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ESTIMATION OF RADIATION RISKS AT LOW DOSE

A REPORT TO THE CONTRACTING PARTIES
TO THE CONVENTION ON THE PREVENTION OF MARINE POLLUTION
BY DUMPING OF WASTES AND OTHER MATTER

A TECHNICAL DOCUMENT ISSUED BY THE
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FOREWORD

Contracting Parties to the Convention on the Prevention of Marine Pollution by Dumping of Wastes and Other Matter, London (1972) commonly referred to as the London Dumping Convention (acronym LDC), are required to promulgate national legislation to enforce the provisions of the LDC in areas within their jurisdiction. In matters relating to sea dumping of radioactive waste, the International Atomic Energy Agency (IAEA) is designated by the LDC as the competent international authority. In accordance with its mandate, the IAEA has periodically formulated a definition of high-level radioactive waste unsuitable for disposal at sea as specified in Annex I to the Convention. The IAEA has also provided recommendations regarding the quantity, conditions and methods for the dumping of other radioactive wastes under the Convention, [Definition and Recommendations for the Convention on the Prevention of Marine Pollution by Dumping of Wastes and Other Matter, 1972, Safety Series No. 78, 1986 Edition] as well as guidance on the nature and contents of environmental assessments of dumping activities [Environmental Assessment Methodologies for Sea Dumping of Radioactive Wastes, Safety Series No. 65, 1984].

Some countries dumped low level wastes at sea until a non-binding moratorium on sea dumping was agreed by the Contracting Parties to the LDC in 1983 pending a review of the scientific and technical aspects of the safety of sea dumping of radioactive wastes presented in 1985 [LDC/PRAD.1/2, 1985]. The results of the review led to an extension of the voluntary moratorium while the wider political, legal, economic and social aspects of the sea dumping of radioactive wastes were considered. The LDC subsequently established an Inter-governmental Panel of Experts on Radioactive Waste Disposal at Sea (IGPRAD) to undertake the study of the wider political, legal, economic and social aspects of sea dumping of low level radioactive wastes.

At its first meeting IGPRAD discussed the question of "whether it can be proven that any dumping of radioactive wastes and other radioactive matter at sea will not harm human life and/or cause significant damage to the marine environment". IGPRAD recommended, and the LDC subsequently requested, that the IAEA, in consultation with other international and non-bilateral agencies: the International Commission on Radiological Protection (ICRP), the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), and the World Health Organization (WHO), should "develop, as appropriate in terms understandable to the layman:

a) an explanation of the basis of the assumption of a linear dose-effect relationship which underlies an assessment of radiological risks;

b) an opinion as to whether it is possible to define radiation doses below which no deleterious effects can be demonstrated in man and other organisms."

Because of its significance in relation to the assessment of radiation risks associated with activities in the nuclear field, the subject is of considerable interest to the IAEA which recently published an updated version of "Facts About Low-Level Radiation" (IAEA/Division of Public Information, February 1989).

So as to comply more specifically with the LDC's request, the IAEA, following consultations with various members of UNSCEAR and ICRP, entrusted Sir Edward E. Pochin with the consideration of the questions posed by IGPRAD.

Sir Edward E. Pochin qualified medically from Cambridge in 1937 and by MD in 1945 obtaining the fellowship of the Royal College of Physicians, London in 1946. He was a Counsellor of that College from 1965 to 1968. He directed the UK Medical Research Council's Department of Clinical Research

from 1946 to 1974 during which time he was an honorary consultant physician of University College Hospital London and a recognised teacher at London University College. He was a participant in the United Nations Scientific Committee on the Effects of Atomic Radiation from its formation in 1956, and its UK Representative from 1956 to 1982 acting as Chairman of its Biological Working Group during the latter years of this period. He was a Member of the International Commission on Radiological Protection's Committee II on Internal Dose from its formation in 1951 and of the Main Commission from 1959, becoming Vice-Chairman of the Commission in 1959, Chairman from 1962 to 1969. He was Member Emeritus of the Commission from 1969 to 1990.

He became a Member of the National Radiological Protection Board of United Kingdom in 1971, and was a Consultant to the Board from 1974 to 1990.

He held an Honorary Fellowship of the UK Royal College of Radiologists and Honorary Membership of certain UK and foreign clinical and radiological societies, including the UK Nuclear Medicine Society, the Hospital Physicists Association and the Society of Radiological Protection. Sir Edward Pochin died on 29 January 1990 shortly after completing work on this review.

This work was co-ordinated in the Waste Management Section of the Division of Nuclear Fuel Cycle and Waste Management and the responsible officer was D. Calmet.

EDITORIAL NOTE

In preparing this material for the press, staff of the International Atomic Energy Agency have mounted and paginated the original manuscripts and given some attention to presentation.

The views expressed do not necessarily reflect those of the governments of the Member States or organizations under whose auspices the manuscripts were produced.

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1. QUESTIONS FOR DISCUSSION

The draft report of the second meeting of the Inter-Governmental Panel on Radioactive Waste Disposal at Sea (LDC/IGPRAD 2/WP.3 draft of 29.9.88) refers at para. 4.20 to the need for:

> (4.20.1) "an explanation of the basis of the assumption of linear dose-effect relationship which underlies an assessment of radiological risks; and
>
> (4.30.2) an opinion as to whether it is possible to define radiation doses below which no deleterious effects can be demonstrated in man or other organisms."

The first question involves two aspects of potential importance to the work of the Panel:

1(a) is it likely that the frequency per unit dose with which, for example, cancers are found to be caused by high doses in epidemiological surveys, is equal to the frequency per unit dose with which they would be induced by radiation received at low dose rate, eg. from environmental contamination by radioactive materials; and

1(b) is it likely that the frequency with which such effects would be caused by different low levels of environmental contamination, would be proportional to the differing dose rates resulting from such levels of contamination?

The second question is important insofar:

2(a) as it asks whether there is likely to be an entirely safe "threshold" dose (or dose rate) below which no deleterious effects would ever be caused in man (or other organisms).

Any direct experimental, or epidemiological, evidence of such a threshold, as implied in the wording "... can be demonstrated ...", raises problems, that are discussed below, in making reliable estimates of risk at low dose. These problems result from the fact that, for example, cancers and hereditary diseases that are caused by radiation are individually indistinguishable from cancers and abnormalities of the same types which occur "naturally". Any excess caused by radiation can therefore only be detected by statistical methods, and this detection becomes increasingly uncertain at low doses if few cancers are induced.

For this reason, the likelihood or not of there being a threshold at low dose can be more effectively inferred from the ways in which radiation causes deleterious effects at low dose, then by any direct "demonstration" of the presence or absence of such effects.

2(b) in practical terms, and since radiation from different sources produces deleterious biological effects on body tissues by similar modes of action, the important issue is whether there may be a threshold dose rate which is not exceeded by the rate at which man and other organisms are already constantly exposed by natural "background" sources of radiation, but which would, or might, be exceeded by an added dose rate due to an environmental contamination.

2. THE EFFECTS OF RADIATION

2.1 Low dose rates as causing effects due to damage to single cells

It seems clear that the occasional severe effects that are caused by radiation in low doses, or at low dose rates, are predominantly due to damage caused in single body cells. This has implications on the probable answers to the questions at issue here on linearity and on the likelihood of thresholds.

On both questions, therefore, the points at issue are best understood in the light of our present knowledge of the way in which radiation from radioactive (or other) sources causes harmful effects in body tissues of human and other species.

Such radiation consists of a stream of particles (electrons, photons, alpha particles, etc.) discharged from the radioactive material, as its unstable atoms break down in the course of their radioactive decay. These particles are initially discharged from the radioactive material with high energy, and progressively lose some or all of their energy as they pass through body tissues, or other materials. The small amounts of energy released to individual body cells, as the "track" of the particle passes through or near these cells, are insufficient to cause any significant damage directly, eg. by heating of the cell. These amounts of energy can, however, break chemical bonds in sensitive and important molecules within the cells, and in particular those of the DNA (desoxyribo nucleic acid) in the chromosomes of the cell nucleus.

2.2 Forms and results of radiation damage to cells

There is now considerable evidence on the possible results of such localised damage that radiation may cause to the structure or the arrangement of sections of the DNA molecular chain and hence to the behaviour of the genes in which the damage occurred.

1) Most commonly, the damage is fully, or at least adequately, repaired so that the cell survives with normal function and a normal capacity for cell division. The chemical enzyme systems for DNA repair are of the very high efficiency that would be expected, considering that all living forms have survived continuous exposure to radiation from natural sources during the whole course of their history.

2) Or, the damage may be of a kind which is not adequately repaired, and the damaged cell is killed (or, more exactly, loses the normal power of cell division and dies when it next "attempts" to divide).

3) The third alternative is that the damage to the cell's DNA is incompletely repaired but that the cell survives, and is capable of cell division, although its function is abnormal in some respects as a result of the abnormality of a section of its DNA. In the great majority of cases, this is quite unimportant since, for example, an increased or decreased formation of some enzyme or hormone, by one cell among the vast number of normal cells in an organ, can have no effect on health. Severe effects may result, however, if the affected cell has, or develops, some selective advantage over other normal cells, so that the "voice" of the single abnormal cell can be heard.

This will occur in either of two circumstances: first, if the affected cell is a sperm or ovum which becomes fertilised and develops to form a child, or is an ovum which has already been fertilised. In such cases all body cells of the child will have the same defective gene and, in a few instances, the defect will cause a detectable inherited abnormality or disease to result.

It will also occur if a change in the structure of a gene, or in its position relative to other genes on a chromosome, causes the cell to have, and to transmit to

its daughter cells, a greater rate of cell division than normal. If this occurs, the resulting clone of cells may escape from the usual control of cell proliferation and may enlarge and spread to form a cancer.

Consideration of the numbers of cells present in the body shows why the cell-killing effects of radiation are in general significant only after high radiation doses, so that this third type of effect, of abnormality induced by radiation in single cells, is the one responsible for such risks as are caused by low doses.

2.3 Multiple cell killing effects following high doses

The human body is estimated to contain some hundreds of million million (ie. more than 10^{14}) cells (1). Most body organs will therefore contain a few million million cells. Cell deaths, as in alternative 2 above, cannot therefore be expected to cause any appreciable impairment of the function of an organ as a whole, even in organs in which normal cell replacement by cell division is slow, unless very large numbers of its cells, eg. of hundreds of thousands of million cells, have ceased to contribute their normal activity to the function of the organ. It is clear, therefore, why failures of organ function, or damage to organ structure, the so-called "non-stochastic" effects of radiation, only occur after radiation doses that have been so large that they have "killed" a large proportion of all the cells in the organ.

The size of the "threshold doses" above which these effects of cell killing become significant or detectable are known with some accuracy from experience in radiotherapy, in the course of which any such effects need to be avoid, and in which the radiation doses to body organs are readily estimated (2). The size of these threshold doses are in general such that they would only be reached after a 75 year lifetime of exposure at many times the rate normally received from natural sources. They do not therefore contribute to radiation effects incurred at low dose rates.

It may however be noted that, even in the case of these non-stochastic effects, the thresholds indicate only the doses above which any organ function becomes detectably impaired, given the reserve capacity that most organs are known to have in maintaining normal function even if part of the organ is removed or destroyed by disease; and given also the vast number of cells in the organ, and their capacity for increased cell division to replace any deficiency. They are therefore thresholds for detectable impairment of normal organ function, and not thresholds for radiation effects on individual cells.

3. CANCER RISKS FROM RADIATION

3.1 Cancer risks of radiation exposures in man

The radiation effects which are significant at low doses, or at dose rates which are comparable with those from natural sources, therefore, are essentially confined to those in which the chromosomal apparatus of a single cell is transformed in such a way that it causes unrestrained growth and the possibility of cancer development, or which cause abnormality in a child born subsequently, either by transmission to it of abnormal genes, or by damage during its development.

The effects of radiation in causing cancer in the exposed individual are discussed first, since there is adequate information on which to review the questions of linearity of the dose-effect relationship directly in the light of studies in man. The inferences as to this relationship, and on the question of thresholds, for inheritable and developmental effects are examined later, since here the data on effects in man are sparse, and the effects of radiation at low dose are likely to be generally similar as regards the dose effect relationship and threshold, as in the case of cancer induction.

3.2 Estimating cancer risks from moderately high doses

Numerous estimates have now been made of the probability that cancer of an organ will be caused by the exposure of that organ to moderately high doses (3). These estimates depend on studies of people in whom the whole body has been irradiated, as in survivors of the atomic bombs in Hiroshima and Nagasaki, or after various body organs have been irradiated in the course of radiotherapy or multiple diagnostic x rays, or as a result of occupational exposure during underground uranium mining or the use of radioactive luminising paints.

For our present purpose it is important to understand the limitations on precision that are involved in these epidemiological studies, since the precision of the risk estimates that can be made at different dose levels determines the confidence with which the risk can be described as varying linearly, in proportion to the size of the dose, rather than in any more complex way.

The problem here is that the investigation must distinguish between the number of cancers following the radiation in the irradiated population, from the number that would have occurred "from natural causes" (whatever those causes may be) if the irradiation had not taken place.

This commonly involves comparing the cancer mortality in the exposed population during 20 or more years after irradiation with that in a comparison population, which was identical with the exposed population in all relevant respects except for not having been similarly irradiated. This comparison
population must be examined over the same period of time and with the same accuracy of surveillance as in the irradiated group.

Reliable estimates of the risk of causing increases in cancer mortality have been obtained in this way, when the cancer mortality records are studied for a number of years

after exposure of an organ or part of the body, in some hundreds of people exposed to a dose in the region of 1 sievert (1 Sv), (which is about 400 times the amount of radiation received by the body annually from natural sources) (4).

How precise can such an estimate be? This will vary with the number of people studied and the length of study since their exposure and whether the whole body was exposed, or only certain organs or parts of the body. It will vary also with the dose at which they were exposed, with the ages of those exposed, and whether the natural cancer rate in the absence of exposure can be appropriately assessed from large existing surveys, eg. of the whole national population, or requires a separate survey (5).

A simple example will illustrate the constraints on precision of the estimates of risk at different dose levels.

Suppose that 2000 persons are followed for 20 years after an average exposure of the whole body to 1 sievert, and that their normal cancer mortality rate in the absence of such exposure is known with good precision from national records to be at a typical level of 240 per 100,000 persons per year (6). In the absence of the exposure the expected number of cancer deaths in 20 years would then be 240×10^{-5} person-years, x 2000 persons, x 20 years, or 96. The added number of cancers expected within 20 years of exposure of the whole body to 1 Sv, at an expected rate of 2 per 100 persons within this time period, would thus be 40 in the 2000 exposed. The total number of cancer deaths would therefore be 136, as an average result in such a trial. This number would, however, vary by chance fluctuations in individual trials, and in two-thirds of all trials of this size, the number would be expected, on statistical grounds, to lie within about 12 of this average figure (this "standard error" of the expected number of 136 being equal to the square root of this average number).

The total number of cancer deaths resulting within 20 years of the exposure would therefore usually (in 2 trials out of 3) lie between 124 and 148, giving reasonable precision. The number caused by the exposure, however, subtracting the 96 which would have occurred naturally in these 20 years, would be estimated as being between 28 and 52. This still gives a rough estimate of the risk within the first 20 years of an exposure of 1 Sv to 2000 people, i.e. as probably lying between 1.4 and 2.6% per Sv.

If however the survey were repeated on an equal number of people who had been exposed to a lower dose, in order to test whether the risk of causing cancer remained proportional to the size of dose, the precision of the estimated risk becomes rapidly worse. For example, after exposure to 0.5 Sv the number of cancer deaths caused would be halved to 20 if the risk was in fact proportional to dose. The number of naturally occurring cancers would remain at 96. The total number of cancers would therefore average 116, and results in individual trials would usually yield numbers lying within plus or minus 11 of this average figure (as being approximately the square root of 116). Estimates of the numbers of cancer deaths caused by the 0.5 Sv, therefore, would range round 20 but with values from 9 to 31 in individual trials, causing a rather greater uncertainty of the risk per Sv at this lower dose, now estimated only as from 0.9 to 3.1% per Sv.

On the same basis, a test of the effects of 0.25 Sv would be essentially worthless for estimating the level of risk in a population of the same size. With the same number of 96 cancers occurring naturally, an excess of 10 cancers induced by this dose would on average yield a total of 106 deaths. This total would be expected to vary, in two-thirds of trials, from about 96 to 116, so that the excess could only be claimed, with moderate confidence, to lie between 0 and 20.

These figures illustrate the general point that, for a population of a given size, age structure, type of exposure and natural cancer mortality rate, the precision with which it

is possible to estimate the frequency of cancers being induced by radiation necessarily decreases very rapidly with decreasing dose at which the estimate is attempted.

The precision of the estimate possible at any particular dose level, however, depends very much on the type or types of cancer studied; and on a variety of other factors, including the age structure of the population and the length of study, as well as the size of the population examined and whether its natural cancer mortality rate can be taken as equal to that known accurately for large or national populations or has to be determined by parallel studies of a comparison unexposed population. In the latter case, the estimated mortality rates will themselves be subject to statistical uncertainties of sampling. There are therefore considerable differences in the precision of risk estimates of total cancer incidence following exposures of the whole body, and in those of cancer induction in particular organs which have been selectively exposed because of their position in the body, eg. during local radiotherapy, or because certain radionuclides have been selectively concentrated in these organs, as during uranium mining or in the early use of luminising paints containing radium (7).

4. THE DOSE-EFFECT RELATIONSHIP

4.1 Investigation of the form of dose-effect relationships

For various types of human cancer, it has now been possible to obtain reasonably precise estimates of the risk of doses well below 1 Sv. Indeed, for thyroid cancer, the risk of doses averaging about 0.1 Sv has been identified (8), but no reliable estimates of cancer risk in man or animals have been made at any substantially lower dose. Such estimates as are available, however, allow tests to be made as to whether the size of risks at different doses are or are not consistent

statistically with a linear proportionality between risk and dose, over the range of doses in which reliable estimates have been achieved.

The position was reviewed in detail by an authoritative working group of the United States National Institutes of Health in 1983 (3), with the finding that the dose effect relationship was consistent with linearity on the available data in the case of two cancers: those of the female breast and of the thyroid gland when exposed to low "linear energy transfer" (low LET) radiations such as beta and gamma radiation.

For these types of radiation, however, the working group assumed a non-linear relationship between dose and frequency of cancer for the other 9 forms of cancer for which data were available, although in many of these cases information was inadequate to distinguish conclusively between a linear and non-linear form. The non-linear relationship adopted in these cases was such that the frequency (F) of cancer induction per unit dose was proportional to the sum of two terms, one of which was constant and the other was proportional to dose (D), expressed as:

$$F = 1 + D/1.16$$

so that the frequency per unit dose when estimated at a dose of 1.16 Sv would be twice that postulated at low dose.

For radiations of high "LET" such as from alpha radiation, the data on cancers of bone after exposure to radium, of lung exposed to radon, and probably of liver exposed to thorium, indicated a linear dose effect relationship; and this was thought likely to apply for other human cancers, as judged by biological evidence of the carcinogenicity of high LET radiations in other species.

The evidence obtained by the NIH working group therefore indicated that for most (ie. low LET) forms of exposure from radioactive materials, the risk of two types of cancer at low

doses or dose rates was likely to be best estimated by simple proportionality from that directly ascertained at higher dose. For other cancers, however in which risk had been ascertained at doses in the region of 1 Sv or less, such an assumption of proportionality might overestimate the risk of low doses by a factor of up to 2. For high LET radiations a direct proportionality was considered to give a valid estimate of low dose risk, as judged by those organs in which risks of human cancer induction had been obtained, although other biological data suggest that these radiations might sometimes have a somewhat higher biological effectiveness per unit dose at low dose than at high dose.

One qualification needs to be added. It has been shown that cells "transformed" by radiation to have the capacity to form cancers, are "killed" by radiation doses of about the same sizes as the doses which kill the normal cells from which these potentially cancer-producing cells are derived. At doses of several sieverts it has been observed in work on cancer induction in rodents, and in some epidemiological data on man, that the curve of increasing cancer frequency with dose ceases to rise, and then falls at higher dose levels at which the potentially cancer-producing cells are themselves being killed in this way with increasing frequency. The relevance of this to risk estimation is, of course, that the risk at low dose could be substantially underestimated if inferred from the risk per unit dose observed at such very high doses.

4.2 Proportionality between risk and dose at very low dose or dose rate

Unless or until the cancers which are caused by radiation can be distinguished directly in some way from naturally occurring cancers due to all other causes, the frequency with which cancers are caused, if at all, by very low radiation doses can never be directly determined. Prohibitively large populations would be needed to estimate the size of a small number of cancer deaths due to small

exposures, in the presence of much larger numbers arising from natural causes. Even a large Chinese survey comparing the cancer mortality in an area of high background radiation, of about 3 times the normal rate (9), with that in an area of normal background rate has hitherto given equivocal results, consistent with the rate in the high background area being either lower or higher than normal. This uncertainty remains, despite the survey having already (by end 1986) examined records of over one million person-years of cancer mortality experience in each area. In addition, the results of two large studies of cancer mortality in workers occupationally exposed to radiation hitherto show mortality rates from all cancers which suggest an increase but are still statistically consistent even with a possible decrease in rate, as compared with rates in unexposed workers (10, 11, 12).

It seems clear, therefore, that reliable direct estimates cannot be expected of the cancer mortality caused by dose rates within the range of those due to natural causes. In particular, therefore, it is hard to foresee any practicable survey which could determine directly whether the number of cancers caused by small increases of dose rate above that due to environmental radioactivity, would be about proportional to the size of such increases.

It does seem likely, however, that this would be the case, in view of the way in which cancers are believed to be caused by radiation.

As indicated above, there is evidence that a cell may be damaged if a particle discharged from radioactive material (or other radiation source) passes through or near the cell and its nucleus; and that the important aspect of such damage lies in a local change in the chemical structure or arrangement of the nuclear DNA. Also that such damage is, in the very great majority of all cases, rapidly and adequately repaired. A cell is only "transformed", so as to have a cancer producing potential, in the rare instances in which the cell survives, but with a residual abnormality in DNA, and

hence in the biological programme of cell behaviour, that allows unrestrained multiplication of its clone of daughter cells. The clinical evidence and effects of a cancer develop if body immune mechanisms fail to kill these dividing cells faster than they are being formed.

Any one track of a particle passing through the body tissues, therefore, has a finite but extremely low probability of transforming a cell to cancer-producing potential. At low radiation dose rates, when particles pass through any part of the body only infrequently it will be very rare for two cells to be "transformed" and liable to produce a cancer in the same individual; and in the majority of individuals so exposed, no cells will be so transformed.

In considering the frequency with which cancers are induced by low doses, therefore, we are not considering changes in average numbers induced per individual, but changes in the percentage of individuals in whom an induced cancer develops. Indeed, it can be estimated that our lifelong exposure to radiation from natural sources is responsible for causing at most a few percent of all cancers, and so of causing cancer in about one in 100 people.

Since this is the case, the number of cancers induced in a given time by low doses in a defined population will depend on the number of particle tracks passing into or through their tissues during this time, and the average, even if very low, probability that any such track will transform a cell in such a way that it survives, proliferates, and develops into a cancer. If this is so, the risk of cancer development in the population so exposed should be simply proportional to the average number of particle tracks passing into their tissues. This in turn is proportional to the mean dose to which their tissues have been exposed since, for any type of radiation, the size of the dose is proportional to the average amount of energy delivered to a given volume of body tissues by the tracks which pass through it.

It seems evident, therefore, that, at dose rates only moderately greater than those due to background radiation, such cancer risk as there is at these low doses must be linearly proportional to the increase in dose rate, as regards low LET radiation; and from high LET radiation the dose effect relationship is commonly linear even at much higher dose rates.

5. THE THRESHOLD NOTION

5.1 Evidence for or against thresholds

The threshold doses, below which no effects of multiple cell killing are demonstrable, have been referred to above, and shown to refer only to the detectability of such uncompensated multiple cell loss at high doses, and not to any threshold for radiation actions on cells.

The important question for radiation protection and practice, however, is whether there is a dose below which cancer, and hereditary abnormalities, are not caused. As will be obvious from the earlier discussion of the impracticability of any reliable direct estimation of risks at low doses, the presence or absence of a true threshold could never be examined experimentally: a zero result at low dose might be due simply to a random variation in low expected numbers, and a positive result at low dose could never exclude consistently zero results at doses rather lower than those which had been investigated.

The argument presented above, however, in regard to the likely proportionality between dose and numbers of cancers caused, is clearly relevant to this question also. For a given type of radiation, it must be assumed, as discussed above, that particles which cause cancer in readily measurable frequency when passing through tissues in large numbers, are

likely to cause cancers at lower dose with frequencies decreasing in constant proportion to the decreases in numbers of particles involved. These particles, must be expected therefore to be capable of causing a single cancer by a single particle track, although with the same low probability per track that applied at higher doses and track numbers.

The presumption must be, therefore, that a finite, although extremely small, probability of causing a cancer exists even at the lowest possible dose from a radiation source, when only a single particle passes into or through living tissues.

This presumption would not apply if increases in cancer frequencies with increasing dose were due to increases in the mean number of cancers induced in the same individual, since it is conceivable, although unlikely, that body immune defences or other mechanisms could destroy a limited number of transformed cells, but would be overwhelmed by larger numbers. As noted above, however, even lifelong exposure to background radiation dose rates is unlikely to cause cancer in more than about one individual in 100, so that interactions between multiple cancers induced in the same individual could not form a basis for postulating thresholds. And there is no foreseeable way in which the transformation of a cell in one individual could alter the probability of such a transformation in another individual.

5.2 The possibility of "practical thresholds"

It has been suggested that a "practical threshold" dose might occur if cancers only developed after a minimum "latent interval" of years after exposure, and if this latent interval increased as the radiation dose decreased. If this were so then at low enough dose, no cancers might develop during the remaining lifetime of the exposed individuals.

There is a general difficulty in establishing the minimum time interval between a single radiation exposure of

an organ, and the detection of the first cancer caused by this exposure. Apart from the impossibility of distinguishing a cancer caused by radiation from a cancer of the same type occurring naturally, an added problem arises because low doses cause fewer cancers than higher doses. As a result, lower doses will cause fewer cancers to appear during the early years of exposure, and hence a greater chance of none appearing in a given period, than following a higher dose; and a fallacious impression, if based on limited surveys, of a longer latency after lower doses

For one form of cancer, namely that of bone, such an increase of minimum latency appeared to be associated with decreasing amounts of radium that were retained in bone, and hence in the dose rate at which bone cells were continuously exposed. This association now seems doubtful in the light of further information (13), and no evidence has been obtained of significant dose-dependent prolongations of minimum latency in the development of any other form of cancer.

It seems necessary to conclude, therefore, that the probability with which cancer may be caused by low doses will decrease in linear proportion to the size of the dose, down to the lowest possible dose, without any fully safe threshold even at the lowest doses.

6. THE INHERITABLE EFFECTS OF RADIATION

6.1 Effects of radiation exposure during prenatal development

Before discussing the evidence on inheritable (or "genetic") effects of radiation, which also, as with cancer causation, depend on damage to single cells, it is useful to review effects which may be caused by radiation doses received by a child during its development in utero.

Various types of structural malformation are known to occur with increased frequency if a child has been exposed to quite substantial doses during certain stages of development. These effects are thought to result from multiple killing of the formative cells, and of cells which could take over their function, and are considered unlikely to occur unless a threshold dose has been exceeded.

It is also clear that cells may be "transformed" by relatively low doses received during prenatal development, with the potential of causing certain types of cancer which occur during early years of life (14). As with cancers caused by radiation during later life, there appear to be no grounds for assuming a threshold below which these effects will not occur.

Important additional evidence has emerged from recent analyses of the doses from atomic bomb exposures and their effects on the subsequent intelligence of children exposed to irradiation at certain stages in their development in utero. It has been shown, firstly, that the frequency with which severe mental retardation has occurred in such children increases with the dose to which they are estimated to have been exposed (15); and, secondly, that the average intelligence quotient of these children, measured at their age of about 10, decreases in proportion to their estimated doses, a decrease with dose being present whether the mentally retarded children were included in the estimates or not (16). In respect both of the retardation and of the IQ levels, the impairments were greatest if the radiation exposure had occurred at between 8 to 15 weeks after the child's conception. They were detectable also, but less, following exposure later during the pregnancy, at 16 to 25 weeks after conception, but were not found if exposure had been earlier than 8, or later than 25 weeks into the pregnancy.

The 8 to 15 week period is significant as being the period during which the cells of the developing brain move into their correct final positions in the cerebral cortex, and

apparently do so by migrating along the course of relatively few structural brain cells which remain in position and in this way act as a form of directional guide (17). It is suggested that this period is one of the greatest sensitivity to radiation damage because the damaging or killing of the relatively few structural cells could disrupt the proper positioning of the very much greater numbers of cortical cells on which brain function depends. In this sense, both the observed forms of impairment of intelligence could be due to radiation damage which was more akin to the effects on single cells which appear unlikely to have threshold doses below which they do not occur, than to the multicellular killing effects which do have such thresholds.

The amount by which the IQ is reduced is estimated to be about linearly proportional to the dose received during the 8-15 week period, without indication of any threshold. For the less sensitive 6-25 week period, a linear relationship is less likely, and a threshold is more probable.

As regards the frequency of severe mental retardation the data indicate a high threshold (of 700 mSv) for this later 16-25 week period, and substantial thresholds (of 250 to 400 mSv) are estimated as the values of maximum likelihood for the more sensitive 8-15 week period, although a linear dose response relationship without threshold is also statistically consistent with the information available for this period(18).

For the purposes of the present review, therefore, it can be stated that a lowering of IQ may be caused at low dose, without threshold, by exposures during these earlier 8 weeks of a pregnancy. It may be noted that the estimated magnitude of this effect is small, the lowering of IQ that would be caused by a dose rate equal to that from natural background radiation during the relevant 8 weeks averaging only about one three hundredths of one percentage point on the (Koga) IQ scale.

Similarly, if severe mental retardation were induced without threshold during this 8-15 week period, rather than being subject to the "maximum likelihood" thresholds noted above, radiation during pregnancy at a dose rate equal to that from natural sources would involve a risk of 1 case being caused in every 20,000 children so exposed.

Exposures at these dose rates during the remaining 32 weeks of pregnancy would cause no further risk of mental retardation, in view of the high threshold indicated for the 16-25 week period, and probably no additional lowering of IQ, in view of the threshold also indicated as likely for this period.

6.2 Radiation induction of inherited abnormalities

Radiation of the parental germ cells in ovary or testis can cause abnormalities or diseases in the progeny in ways which are broadly similar to the ways in which cancer can be caused. Thus there is clear evidence from studies on rodents that irradiated germ cells may survive with inadequately repaired damage to the chemical structure, and therefore to the coding, of individual genes or sections of the DNA; and that such "point mutations" may in some cases cause abnormalities in descendants whose cells carry these abnormalities. In addition, radiation may cause breakage of a chromosome which can result in part of the chromosome being lost during cell division, or incorrectly located or transmitted to the resulting daughter cells, with the possibility that serious effects are caused in progeny, just as comparable rearrangements of chromosomal material may lead to cancer.

These essential similarities in the ways in which radiation can cause cancer and inherited abnormalities suggest that the conclusions reached for linearity of dose effect relations and for thresholds in respect to cancer are likely to obtain also for inherited abnormalities. For the latter, however, the sources of evidence differ. There are

essentially no data on human populations relating the frequency with which such abnormalities are caused to radiation dose, although evidence on various aspects of this question is available in some other mammals, and particularly in mice. In addition, however, and unlike the situation regarding cancer, the frequency with which structural changes of chromosomal arrangement are caused by radiation has been extensively investigated, both in blood lymphocytes of individuals who have been irradiated at known dose in the course of radiation treatment, and in the lymphocytes of blood which has been equally irradiated in vitro.

These studies are important, insofar as some such chromosomal aberrations, if occurring in other, germinal, cells, underlie a large proportion of the inheritable effects that may be caused by radiation. On this basis, they offer an easier way of obtaining reliable estimates of the frequency with which radiation causes potentially harmful effects at low dose, than is obtainable more directly by epidemiological reviews of cancer frequencies.

The results of these studies seem relevant to the Panel's questions, even though most types of chromosomal aberration may not give rise to detriment, and although other forms of inherited detriment are not detectable microscopically as chromosomal aberrations. With these reservations, the indirect evidence of harm obtainable from chromosome studies at different dose levels, are consistent with the direct evidence of harm caused at different dose levels examined in epidemiological cancer studies. Thus, the frequency of relevant types of chromosomal aberrations (of dicentric and ring form) typically varies non-linearly with dose at high doses, at which it would be expected that the interaction of two particle tracks might be required to cause a chromosomal breakage. At lower doses, however, (of below 50 mSv of x-rays, equal to about 20 years of exposure to natural sources) the relationship is well fitted by a linear relationship, the frequency of such aberrations being consistant with proportionality to dose down to substantially lower doses (19).

7. CONCLUSIONS

For the inheritable (or "genetic"), as well as for the cancer producing effects of radiation, therefore, present evidence is consistent with:

(a) a non-linear relationship between the frequency of at least some forms of these effects, when comparing frequencies caused by doses many times those received annually from natural sources, with those caused by lower doses.

(b) a probably linear relationship, however, between dose and frequency of effects for dose rates in the region of that received from natural sources, or at several times this rate.

(c) no evidence to indicate the existence of a threshold dose below which such effects are not produced, and a strong inference from the mode of action of radiation on cells at low dose rates that no such thresholds are likely to apply to the detrimental, cancer-producing or inheritable, effects resulting from unrepaired damage to single cells.

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