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Assumption of Linearity in Dose–Effect Relationships

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As a basis for establishing radiation protection standards, a substantial amount of quantitative information is now available on the frequency with which malignant diseases are induced in man by moderately high doses of radiation. Such estimates can now be made not only for irradiation of the whole body but also for exposure of a number of body organs individually. The frequency with which cancers might follow the much lower doses involved in occupational or environmental exposure to radiation, however, cannot be derived from any available epidemiological surveys. It can at present only be inferred by the (probably pessimistic) assumption that the frequency of such effects is linearly proportional to the size of dose received, even down to the lowest doses. Increasing information as to the probable form of the actual dose–effect relationship for radiation is indicating the extent to which the use of this "linear hypothesis" may overestimate the risk of low doses as inferred from the observed risk of higher doses.

A linear hypothesis has been used in the same way for estimating the likely frequency of harm from low doses of chemical substances which have defined harmful effects at high dose. The appropriateness of this procedure depends critically upon the way in which chemical pollutants, or the relevant products of their metabolism in the body, are likely to become distributed through body tissues and cause the relevant harmful effects on cells.

The second problem presented for discussion in the report from the international symposium on air pollution and health effects (*1*) is "Can the risk from low doses of combustion pollutants be inferred from that observed at high doses, using linear extrapolation of a dose effect relationship, as is done in deriving radiation protection standards?"

This question needs to be reviewed on two levels. Firstly, is this a reasonable, and reasonably safe, empirical procedure, when it seems possible that some risk may result even from low doses, and when there is no evidence, or no better evidence, about the form of the dose–effect relationship with decreasing dose? Secondly, is it the most reasonable assumption in the light of what is known or presumed about the cause of late effects?

The distinction is important, because there have been three phases in the development of radiation protection standards. Originally, it seemed likely that no harm was caused unless quite a high dose was delivered, so that no protection problems arose with procedures delivering only low doses. Later it became clear, first from genetic experiments and then from work on cancer induction, that even the lowest doses might involve some risk. At this stage the necessary estimate of the possible risk at low dose was made by linear extrapolation from that observed, in human populations developing various types of malignancy, after exposure at known high dose. This use of linear extrapolation was empirical in the sense that virtually no information of statistical validity was available as to the form of the dose–effect relationship for any form of human cancer induction by radiation. It was justifiable however, on the grounds that:

In a few instances, e.g., of rat mammary cancer induced by x-rays (*2*), the dose effect relationship was linear from high to low doses. Similarly some genetic effects were linearly dependent on dose to very low doses (*3*). On the rather widely accepted "target theory" of the mechanism of radiation action (*4*) it was to be expected that the dose–effect relationship for certain effects, although not necessarily for carcinogenesis, would probably be linear or quadratic (or intermediate) in form. Consequently a linear extrapolation from high dose to low dose would give a correct estimate of the frequency of effects of low doses if the linear term predomi-

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nated, and an overestimate if the quadratic term predominated, but should not give an underestimate. Clearly if the relationship was purely quadratic, inferences as to the effect of a few rads, derived linearly from those observed at a few hundred rads, could be too high by a factor of a hundred.

More recently, the likely form of the dose–effect relationship has become clearer, at least for the mutagenic and cell killing effects of radiation, although only to a limited extent for carcinogenic effects.

Arguments from microdosimetric and other models make it increasingly likely that linear and quadratic (i.e., in dose–squared) terms may determine the dose–effect relationship from low to moderately high dose levels (*5, 6*).

The relative importance of the linear and the quadratic terms to which mutagenic and cell killing observations can be fitted has been estimated. Specifically, if the effect E of a given dose D is given by:

$$E = aD + bD^2$$

the ratio a/b typically has a value of a few hundred rads for cell killing, or of rather less than 100 rads for mutagenic effects (*7*). This value indicates the extent to which a linear extrapolation may overestimate the effect of low doses, since the effect per unit dose at low doses approximates to $E/D = a$, while for higher doses

$$\frac{E}{D} = a\left(1 + \frac{D}{a/b}\right)$$

These values apply for radiation of low linear energy transfer (LET), e.g., x-rays, or β or γ radiation. For high LET radiation, e.g., from neutrons or α radiation, the ratio a/b appears to be considerably greater, and the dose–effect relationship is found to be linear over a wide range (*8*).

At high dose, in various forms of mammalian carcinogenesis the dose–effect relationship reaches a maximum; and the tumor yield then decreases with increasing dose, an effect which is often presumed to be due to death, or loss of reproductive capacity, of the relevant cells, in this case of transformed cells. This maximum occurs at doses as low as 200 to 300 rad for some tumors in rodents (*9, 10*) and may possibly occur at comparable levels for human breast or lung cancers (*11*). It is relevant to the low dose extrapolation in two ways. Firstly, linear extrapolation from effects of doses higher than the maximum could give an underestimate of the effects of low doses. Secondly, it adds a further constraint to the amount by which linear extrapolation could overestimate the effects from low dose.

It has been shown that there are cellular mechanisms which "repair" abnormal DNA molecules (*12*). It has been claimed that these mechanisms may therefore be capable of reversing the effects of ionizing radiation delivered in low doses or at low dose rates, and that there may well therefore be a "threshold" rendering very small doses ineffective. This argument seems specious, since such small doses add to the constant radiation from the natural radiation background. The question is not whether the dose–effect relationship has zero slope at zero dose, but whether the slope is zero at the dose corresponding to that constantly received from natural sources.

Inferences for Chemical Carcinogens

The use of a linear model for a dose–effect relationship in setting radiation standards seems to have a rather limited relevance for chemical carcinogens, because its use as an empirical model would not depend on any analogy with radiation, but on its reasonableness in the absence of better information, and because the increasing information about the validity or limitations of linear extrapolation for radiation is very specific to the facts and theories on the mechanism of radiation effects on cells.

It may be noted, however, that for many chemical pollutants, the metabolic products which are carcinogenic may have zero tissue concentration under "normal" circumstances. This would if so differ from radiation increments to natural radiation exposure, and imply that chemical repair mechanisms might be more likely to impose a "threshold" below which no effects occurred. The major difference between the two situations (radiation and chemical carcinogenesis) seems to lie in the contrast between the physically predictable nature of the radiation dose to particular tissues or cell structures, given adequate knowledge of the normal metabolism of the ionic or molecular form in which radionuclides are taken into the body, and the less certain knowledge of the way in which many chemical pollutants may become distributed and metabolized within the body and at the cellular level. It is easy to imagine ways in which the difference could drastically affect the validity of extrapolating from high to low dose effects—for example, either by small amounts of metabolically unusual chemicals saturating enzyme or immune systems of small capacity so that high doses were no more effective than low doses; or by low doses of such chemicals being metabolically degraded so that a threshold occurred below which no effects were produced.

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