1974 [S21]. It may be concluded, therefore, that by 25-30 years after injection the vast majority of bone sarcomas have already become manifest.

449. There was some tendency towards a lower risk of bone sarcoma per unit dose with advancing age at injection, but this could be an artifact due to uncertainties in dosimetric assumptions, a possibly non-linear response, or a more pronounced fractionation of injected activity in juveniles. Fractionated administration appeared more effective: a protracted weekly administration over a few years carries a 5-times greater risk per unit dose than single injection [S18]. This observation is in agreement with studies on mice injected with ^{224}Ra in various fractionation schemes [L20, M67]. Original data from reference [S18] were examined [P8] for partial correlations between the increment of incidence per unit dose, average injection span and the average skeletal dose. Significant positive correlations were found between the span and dose, and also between the incidence increment and the span. The correlation between the increment of incidence and the fractionation span itself was non-significant (in fact it was negative) when the above partial correlations were accounted for. Thus, the suggestion of an increased effectiveness of fractionated versus single administration of ^{224}Ra, based upon human experience, appears unfounded. The dose-response relationship for bone sarcoma incidence in the treated patients was compatible with linearity. The slopes for juveniles and adults differ by a factor not greater than 2 (Figure XXXIV, [S21]). However, a dose-squared trend of the effect could not be rejected on statistical grounds. No carcinomas of the head sinuses were observed in patients injected with ^{224}Ra due to lack of sufficiently long-lived radon nuclides in the thorium decay series.

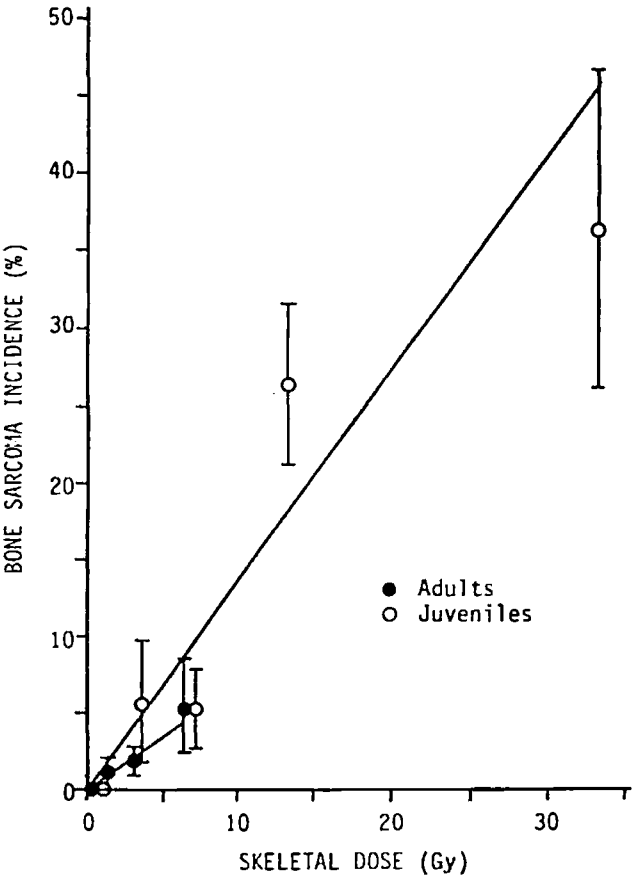


Figure XXXIV. Bone sarcoma incidence versus skeletal dose from ^{224}Ra. For the linear non-threshold lines shown the cumulative risk of bone sarcoma during 14-21 years post-exposure is 0.7% (adults) and 1.4% (juveniles) per unit average skeletal dose.
[S21]

450. Schlenker [S50] calculated the dose-response relationship for ^{224}Ra-induced osteosarcoma cases. For incidence I_{TA} (uncorrected for competing risks) in subjects older than 16 years at injection, the function had the form $I_{TA} = 1 - e^{-3.0\,10^{-5}A}$. At the widest separation, the 95% confidence limits span a range of 750, reflecting much less information at low doses for ^{224}Ra than for $^{226+228}$Ra. This can be explained by the smaller number of cases and shorter follow-up times.

2. The model of Marshall and Groer

451. Theories of bone sarcoma induction were developed in the past [B21, M26] but the most comprehensive one based on human epidemiological data has been presented by Marshall and Groer [M4]. They based their model on several observations. The first is that a linear dose-response relationship gave a poor fit to the incidence rate of bone sarcoma versus dose (bone averaged) from ^{226}Ra and ^{228}Ra, as discussed in detail by Rowland [R18-R20]. There were no cases of osteosarcoma below 9 Gy, and pure linearity of incidence rate versus dose was therefore highly unlikely on statistical grounds. They postulated, therefore, that two events produced by alpha radiation in a cell at risk are necessary to initiate the malignant transformation.

452. Marshall and Groer assumed that there are about 10^{11} cells at risk in the endosteum of a "reference man". These cells are subject to sarcoma initiation in two steps, but also to cell killing, the killing being by a factor of 10^5 more probable than initiation (D_0 for the cells must be of the order of 1 Gy). Thus, doses which produce bone sarcoma (at a rate of a few tens of mGy per day) should also completely sterilize the population of cells at risk before any transformation could have occurred. To eliminate this difficulty, the authors assumed that cells within a 0-10 μm distance from the bone surface, if killed by alpha particles, can be replaced at a rate of 0.1 per day from a stem-cell compartment which itself is beyond the range of 5.7 MeV alpha particles. A conceptual outline of the model is shown in Figure XXXV. At all stages of malignant development,

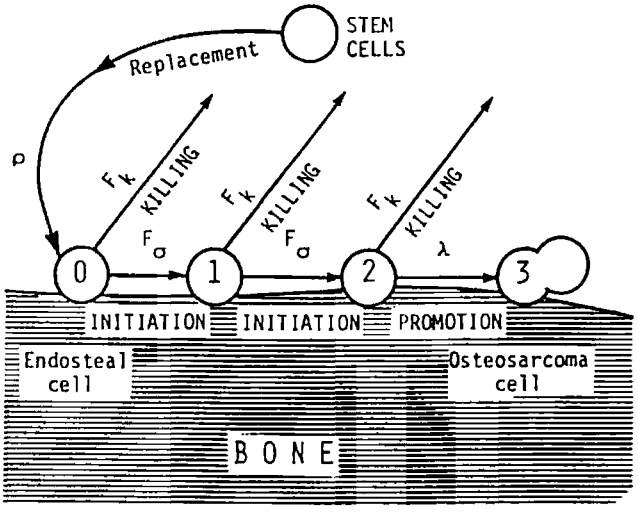


Figure XXXV. Schematic representation of the Marshall and Groer [M4] model of bone sarcoma induction by alpha particles. An original endosteal cell is initiated twice and promoted to become an osteosarcoma cell; cells killed at any stage before promotion are replaced by stem cells. The rate of killing, F_k, is 10^5 times larger than the rate of initiation $F\sigma$ (F = endosteal dose rate). The rates of replacement ρ and of promotion λ are independent of radiation dose.

the cells are at risk of killing, which is proportional to their numbers (M_0, M_1, M_2) and to the dose rate F. The dose rate in turn is proportional to the content of radium per unit mass of the diffuse radium component in bone. The fully transformed cells (M_3) promoted to cellular division are not assumed to be at significant risk for cell killing due to a rapid multiplication of the clone and escape of the tumorous cells from the volume irradiated by alpha particles.

453. To summarize, the model incorporates the following parameters:

(a) initiation probability per cell per unit dose (σ);
(b) killing probability per unit dose (k);
(c) number of cells at risk (s);
(d) promotion probability per unit time (λ);
(e) replacement probability of killed cells (ρ);
(f) growth time of a tumour to become recognizable (g);

(g) dose rate (F) proportional to activity per body weight (c).

These parameters were incorporated in a set of differential equations to give a probability of appearance, P(t), of an osteosarcoma per unit time per individual and unit activity of radium reaching the blood stream. The values of ρ, σ and s were held fixed, and initiation probability, promotion rate, tumour growth time and dose rate were adjusted through a solution of the model by best fit of the data obtained from observation of individuals with radium body burdens followed through December 1973 at the Argonne National Laboratory [A10].

454. From the solution of the model for man, it follows that the time of sarcoma appearance after radium uptake should increase with decreasing values of the intake q reaching a constant plateau at about 30-35 years at the level of 40 kBq per kg body weight. The theory predicts [G23, M4] an enhanced effect on bone sarcoma induction by fractionated administration of a short-lived bone-seeking alpha emitter. The existence of such a phenomenon was, in fact, suggested when bone sarcoma incidence was studied after injections of ^{224}Ra. When the isotope was administered over one month, the incidence was lower than that seen after prolonged (average 2 years) administration of the nuclide (P = 0.16) [S18]. The lower sarcoma incidence in this case should result, according to Marshall and Groer [G23, M4], from suppression of the population of viable endosteal cells M_0 by very high dose rates delivered over short intervals (the empirical basis to support this contention is open to critique, see paragraph 449).

455. The theory fits satisfactorily the preliminary data on the induction of bone sarcoma by ^{226}Ra in Utah beagles, in which the cumulative incidence reaches a plateau of about 92%, a factor of 3-4.5 higher than in man. The parameters of the theory, which give a good fit to the experimental situation, were rather similar to those for man, with the exception of higher promotion and initiation rates (both roughly by a factor of 10). Reasons for this interspecies difference in initiation probability are not clear.

456. Marshall and Groer [M4] correctly stated that fit of the model to the measured data does not prove correctness of the postulates. Some results of the theory were not envisaged a priori, e.g., the plateau of incidence rate at high doses (Figure XXXVI). This point of agreement enhances the credibility of the theory. However, in the light of the evidence that the cumulative incidence of ^{226}Ra-induced bone sarcoma, both in man and in beagles, can be reasonably approximated by a linear model, the basic assumption of two-hit initiation is open to question. A model similar to that of Marshall and Groer, but postulating a one-hit initiation has been proposed [P23]. The model explains the non-linear part of the activity-incidence rate curve by the promoting action of alpha radiation exerted via repopulation of the target cell pool (osteogenic cells).

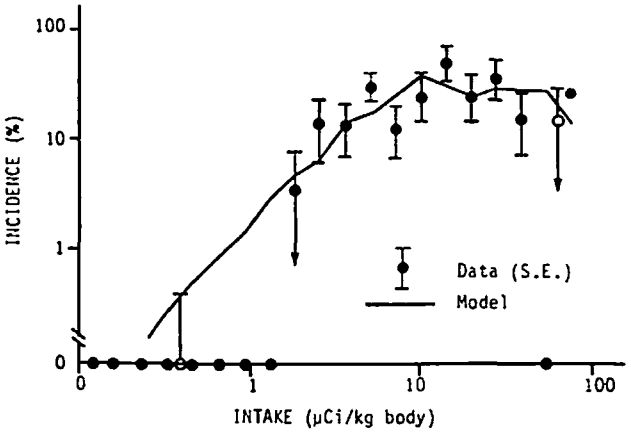


Figure XXXVI. The cumulative incidence of osteosarcomas in man versus the total intake (μCi per kg body weight) of radium-226 plus radium-228. Up to about 1 μCi per kilogram body weight systemic intake the slope of the line, according to the model of Marshall and Groer [M4], is close to 1.

F. INTERSPECIES COMPARISONS

457. In numerous instances in the course of the review of experimental (chapter IV) and human data (chapter V), qualitative similarities have been pointed out between animal and human data that may usefully be summarized here. From such comparisons, the pattern seems to emerge that the shape of dose-response relationships may be basically similar in various species.

458. Thus, the linear non-threshold type of dose-response relationship for female mammary carcinoma induced by x rays finds its counterpart in the results of studies on at least four strains of rats: (a) the Sprague-Dawley females irradiated externally by x rays and/or gamma rays, and internally by β particles from tritium: the linearity applies to adenomas but the results for adenocarcinomas are also consistent with the notion; (b) females of the WAG/Rij rat strain and the AC strain irradiated externally with x rays showing linearity for adenomas and carcinomas, respectively; and (c) non-inbred female rats irradiated from a β-particle source also showing a linear rise of incidence of mammary carcinomas. The dose-response curve for mammary carcinomas induced in BALB/C mice by gamma rays shows irregularities that defy any possible comparison.

459. A strong linear component is manifest in the non-threshold dose-response relationship for x-ray induced thyroid carcinoma in man; effects of dose-fractionation are virtually absent. Data on Long-Evans rats, even if the number of animals is limited and the observations were terminated 2 years after irradiation, are compatible with linearity. They also show a lack of a pronounced dose-rate effect, as shown by the comparison of x-ray and ^{131}I dose-response curves. The absence of an excess of thyroid cancers in humans exposed to diagnostic quantities of ^{131}I is not consistent with the above observation, but

the relevant sample is highly selected and the observations made on this cohort do not necessarily invalidate the basic similarities between the dose-response relationships from the human species and the rat.

460. Cancer of the respiratory tract induced in several groups of miners, exposed to daughter products of ^{222}Rn, consistently yields a non-threshold linear dose-response relationship up to a cumulative exposure of about 300 WLM, with some decline of the risk coefficient (F_{TA}) at higher exposures or exposure rates > 50 WLM per year. A very similar relationship is observed in male Sprague-Dawley rats made to inhale ^{222}Rn decay products or exposed to fission neutrons. The analogy holds when the data from the two species are analysed in terms of both the absolute and the relative risk model.

461. Dose-response relationships for bone sarcoma induced by long-lived isotopes of radium in man, beagles and mice are compatible with linearity between dose and cumulative incidence over the initial part of the curve. In all three species a decline of the tumour yield is seen at high and very high doses in the skeleton. In the three species there is also a pronounced inverse relationship between dose (or initial activity in the body) and the latent period.

462. In summary, it appears that the shape of the dose-response relationship for radiation-induced cancer of some organs in man generally follows the pattern seen in a number of experimental animal species. This qualitative finding will have to be verified in the light of future data. The similarity may not be surprising for those types of human malignancies that have a reasonable counterpart in other mammalian species, in view of the basic similarity of patho-physiological phenomena on which rests the rationale of using experimental animals to predict the response of man. However, the regularities pointed out do not imply that data from experimental animals may be used to derive risk coefficient applicable to man, because, so far, such similarities may not be shown to apply to the quantitative expression of the carcinogenic effect in various species.

G. SUMMARY AND CONCLUSIONS

463. Epidemiological data useful for an analysis of the shape of the dose-response relationships for radiation-induced cancer are limited. This applies to external and internal, to instantaneous and prolonged exposures. Caution should therefore be exercised in formulating broad generalizations. Several factors are known to affect the magnitude of the neoplastic response. Among those identified, age at irradiation, sex and genetic or ethnic characteristics are of importance, but the extent to which these factors may affect the form of the dose-response curves is almost totally unknown. For some tumours, e.g., cancer of the lung, the characteristics of the environment and the living habits may consistently affect the expression of malignancies.

464. With the Hiroshima and Nagasaki atomic bomb dosimetry still uncertain, the epidemiological information on leukaemia incidence in the survivors cannot yet be fully utilized. Information on induction of leukaemia derived from the follow-up of spondylitis patients is insufficient to allow firm conclusions as to the most likely form of the dose relationship, particularly because leukaemia incidence in this group may have been influenced to an unknown extent by dose-fractionation effects. Therefore, further discussion of dose-response relationships must be postponed until new information on the atomic bomb survivors becomes available.

465. Regarding breast cancer, there is no suggestion of a threshold for low-LET radiation; either a pure linear relationship with dose or one with a small dose-squared term might apply. This conclusion is supported by the small or absent effect of dose fractionation and by the lack of a detectable relationship of latency to dose. For this tumour, there is, however, a pronounced variation of the risk with the age at exposure, as women in the age range of 0-30 years are at the highest risk.

466. Dose-response relationships for carcinoma of the thyroid have a strong linear component and the data do not suggest a threshold. There appears to be no inverse relationship between latency and dose and this is consistent with the observed linearity. Infants and children are more susceptible to cancer of the thyroid than grown-up persons. Dose-rate effects cannot be excluded, and data on patients given ^{131}I for diagnostic purposes might be interpreted in this way; however, other interpretations are also possible, particularly since dose-rate effects have not been seen in recent animal experiments. The induction of benign thyroid adenomas is linearly related with x-ray doses at low doses, but with a decrease of the slope at doses above 1 Gy.

467. The available data on lung cancer induced by exposure to radon and its decay products in mines show, without exception, linear exposure-response relationships, with a decreasing slope at the highest exposure rates (above 50 WLM per year); there is no indication of a threshold. This type of relationship has also been consistently observed for airborne short-lived α-emitting radionuclides in animal experiments. For low-LET radiation the form of the dose-response curve is essentially unknown.

468. Alpha-emitting bone-seeking radionuclides, such as ^{226}Ra and ^{228}Ra, may induce bone sarcoma in man with a significantly elevated frequency at mean skeletal doses above 10 Gy. Plotting the incidence or incidence rate against cumulative dose results in relationships that may be interpreted as either linear or quadratic. In the latter case, below about 10 Gy there is a significant deficit of tumours when a linear interpolation to zero dose is attempted and I_{TA} fits very well a dose-squared model with a cell-killing term. In this case, linearity may be rejected. It appears impossible at present to decide whether linear or quadratic models, or a combination of both, provide better fits to incidence (I_{TA}) versus dose from radium

isotopes over the initial portion of the curve. Animal experiments suggest linearity. Bone sarcomas induced in man and animals by α-emitting bone seekers show a pronounced inverse relationship of latency to dose. The deficit of tumours in man, at the lowest end of the scale mentioned above, could therefore reflect an apparent "practical" threshold, and a decreasing tumour-related life shortening with lowering of the dose.

469. A dose-response relationship for bone sarcoma induced in man by short-lived α-emitters (^{224}Ra) is compatible with linearity, even though alternative models may not be excluded. The latent period for bone sarcoma appears to be rather short; the age at the beginning of exposure has no strong influence. There are no human studies of bone sarcoma caused by low-LET irradiation. However, irradiation of experimental animals by β-emitting bone seekers (^{45}Ca, ^{90}Sr, ^{89}Sr) invariably resulted in upwards concave relationships and a pronounced inverse relationship between dose and latent period. It would be expected that the same kind of relationship might also apply to man.

470. In summary, the model applying to the dose-response relationship for leukaemia is unknown and must remain so until new dose-incidence data for atomic bomb survivors become available. The reviewed evidence suggests that incidence of lung, mammary and thyroid cancers is probably related with dose by a generalized linear or linear-quadratic relationship. However, dose-incidence information is not available for lung cancers after low-LET and for breast and thyroid after high-LET irradiation.

471. In a comparison of data from experimental animals, reviewed in chapter IV, and from human epidemiological studies in the present chapter, UNSCEAR has identified a number of tumours for which the dose-response relationships appear to follow the same basic pattern in various species. Such a comparison will have to be verified as more data are accumulated. In any case, the qualitative similarity of the induction kinetics does not justify any simple quantitative extrapolation of incidence data from animals to man.

VI. SUMMARY

472. In order to estimate the absolute risk of radiation-induced cancer (number of induced tumours per million people exposed per unit dose, i.e., cases 10^{-6} Gy^{-1}), or the relative increase of tumour frequency per unit dose over the "natural" incidence at low doses and dose rates, two types of information are required: first, empirical data on the incidence of various forms of malignancy at relatively high doses where observations have actually been made; second, knowledge of the mathematical form of the relationships linking the incidence of cancers with the dose of radiation. Such data would allow predictions to be made of the cancer incidence at doses (and perhaps also at dose rates) very much lower than those at which direct observations in man have been gathered.

473. When the incidence of a given tumour in exposed animal or human populations is followed as a function of increasing dose, several observations may usually be made. At relatively low doses (at about 0.1 Gy of sparsely-ionizing radiation), only seldom (and then mostly in controlled animal experiments) can a statistically significant increase of cancer or leukaemia be shown. At higher doses (up to a few Gy, but with considerable differences between different tumours), the incidence of such malignancies may be shown statistically to exceed the level observed in non-exposed control populations, following some increasing function of the dose. At still higher doses (many Gy), the incidence gradually starts to fall off because of cell killing. Dose-response relationships of this type, going through a maximum at some intermediate dose, are often found in experimental animals. They are termed "biphasic".

474. A common interpretation attached to such a shape advocates the concurrent presence of two different phenomena: (a) a dose-related increase of the proportion of normal cells that are transformed into malignant ones; and (b) a dose-related decrease of the probability that such cells may survive the radiation treatment. Both these phenomena are normally operating in the region of doses where data are available, but to a different degree for various doses and different types of cancer. What may happen at the low doses, where direct information is lacking, may only be inferred from a combination of empirical data and theoretical assumptions, linked together into some models of radiation action.

475. The models referred to are simplified semi-quantitative representations of complex biological phenomena. Present knowledge of the mechanisms of carcinogenesis, including radiation carcinogenesis, is inadequate to design comprehensive models accounting for all physical and biological factors known to influence the induction of cancer. To avoid some of the complications involved, UNSCEAR suggests that the range of doses over which extrapolations may meaningfully be performed should be limited to low and intermediate doses. Under these conditions, it seems likely that no serious distortions would result from other radiation effects, called non-stochastic, that are observed when doses exceed fairly high thresholds, typical for each tissue and each effect.

476. The formulation and analysis of models of radiation carcinogenesis must rely on a few basic assumptions, as follows:

(a) The observed dose-response relationships for clinically visible tumours in vivo approximately reflect the relationships between dose and frequency of the initial triggering events in the cells where cancer will eventually arise, despite host reactions and the effect of latency, which may modify such relationships to some degree. This assumption is based on the overall similarity of the dose-response curves for cancer induction with those of various other cellular effects of radiation. UNSCEAR postulates this concept simply as a working hypothesis:

(b) Cancer initiation is basically a unicellular process occurring at random in single cells. This is also a working hypothesis that has not yet definitely been proved. However, evidence to the contrary, i.e., that cancer initiation takes place in several cells, is not entirely convincing. The uni-cellular theory of cancer induction is compatible with the notion that some, still ill-defined, influences resulting from irradiation of other neighbouring cells or other organs may modify the probability of an initiated cell to develop into an overt malignancy. Firm biological evidence in favour of this latter notion is very fragmentary;

(c) Absence of a dose threshold is characteristic of many, if not all, tumours. For some animal tumours (e.g., tumours of the ovary or thymic lymphoma of the mouse) threshold-type dose-response relationships are observed. In other cases (e.g., tumours of the skin) cancer is only induced with great difficulty, i.e., after high doses of radiation. In still others (i.e., epidermoid lung cancer in man) the data are unclear, owing perhaps to a short follow-up of the patients. However, in spite of these exceptions, absence of a threshold dose for the development of cancer is assumed by UNSCEAR as a working hypothesis for the time being;

(d) Susceptibility of an irradiated animal or human population to tumour induction is assumed to follow a unimodal distribution. Although genetic predispositions to the development of some forms of malignancy are well documented (see annex A), efforts to show that such phenomena apply also to radiation-induced human cancer have not been successful so far. Therefore, pending further studies, the same unimodal distribution of susceptibilities to the induction of cancer in irradiated and non-irradiated populations is also provisionally accepted as a working proposition.

477. On the above assumptions, it is possible to infer likely shapes for the dose-response relationships of radiation-induced cancer. Such inferences rely on the analysis of various other radiation effects observed at the cellular level. These effects involve the cells' genetic material, which is also thought to be the primary target for cancer initiation. The production of mutations and chromosomal aberrations in somatic and germinal cells, and the oncogenic transformation in vitro of mammalian cell lines, are examples of such effects. If cancer induction in vivo involves mechanisms similar to, or related with, those underlying the effects listed above, one would expect all these phenomena to respond similarly in respect of changes in dose, dose rate and fractionation. As such similarities have actually been observed, it may be possible to extrapolate the shape of dose-response relationships between such effects and the phenomenon of cancer induction.

478. Three basic non-threshold models of radiation action as a function of dose have been discussed with respect to such cellular effects and to cancer induction: the linear, the linear-quadratic and the pure quadratic. Notwithstanding some exceptions, these may provide a general envelope for a variety of radiation-induced end-points at the cellular level, as well as for tumour induction in experimental animals and human populations.

479. The vast majority of dose-response curves for induction of point mutations and chromosomal aberrations by sparsely-ionizing x and gamma rays may be described by a linear-quadratic model. For the same end-points, when cell killing is corrected for, a linear model usually applies to densely-ionizing neutrons or alpha particles. As a rule, for a number of chromosomal structural abnormalities, curvilinearity (upward concavity) is observed for low-LET radiation, while, for the same effects and a wide range of doses, linearity prevails for high-LET particles. Linearity of the dose-response for somatic mutations and terminal chromosomal deletions has been found in some cell lines, even for low-LET radiation, but these findings are relatively infrequent.

480. Approximate estimates of proportionality constants linking the chromosomal effects with the dose or its square may be obtained experimentally. They allow the frequency of such effects to be predicted at low doses and dose rates from observations at higher doses. For cancer induction, however, only fragmentary information supports the notion that similar quantitative relationships with the dose might apply. UNSCEAR has estimated that if the risk of tumour induction at 1 or 2 Gy of sparsely-ionizing radiation (at high dose rate) were extrapolated linearly down to zero dose, this procedure would over-estimate the risk by a factor of perhaps up to 5 in typical situations.

481. Over the last few years much information on radiation-induced oncogenic transformation of mammalian cells has become available. The cancerous nature of the transformed cells is shown by the fact that after transformation in vitro they are able to form malignant tumours upon transplantation into an animal of the same species. Transformation in vitro is therefore regarded as a model, albeit a simplified one, of radiation carcinogenesis at the cellular level. Cells exposed in vitro to sparsely-ionizing radiation 24 hours after seeding are transformed according to complex kinetics that cannot be fitted to models used for other cellular effects. Moreover, fractionation of the dose (below 1.5 Gy total) enhances transformation, which effect is contrary to what would be predicted by a linear-quadratic model. If similar phenomena would apply to the induction of cancer in vivo, extrapolation to low doses and dose rates might result in a significant under-estimate of the risk. Further research is needed to elucidate these phenomena, but several experiments indicate that the observations on in vitro systems referred to above may result from non-typical conditions of cellular growth during the early periods after establishment of the culture. Actually, irradiation of non-dividing cells or cells under exponential conditions of growth (which are thought to be more representative of an asynchronously dividing cell population) produces results that are compatible with those obtained for other cellular effects; thus, for example, high-dose-rate gamma irradiation results in a greater frequency of transformation than low-dose-rate exposure.

482. There are indications that when cells are irradiated with neutrons, low-dose-rate or dose fractionation may increase the rate of transformation, even at low doses; however, whereas some observations on tumour induction in experimental animals clearly support these findings, others do not. In other experiments, enhanced transformation by neutron fractionation or protraction were seen only at intermediate and high doses. In view of the scarcity of such data, and of the uncertainties regarding the mechanisms involved, further research is needed before enhancement of cancer induction by neutron fractionation and protraction (relative to single or high-dose-rate exposure) may be accepted for the purpose of risk assessment. Such a possibility should, however, be kept in mind even though the theoretical basis to explain such phenomena is uncertain at present.

483. Recent experimental findings on radiation-induced tumours in experimental animals have not substantially changed the main conclusions reached in annex I of the 1977 UNSCEAR report. Most data support the notion that dose-response relationships for x and gamma rays tend to be curvilinear and concave upward at low doses. Under these conditions, tumour induction is dose-rate dependent, in that a reduction of the dose rate, or fractionation, reduces the tumour yield. A linear extrapolation of the risk from doses delivered at high rates to zero dose would thus, as a rule, over-estimate the real risk at low doses and dose rates. However, in one experimental mammary tumour system (matched by epidemiological data on human breast cancer) x and gamma radiation produced a linear dose-response with little fractionation and dose-rate dependence. This was recognized as an exception in the 1977 UNSCEAR report. It appears likely that a similar dose-response relationship could also apply to the induction of thyroid cancers, but the data are too limited to permit any definite conclusion to be drawn in this respect.

484. For densely-ionizing neutron irradiation, tumour induction in animals follows, in general, a very nearly linear curve at the lower end of the dose scale and shows little dependence on dose rate. In some cases, however, enhancement upon fractionation (and possibly protraction) has been noted. Above about 0.1 Gy or so, the curve tends to become concave downward, markedly in some cases. Under these conditions, a linear extrapolation of the risk down to zero dose from intermediate or high doses and dose rates would involve a variable degree of under-estimation.

485. Having reviewed existing data on dose-response relationships for radiation-induced tumours in man, UNSCEAR considers that this whole matter must be treated with caution because at the present time observations are fragmentary. Those for neutrons are totally absent, and definitive data for atomic bomb survivors at Hiroshima and Nagasaki are still not available. For example, dose-response information for sparsely-ionizing radiation have not been reported for lung and bone tumours, and data for densely-ionizing radiation have not been reported for thyroid and mammary cancer. For sparsely-ionizing radiation, in some cases (lung, thyroid, breast), the data available are consistent with linear or linear-quadratic models. For breast cancer, however, predominant linearity may apply, as the incidence is little affected by dose fractionation. Linearity of the response for lung cancer after irradiation by alpha particles from radon decay products does not contradict the above statement, because with alpha particles the dose-squared component is practically absent. Some doubts still remain, however, as to osteosarcoma induced by bone-seeking alpha- or beta-emitting radionuclides. However, in spite of the fragmentary character of the human data, a general picture may be emerging from which several tentative conclusions can be derived.

486. For sparsely-ionizing radiation, linear extrapolation from about 2 Gy down would not over-estimate the risk of breast and possibly thyroid cancer. It would slightly over-estimate the risk of leukaemia, and it would definitely over-estimate the risk of bone sarcoma. For lung cancer, lack of direct evidence does not permit any assessment to be made of the magnitude of the over-estimate.

487. For densely-ionizing radiation, the risk of lung cancer from accumulated exposures to radon decay products at low dose rates from 300 WLM down (roughly corresponding to 20 to 50 Sv) would not be over- or under-estimated by linear extrapolation. However, extrapolation from observations made at higher cumulative exposures might result in a significant under-estimation due to observed flattening (saturation) of the dose-response curve in this region. It should be stressed that absolute risk coefficients derived for male miners, of whom a high proportion are smokers, should not be applied to the general public without due corrections for various factors (intensity of smoking, lung ventilation rate, presence of other contaminating pollutants, etc.) that are thought to increase the risk in the miners.

488. The incidence of bone sarcoma after internal irradiation by alpha particles from long-lived bone-seeking radionuclides is distorted by the existence of a pronounced inverse relationship between accumulated dose and latent period. This results in an apparent threshold at low doses, and in a reduced loss of life span per induced tumour, as a function of decreasing dose, down to zero loss at low doses. If this is a correct explanation for the upward concavity of the dose-response relationship, a linear extrapolation from a few tens of gray mean skeletal dose down to the gray or milligray region would grossly over-estimate the risk.

489. No human data for induction of breast cancer and leukaemia by densely-ionizing radiations are available at present and, therefore, no direct inferences can be made about risk extrapolation to the low-dose domain. On the basis of general knowledge, if the risk at intermediate doses could be derived from data on sparsely-ionizing radiation (suitably corrected for the higher effectiveness of the densely-ionizing particles), a linear extrapolation down to low doses might either under-estimate or correctly estimate the real risk in these cases.

490. For radiation-induced cancers of other organs, only experimental data are available. For sparsely-ionizing radiations upward concave curvilinear dose-response relationships with pronounced dose-rate and fractionation effects are usually found. If similar curves should apply to cancers in man, a linear extrapolation of risk coefficients (obtained at the intermediate dose region after acute irradiation) to the low dose and low dose rates, would very likely over-estimate the real risk, possibly by a factor of up to 5. For densely-ionizing radiation, should relevant values become available, a linear extrapolation would probably under-estimate the risk.

491. Upon close inspection, some regularities seem to emerge that may indirectly help in assessing the character of dose-response relationships in man. A similarity of the shape of the relationships was noted between man and experimental animals for tumours of several organs for which reasonably good information exists. These are: mammary and thyroid cancers (low-LET radiations), and lung and bone cancers (high-LET radiations). Should this pattern be confirmed, knowledge of epidemiogical studies in man at intermediate or high doses, and of the shape of the dose-response relationships from several animal species, might make it possible to assess the bias introduced by linear extrapolation of the risk coefficients to low doses.

VII. RESEARCH NEEDS

492. At the conclusion of this analysis, it appears quite obvious that there exists a wide intellectual gap between the abstract and general nature of the models discussed and the very complex biological reality, particularly in respect of the molecular mechanisms of tumour induction that are gradually being uncovered. Assigning a biological meaning to the numerical constants of the models, searching for the compatibility between the mechanisms identified and the models' predictions, and formulating new models based on hard data rather than on a priori generalizations, are the formidable tasks facing this type of research today. Any advancement in the field of radiation carcinogenesis will presumably come in parallel with progress in tumour biology, of which the former is only a special aspect. Within these very general guidelines, specialized studies in the following subjects could be valuable and UNSCEAR would like to recommend them to the attention of the interested research worker:

(a) Studies on the nature of the cellular and sub-cellular changes involved in the transformation of normal into cancerous cells. These should aim at establishing and possibly identifying the stages in the induction process that have been postulated. Within these studies, the mechanisms of oncogenic transformation on a wide range of cell types in vitro, and the influence of the main radiobiological variables on the form of the relevant dose-effect relationship, should have a special place, because the biological end-point in question is probably very relevant to the initiation of cancer. Studies on the relationship between transformation of cells to a potentially malignant state in vitro, and the production of malignancies in vivo, should be particularly pursued. Mechanisms by which sub-transformation and potential transformation damage is repaired in cells after exposure to low- and high-LET radiation should also be explored.

(b) In experimental animals, a better understanding of the pathogenesis of radiation-induced tumours should allow the formulation of quantitative models more firmly founded than those available so far. More attention than in the past should be paid to the end-points tested and to the experimental design which will allow a correct statistical analysis of the experimental data. In particular, studies should aim at elucidating the mechanisms by which radiation interacts with oncogenes and the genetic material. Recommendations in respect of experimental work on animals were formulated in annex I of the 1977 UNSCEAR report and, in view of the rather slow rate of accumulation of the data for such long-term effects, many of these recommendations are still valid at present. Particular attention should be devoted to studies in the range of low doses. Comparative studies would be useful of dose-response relationships for those tumours that presumably represent adequate models for human malignancies, and especially those for which quantitative information on dose-response relationships is likely to become available in man in the not too distant future. Studies could usefully be devoted to the RBE of different types of low- and high-LET radiation, particularly in those instances where reliable epidemiological information does not exist, as is now the case for fast neutrons. A subject which remains to be explored in greater depth is that of effects of exogenous and endogenous factors on the shape of dose-response relationships for radiation-induced cancer, particularly the influence of the immunological state and the effects of promoting and inhibitory factors. Another important subject concerns the mechanisms by which downward-concave dose-response curves and enhanced fractionation (or protraction) effects are seen after various doses of neutrons.

(c) In human populations, the follow-up of groups already under study should be continued as a matter of high priority. New studies on groups that might potentially yield further information should also be considered and, if warranted, carefully undertaken. The topics on which further information would be required are, in general, the following:

  (i) The shape of the dose-response relationships for a wide spectrum of tumours and an extended range of doses, with special attention to the correct assessment of doses, as well as its distribution in space and time;

  (ii) The time distribution of the latent periods for tumours with long latencies;

(iii) The existence and the possible form of a relationship between the length of the latent period and the magnitude of dose;

(iv) The influence of age, sex, genetic factors and some habits (e.g., smoking) on the quantitative characteristics of dose-response relationships and the resulting variability in risk estimates;

(v) The adequacy with which relative and absolute risk models for different cancers permit projection of the risk for long periods after irradiation.

Table 1

Observed (O) and expected (E) breast cancers with relative risk estimates as a function of radiation dose for the interval 10-34 years after radiation treatment for mastitis
[S16]

A. Analysis of persons with average dose to both breasts

Dose range (Gy)	Mean dose (Gy)	Breast cancer			
		PY a/	O b/	E c/	RR d/
4.50-12.00	5.84	974	4	1.79	2.24
3.50-4.49	3.92	693	4	1.27	3.14
2.50-3.49	2.94	1084	9	3.09	2.91
1.50-2.49	1.93	2971	12	5.22	2.30
0.40-1.49	1.12	2620	7	4.78	1.47
Control		15767	28	28.0	1.0

B. Analysis of single breasts with total dose per breast

Dose range (Gy)	Mean dose (Gy)	Breast cancer			
		PY a/	O b/	E c/	RR d/
6.00-14.00	8.00	1328	2	1.12	1.78
4.00-5.99	4.67	3183	7	2.58	2.71
3.00-3.99	3.49	2430	11	1.96	5.60
2.00-2.99	2.49	3271	11	2.73	4.03
0.60-1.99	1.50	1843	2	1.47	1.36
Control		37857 e/	31	31.0	1.0

a/ For benign tumours no latent period was assumed, so the person-years at risk include the full interval 1-34 years after irradiation for the single breast analyses.

b/ Observed cancers.

c/ Expected values were calculated by the combination χ^2 method, with adjustment for age at irradiation and yearly intervals since irradiation, and were standardized so that O/E = RR = 1 in the control group.

d/ Relative risk.

e/ Observed cancers and person-years at risk for control group in this analysis include 392 non-irradiated breasts (with three cancers) of women with unilateral irradiation.

Table 2

Curve-fitting analyses of breast cancer data from Massachusetts fluoroscopy series
[L22]
(All parameters are scaled by a factor of 10^6)

Model	Parameter a/	Massachusetts fluoroscopy series: Estimate ± S.D.	Goodness of fit: x^2	df	P
Linear	α_1	560±120	1.6	4	0.81
Linear-quadratic	α_1	450±300			
	α_2	29± 76	1.5	3	0.68
Linear + killing	α_1	450±230			
	β_2	0 b/	1.6	3	0.66
Linear-quadratic + killing	α_1	450±860			
	α_2	29±570			
	β_2	0 b/	1.5	2	0.47
Quadratic	α_2	130± 40	3.0	4	0.56
Quadratic + killing	α_2	220±140			
	β_2	(1.6±2.2)10^4	2.5	3	0.48

a/ The dimensions of the parameters are as follows:
α_1: 10-6 a-1 Gy-1
α_2: 10-6 a-1 Gy-2
β_2: 10-2 Gy-2.

b/ The best-fitting parameter would be negative; the value of zero results from the prior constraint that the parameter be non-negative.

Table 3

Curve-fitting analyses of breast cancer data from Rochester mastitis series [L22]
(All parameters are scaled by a factor of 10^6)

Model	Parameter a/	Mean doses bo both breasts				Curves for dose to single breast			
		Estimate ± S.D.	Goodness of fit			Estimate ± S.D.	Goodness of fit		
			x^2	df	P		x^2	df	P
Linear	α_1	560±150	2.0	4	0.74	390±180	12.8	4	0.012
Linear-quadratic	α_1	560±430				390±540			
	α_2	0 b/	2.0	3	0.57	0 b/	12.8	3	0.005
Linear + killing	α_1	860±290				980±370			
	β_2	$(1.8\pm1.4)10^4$	1.2	3	0.75	$(3.4\pm1.6)10^4$	3.9	3	0.27
Linear-quadratic + killing	α_1	320±1140				780±1480			
	α_2	370±690				100±660			
	β_2	$(4.8\pm4.0)10^4$	1.1	2	0.58	$(4.2\pm4.9)10^4$	3.9	2	0.14
Quadratic	α_2	110±600	5.5	4	0.29	55± 49	27.0	4	0.00002
Quadratic + killing	α_2	550±170				470±210			
	β_2	$(5.6\pm1.5)10^4$	1.2	3	0.75	$(6.6\pm2.4)10^4$	4.1	3	0.25

a/ See footnote a/ in Table 2.
b/ The best-fitting parameter would be negative; the value of zero results from the prior constraint that the parameter be non-negative.

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