RISK OF RADIATION AT LOW DOSES

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INTRODUCTION

RISK AND risk sources have been increasingly studied in recent years. The essentials of risk consist of a combination of the idea of loss with that of chance or probability. The idea of chance is crucial: the inevitable can be utterly unpleasant but, lacking the element of chance, is not a risk.

Even without analyzing the different components of the concept of "loss," it should be recognized that to be exposed to risk is not necessarily bad. The achievements of modern life imply the exposure to several sources of risk, and past evolution would have been impossible without the risk incurred by our ancestors.

A special type of risk, pertinent to our discussion, is exemplified by the health threats due to low levels of natural or man-made chemicals and low radiation levels. It constitutes a risk very difficult to analyze, not because the effects are unknown but because they are already very familiar, and exposed groups only manifest a slightly increased frequency of such effects.

RADIATION RISK

At high doses ionizing radiation is clearly detrimental, the scene being dominated by the deterministic effects, e.g., death via the acute radiation syndrome. There is no doubt here of the causal relation between radiation exposure and effect. At somewhat lower doses, deterministic effects are not produced, but, if the exposed group of individuals is large enough, a clear increase of induction of cancer over the spontaneous rate can be demonstrated. While the relationship between radiation and cancer is quite clear in these cases, it is not possible to state with certainty if a given individual will be affected or if a given case of cancer is the result of the exposure.

At even further lower doses, the observed relationship between radiation and cancer blurs due to increasingly larger uncertainties, reaching a point where an effect, if it exists, can not be detected. Many discussions have stemmed from this fact, where defenders of the existence of a threshold have claimed that no effect exists at all below such doses. This, of course, could be true but certainly not because of the lack of observation.

Statistical detectability and claims of threshold

Even assuming a non-threshold linear relation between risk (here used in a loose way meaning probability as the considered effect is only cancer) and dose, the required number of individuals, N, incurring a dose D, for achieving detectability increases steadily with a reduction of dose. If all other influencing factors are kept constant, the excess number of cancers attributable to radiation and its standard deviation are given by

$$\text{Excess} = rDN \qquad \text{and} \qquad \sigma = \sqrt{2bN + rDN} \tag{1}$$

where b is the "natural" risk of cancer, appropriate to the group under study, and r is the risk per unit dose in the group.

In order to be detectable the excess must be larger than a stipulated number of standard deviations (usually two, for a level of significance of about 95%). Therefore,

$$rDN \geq 2\sqrt{2bN + rDN}. \tag{2}$$

In most cases, the "natural" cancer risk is substantially larger than rD and therefore $(2b + rD)$ is practically constant. It follows after a simple algebraic manipulation that, for that stipulated level of significance, $D^2 N \geq$ constant.

For example, if a given type of cancer has been shown to be related to radiation in a group of a few thousand having incurred a dose of the order of 1 Gy, then to show the same relation with doses of the order of 100 mGy one would require groups of a few hundred thousand individuals.

This argument is simplistic as it ignores most of the complicating factors involved in epidemiological studies but is sufficient to dismiss most of the reported efforts to prove significant thresholds. On the other hand, it must be recognized that epidemiological studies at the lower dose, specially those of cancer types of smaller "natural" incidence can contribute to the progress of our knowledge, but extreme prudence is required when the results are negative.

Animal experiments and the dose-effect relation at low dose

Experiments with animals, usually small, offer the possibility of increasing the number when necessary and to plan the exposures in order to cover the required range.

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Obviously the results are not directly applicable to humans (for example the observed slopes), but general information can be derived on the shape of the dose-effect relationship and on the action of parameters thought to influence the relationship.

On the other hand, the same problem of detectability appears at low doses. To improve (but not solve) the situation, the experiments would require, as it is usually stated, too many "mice," too much money and too much time to be practicable. Even if the experiments were possible, they would always leave a region of dose where direct observations are not available, and it is that region that interests us the most. The main issue is how valid are the extrapolations of results observed at higher dose to the dark region.

Extrapolation from doses at which observations were made

Sometimes it is claimed that searching for the function that best fits the observations would provide the solution to the extrapolation problem. This, of course, is nonsense: there are infinite functions that would pass exactly through all the points representing the observations.

In order to carry out regression analysis, it is necessary *first to select the functions to be tested.* It is then possible to make conclusions about the goodness of the fit, to compare the two or more pre-selected functions, etc. It seems, then, unavoidable to conclude a) neither epidemiology nor animal experiments will establish the shape of the dose-effect relationship at low doses; and b) if a shape is selected on other grounds, they will help in obtaining values of the parameters applicable to humans and in testing the model when any new datum is obtained below the existing set of data.

Cellular and molecular radiobiology and the model dose-effect relationship

One common criticism against the use of modeling of the dose-effect relationship (on the basis of the results of fundamental radiobiological research) is that the predictions made by such modeling are "unscientific," because of the lack of epidemiological data in the region of doses of the prediction.

This criticism is in itself utterly unscientific. It is sufficient just to mention the discovery of a new planet and the observation of the predictions of relativity to dispose of the criticism. While some natural science is description of what is observed, most of it is the blend of modeling from some observations, predictions sometimes leading to other observations, theoretical constructions and searching for new and crucial experiments.

A very wide knowledge exists on the effects of radiation on cells. At present the consensus is that for all effects of interest the target of radiation is the DNA. Energy deposition by ionizing radiation occurs by ionization and excitation. About half the energy deposited in the cells is due to excitation, but this is of less consequence than ionization. Energy deposited in DNA affects the molecule either by direct ionization or by the action of free radicals generated by ionization in the immediate vicinity.

The immediate effects of such energy deposition are the loss or damage of one of the bases or a segmental loss in the DNA molecule. Sophisticated and efficient repair mechanisms become operative and usually cancel the effect, except in a small proportion of cases, resulting in what is called a misrepair.

The existence of the natural background of radiation reduces the importance of the dose-response relationship at doses close to zero. Almost all the data on stochastic changes in cells, irradiates *"in vitro"* with low LET radiation can be summarized and interpreted as follows:

- at low doses (and even at higher doses but with low dose rates) it is very unlikely that more than one ionizing event will occur in the relevant parts of DNA within the time the repair mechanisms operate. Taking account of the Poissonian distribution of ionizing events, the small exponent involved and a small fraction of misrepairs, the dose-response relationship will be linear, as in fact it is; and
- at higher doses and dose rates, two ionizing events may be able to combine effects before the repair mechanisms could cancel the effect of the first event, producing an enhanced probability of DNA transformation, which is reflected by a dose quadratic term in the dose-response relationship.

Obviously, there is quite a distance between a transformed cell and clinical cancer. There is, at present, consensus that cancer initiates in a single cell. When the stem cells of a tissue are irradiated, more than one transformation is likely to occur, and the number of such transformations is a Poissonian random variable with an average of NP, where N is the number of stem cells and P is the probability per cell of transformation. In turn, this probability is a linear-quadratic function of dose.

It can be shown that, provided the transformed cell has a developing advantage (somewhat shorter division time), the overall probability that at least one transformed cell results in an established clone that would grow without bound, is also related to dose by a linear-quadratic relationship.

It should be noted that as the dose increases, another cell effect becomes competitive with transformation: interference with cell division and cell death. This would result in a decrease of the probability of inducing cancer.

Linear-quadratic relationship and epidemiology

Good epidemiological results (at high doses and dose rates) correspond presumably to the region of dose where the effects are most probable. It is interesting to predict the location of this region of dose using the linear-quadratic relationship:

$$P = (\mathrm{a}\, D + \mathrm{b}\, D^2)\, e^{-cD} \qquad (3)$$

where P is the probability of cancer, a and b are constants and the factor e^{-cD} is the survival fraction of exposed cells.

Deriving and equalizing to zero, the following expression can be obtained:

$$cD_m = \frac{a/b + 2D_m}{a/b + D_m}, \quad (4)$$

where D_m is the dose that maximizes the probability of induction of cancers.

Without indulging in discussions of the values of a and b, one can take two extreme cases: in one the ratio a:b is assumed to be vanishingly small compared to D_m and in the second ratio a:b is assumed to be very much larger than D_m. For these two cases, the product cD_m would tend to the values of 2 and 1, respectively. The cell killing coefficient c has been experimentally measured for many tissues, and for humans a value of 1 Gy^{-1} can be taken as typical.

It follows that the region of dose with good epidemiological results is predicted to be between 1 and 2 Gy, in very good correspondence with reality.

A very important issue in the evaluation of the risk (probability of attributable cancer death) per unit dose at low doses is the extrapolation to the low dose region of the epidemiological observation at high doses and dose rates. A usual procedure is firstly to assume a straight line between the observation and the origin of the coordinates and then divide the resulting slope by the so-called Dose and Dose Rate Effectiveness Factor.

In terms of the linear-quadratic relationship, the risk (probability of attributable cancer death) at a high dose D with high dose rate extrapolated linearly to the origin would give a slope of $a + bD$, and the DDREF is given, therefore, by:

$$DDREF = 1 + \frac{b}{a}D. \quad (5)$$

It can be observed that the factor will increase linearly with D, the dose at which the epidemiological results apply. At typical values, where the linear component of the relationship contributes to the probability about the same, than the quadratic in the vicinity of 1 Gy and taking the range of observations as 1–2 Gy, the factor appears to be in the range of two to three. This range of values agrees well with many reported human data. Animal experiments that have a wider range of factors, have also a range of doses greater than the human experience.

Criticism of the linear non-threshold relation

As always with emerging solutions of scientific issues there is a main stream of consonant opinions and voices of dissent. The dissent is sometimes a valid scientific discussion but in other cases reflects an assortment of gut feelings, reactions to public opinion, and even interests.

Scientific discussions. Of the many issues raised, two recent ones are dealt with here. One stems from the genetics of cancer development and the other from consideration of the "adaptive" response to radiation.

It has been shown that several mutations are required for transformation and acquisition of malignancy of given cancer types. If this is true, the argument goes, then radiation cancer probability should be strongly curvilinear with dose with negligible risk at low doses. If the target for each mutation requires at least one ionizing event then the probability of mutation can be expressed as $(1 - e^{-kD})$, and for similar n targets the overall probability P will be given by

$$P = (1 - e^{-kD})^n. \quad (6)$$

With usual values of k (mutation rate per unit dose) and with n having reported values ranging from 2 to 7, the argument seems quite correct. However, it should be remembered that there are also "spontaneous" mutation rates for the same targets. These rates must be substantial to account for the cancer frequency prevailing in humans. The radiation attributable cancer probability is then given by the difference

$$\Delta P = [1 - e^{-(St + kD)}]^n - (1 - e^{-St})^n, \quad (7)$$

where S is the rate of spontaneous mutation of a target and t is the age. Two basic concepts emerge from the analysis and graphical representation of the above expression: a) provided St is substantially larger than kD, then the radiation attributable risk AP appears to be linear with dose; and b) it is necessary to have important spontaneous mutation frequencies to experience radiation risks at low doses. Our risk values per unit dose would then be valid for our present environment.

Another scientific argument against the linear-quadratic relationship (which at low doses or low dose rates becomes the linear non-threshold relation) relates to the denominated adaptive response to radiation. It has been shown by experiments involving irradiation following a pre-given dose that repair mechanism can be stimulated and the repair rate increased. This, it is claimed, would completely change the shape of the relation at low doses.

The issue is very complex. An increased rate of repair could also increase the rate of misrepairs, being the misrepairs are a fraction (small) of the repairs. In an extensive analysis, UNSCEAR has concluded that "Extensive animal experiments and limited human data provide at present no evidence to support the view that the adaptive response in cells either decreases or increases human risk at low doses."

Other types of criticism. It is difficult even to attempt to classify all the non-scientific criticism raised against the linear non-threshold relation. In most cases one can find elements of arrogant ignorance, apparent concern for the peace of mind of the public, and gut feelings.

In many cases the criticism is only one component of a larger "defense" of a particular risk source. This is particularly the case of nuclear power, which does not need nor does it deserve these self-appointed defenders. Even the more honest types of such defenders indulge in statements such as "if the public would just know the facts (of course not presented as the radiation protection community would present) then. . . "

Some criticisms are really requests for "putting the risk in perspective," referring to a risk source, usually nuclear power. Since a risk source has many attributes, the comparison must involve comparable attributes. An essential fact, often ignored is called the principle of "ceteris paribus," which means that all factors that are not explicitly presented in the risk characterizations must be mutually equivalent in a valid risk comparison.

CONCLUSION

The linear non-threshold relationship is at present the best tool to predict the risk probability of radiation at low doses. It fulfills all the requirements to be considered "realistically representative," using modeling terminology.

Practical decisions can be made under this relationship, and the radiation protection system recommended by the ICRP provides a method for such decisions. ■ ■