Cancer Risks

Strategies for Elimination

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With 34 Figures

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Assessment of Cancer Risks Due to Ionizing Radiations

A. M. KELLERER

Introduction

The enduring controversy on nuclear energy and the recent reactor accident have made ionizing radiation one of the most widely discussed tumor-inducing agents, although compared with major contributors, such as tobacco, its role appears to be minor. There is also little doubt that ionizing radiation is probably the one carcinogen which has been most extensively studied. X-rays were discovered in 1895, and 17 years passed before physicists began to understand their nature. But it took merely a few weeks before the first skin lesions were seen, and only 7 years before an X-ray induced skin cancer was recognized (Frieben 1902). In 1911 when Max von Laue obtained the first X-ray diffraction patterns in Munich, von Jagie et al. (1911) in Berlin reported a cluster of five leukemias in radiologists. The lesson was learned slowly. The hands of radiologists were less widely used as routine test objects for focusing the X-ray equipment, but scattered radiation or even the primary beam were not generally avoided, and before long leukemia became the professional affliction of radiologists.

A first dose limit was set in 1921 in terms of an observable skin reaction, a level 100 times the present limits. In 1928 the International Commission for Radiological Protection (ICRP) was founded, just 1 year after H. J. Muller (1927) had shown the mutagenic potential of X-rays and the apparent absence of a threshold. At the time the limit for radiation workers was set at 6 roentgen per month, a dose roughly comparable to 0.06 Sv per month, in today's units. The value was about 15 times higher than present limits, and adherence to the regulations may then have been far below present standards. The prevailing philosophy was still, that tumors could be induced by radiation only after a persistent accumulation of high radiation doses.

As a little-known aside of some historical interest one may note that Giachino Failla, the distinguished radiologist and physicist, had recommended at the time a "tolerance dose rate" of 0.6 roentgen per month, a value nearly equal to today's limit. The proposal was based on animal and human data (Failla 1932). He "had at the hospital a canary which has been continuously (day and night) in a beam of X-rays for about five months... In this time the bird has received about 6000 roentgen of hard X-rays without apparent deleterious effects." However, Failla was also aware of effects that may develop later, hence the need for an epidemiological study – also of modest proportions. Three of his technicians were in charge of administering the 4 g radium pack at Memorial Hospital. Averaging over several years a dose of roughly 0.6 roentgen per month, they exhibited no substantial depression of white blood counts and no degree of lowered vitality. Thus, the limit seemed appropriate.

Between 1920 and 1930, and even later, appalling misuses of X-rays – even their utilization to terminate pregnancies – were still common. Treatment of benign conditions with X-rays or radionuclides was fairly general, which led to a wide range of observations on radiation-induced tumors (UNSCEAR 1977; NAS/NRC 1980). Diagnostic application of X-rays and technical uses of radionuclides were other areas where little or no concern was given to radiation protection.

Former Misuses of Radionuclides

The tragic heritage of the misuses of ionizing radiation in three main fields of application can be seen in the fate of patients treated with the short-lived radium-224, of patients (mostly soldiers) subjected to angiography with the α-emitting contrast medium thorotrast, and in industrial workers (mostly young women) who incorporated large amounts of radium-226 and radium-228 when they painted luminous dials. A brief consideration of these experiences may help to put some of the present problems and anxieties into perspective.

The last-named example concerns the most disastrous industrial misuse of a radionuclide. There were nearly 2000 workers, in the United States alone, who painted luminous watch dials with the long-lived radium-226. These workers, mostly young girls, were paid by the piece, and consequently they used the quickest method to sharpen the tips of the brushes. Employing their lips to sharpen the brushes they ingested large amounts of the radium paint. The high doses of incorporated radium led to numerous osteosarcomas and carcinomas of the paranasal sinuses or mastoids. Up to 1983, these tumors had contributed 12% of all deaths that have occurred in those whose radium intake has been measured. The Center of Human Radiobiology at Argonne National Laboratory has been in charge of the epidemiological study (Rundo et al. 1986); it has recently been reduced to a size which will make it nearly impossible to continue a valid follow-up of the fate of the dial painters. The resulting loss of singular medical and scientific information will be irreversible as well as indefensible.

The dentist of one of the dial painters first assumed red phosphorus to be a component of the luminous paint and blamed it for his patient's grave jaw damage. When this explanation failed, he continued to search for an explanation. Harrison Martland, whom he had consulted, focused his suspicion on radium-226. When this became known, he received an angry letter from Mme Curie; herself a victim of radiation, she called him a charlatan for failing to acknowledge that radiation can do no harm except at very large doses (Merril Eisenbud, personal communication). Although the letter has been lost, it remains a telling sign of the lack of appreciation of radiation risks in the first half of this century.

Decades later an equally tragic misuse of an α-emitting radionuclide occurred in Germany where, at a private clinic shortly after the Second World War, numerous children with bone tuberculosis were injected with large amounts of radium-224 and where the same treatment was given to adults with ankylosing spondylitis (Morbus Bechterew). The fate of the patients might never have become known, except for the actions of a young pediatrician who observed the treatment and spoke out against it. Heinz Spiess secured against the opposition of the director of the clinic the patient data and he has, jointly with Charles Mays, conducted one of the most important

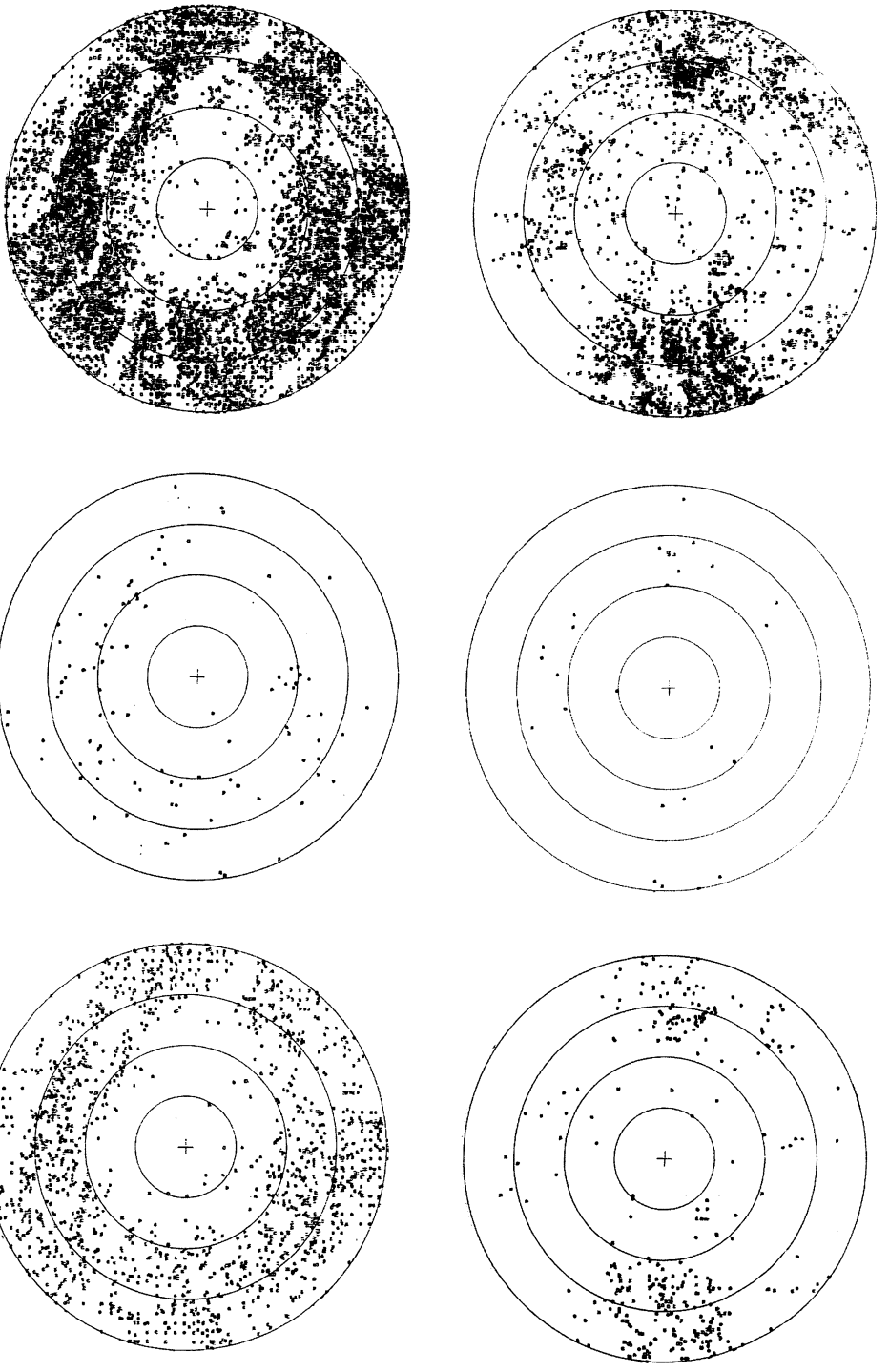
studies of a group of patients subjected to the effects of ionizing radiations (Mays et al. 1986). Unlike the British ankylosing spondylitis patients who were treated with X-rays and developed, as Court Brown and Doll (1956) and Smith and Doll (1982) have demonstrated, an excess rate of leukemias and other tumors, the radium-224 patients incurred a large number of osteosarcomas. There were more than 50 osteosarcomas in the group of roughly 800 patients who were followed. Among the children with the largest doses, the rate of osteosarcomas was extremely high. Radium-224 has a short half-time of only 3.5 days, and the temporal pattern of the occurrence of osteosarcomas is, therefore, the undistorted response to irradiations fractionated over treatment periods of only several months. A maximum of the rate of osteosarcomas was found 5 to 10 years after the treatment, in later years the number of cases has declined. The quantitative analysis of the data has led to a linear-quadratic dose dependence with the risk estimate of $8.5 \cdot 10^{-3}$ per gray of mean skeletal dose (Chmelevsky et al. 1986). The study has been extended now to include various other types of radiation damage, including radiation-induced cataracts.

The observations on the radium-224 patients are directly relevant to a continuing medical practice. Treatment of ankylosing spondylitis with radium-224 is still practised in Germany, but far lower doses are given which amount to a mean skeletal dose of less than 1 gray. The osteosarcoma risk from this treatment would appear to be less than 1% according to the results of the Spiess study. The continued epidemiological investigation of the low dose treatment is consistent with this estimate (Wick et al. 1986). Despite the remaining hazard of osteosarcoma induction, there are valid arguments to defend the present-day radium-224 treatment of ankylosing spondylitis.

The deplorable consequences of another major misuse of a radionuclide are being studied in Heidelberg by von Kaick and his colleagues (1986). Thorotrast was probably the best contrast medium ever available for angiography. However, it contained thorium-232, an α-emitter of extremely long life time. Although numerous lives were saved by the use of thorotrast, it is by now inconceivable that thorotrast was still utilized up to and even beyond 1950. A number of scientists in different countries have studied, and are still studying, the effects of thorotrast which stays in the tissue and blood vessels of the patients, and which has caused a large number of liver tumors. For the remaining patients, liver tumors are now responsible for roughly half of all deaths.

Observation of the Atomic Bomb Survivors and the Estimation of Risk Coefficients

The main source of knowledge on radiation-induced tumors has been and continues to be the fate of the survivors of the atomic bombings. Studies have been performed during the past 40 years, first by the Atomic Bomb Casuality Commission (ABCC) and later by the Radiation Effects Research Foundation (RERF) in Hiroshima (see Yoshimoto et al. 1981; Ellett et al. 1985). The Life Span Study sample (LSS) contains about 60000 survivors of the bombing in Hiroshima and about 30000 survivors of the bombing in Nagasaki. When the bombs were used against Japan no radiation effects were foreseen, since those who would be highly exposed were expected not to survive the heat and the blast.



The diagrams of Fig. 1 show the positions of the survivors at the time of the bombing up to a distance of 2000 m from the hypocenters; they also show the extent of acute deaths at smaller distances and the number of cancer and leukemia deaths. Against expectation, and after merely a few years, leukemias appeared in excessive numbers among the survivors in Hiroshima and Nagasaki. The excess rates were so high that almost all leukemias among the highly exposed and about half of all leukemias recorded in the diagrams are due to the irradiation. These observations, the earlier data on the British ankylosing spondylitis patients (Court Brown and Doll 1956), and the leukemias in radiologists led E. B. Lewis to the hypothesis that leukemia could result from a radiation-induced mutation in a single blood-forming cell and to the assumption that the incidence of cancers might increase as a linear function of dose without threshold (Lewis 1957, 1963). At the time, this assumption was less controversial than it is nowadays, because it was still held that hereditary damage was the principle hazard of low doses of ionizing radiations.

Subsequent studies, mainly on the survivors of the atomic bombings and among the British ankylosing spondylitis patients, have provided a wide range of data on various tumors produced by ionizing radiations in man. For solid tumors, the relative increase of the spontanous rates turned out to be much lower than for leukemia. But the total number of cases is sufficiently large to derive dose dependences for tumors of various organs. Although significant excesses have been seen only at doses of about 1 Gy or more, risk coefficients have been derived which are now applied to very small doses. Table 1 contains risk coefficients presented by ICRP (1977), and a few essential observations must be made.

First, the numerical values of the risk coefficients are such that the total risk for life-time cancer mortality exceeds the risk for hereditary damage. In fact, the comparison can only be valid if a dose dependence without threshold is assumed for radiation-induced tumors. The ICRP has made this assumption, and has made it the basis of its radiation protection philosophy.

In the present context it is interesting to note that hereditary damage due to ionizing radiation has never been demonstrated in man, not even in the descendants of the survivors from Hiroshima and Nagasaki. Great efforts have been made and are still being made to demonstrate the genetic effects. Plans are considered, at present, to supplement past work on protein analysis by an extensive program of DNA studies. That past efforts have failed to demonstrate genetic effects of the irradiation is due to the predominance of other factors which mask the small expected increments. It is, nevertheless, agreed that hereditary effects are caused by ionizing radiations and that they are produced without a threshold of dose. One can, furthermore, assume that the numerical estimates of the risk coefficients are of the right order of magnitude.

For radiation carcinogenesis the situation is reversed. There is a wealth of data, but the extrapolation to low doses remains a conjecture. The linear hypothesis can

Fig. 1. Coordinate plots (Yoshimoto et al. 1981) of the persons in the LSS sample who were within 2000 m of the hypocenters at the bombing of Hiroshima *(left column)* and Nagasaki *(right column)*. *Upper row,* all persons in LSS sample; *intermediate row,* all leukemia deaths till 1978, *bottom row,* all cancer deaths (except leukemia) till 1978.

Preliminary estimates (Ellett et al. 1985) of kerma in free air distances 1000 m, 1500 m, 2000 m: Hiroshima, 5.3 Gy, 0.65 Gy, 0.07 Gy; Nagasaki, 10 Gy, 1.2 Gy, 0.16 Gy

Table 1. Risk coefficients of ICRP (averaged over age and sex)

Life-time mortality of cancer	Per Sievert
Leukemia	0.002
Mammary tumors	0.0025
Lung cancer	0.002
Osteosarcoma	0.0005
Thyroid tumors	0.0005
Other organs	0.005
	0.0125
Severe hereditary damage (2 generations)	0.004

neither be proved nor disproved at present, and it remains uncertain whether improved knowledge of the molecular mechanisms of cellular transformations will ever settle the question.

Basic principles of microdosimetry permit the statement that radiation effects on individual cells can have no threshold in dose and that their probability must be proportional to dose at low doses (Kellerer and Rossi 1982). This is so because energy is transferred to the cells by individual charged particles. At sufficiently low doses – fractions of one milligray for sparsely ionizing radiations and several milligray for densely ionizing radiations – only few cells are traversed by a charged particle. The dose determines then merely the number of cells affected, but not the energy deposition to these cells. Effects on autonomous cells must therefore be proportional to the number of cells affected and thus to dose. The statement remains valid even if the possible, and still largely unknown, role of various intracellular DNA-repair systems is taken into account. Somatic mutations are, therefore, produced without a threshold of dose. However, host factors, i.e., effects on the tissue level, may depend on dose in a way which can not be predicted. Their possible contribution to the progression of a transformed cell towards the growth of a tumor remains unknown.

A second statement on risk factors must be added. Although the estimates are largely based on the observation of the survivors of the atomic bombings, they are consistent with a wide range of studies from the medical application of X-rays. If the atomic bombings had not taken place, there would still be risk estimates of the same order of magnitude. It is less certain whether there would be the ICRP philosophy of linearity for radiation-induced tumors. However, this is the prevailing philosophy in radiation protection, and it has important implications.

Definition of the Effective Dose

For the consideration of risk factors, a few technical notions are required. The first concept is that of dose equivalent which equals absorbed dose of radiation multiplied

Table 2. Weight factors[a] representing the contribution of each organ to the risk of hereditary damage or mortality from radiation-induced tumors

i		w_i
1	Gonads	0.25
2	Breast	0.15
3	Red bone marrow	0.12
4	Lung	0.12
5	Thyroid	0.03
6	Bone surfaces	0.03
7	Remaining organs	0.30

[a] They equal the risk coefficients (see Table 1) normalized to their sum

Definition of effective dose:

$$H_{\text{eff}} = \sum_{i=1}^{7} w_i H_i$$

where H_i is the mean dose equivalent to the organ i, and w_i is the weight factor for this organ

by a quality factor. The quality factor is, by convention, defined as a function of the linear energy transfer of charged particles and it accounts for the assumed biological effectiveness of a radiation at small doses. It is set equal to unity for all sparsely ionizing radiations, i.e., for γ-rays, X-rays, or electrons. Roughly speaking, it is equal to 10 for neutrons which transfer energy to the exposed material by releasing densely ionizing recoil nuclei. It is approximately 20 for α-particles which are also densely ionizing and produce thousands of ionizations while they traverse a cell nucleus. To avoid confusion, one has chosen the special name gray (Gy) for the unit J/kg when it is used with absorbed dose, while the special name sievert (Sv) is used when the unit is applied to dose equivalent.[1] There are proposals, at present, to change the values of the quality factor (ICRU 1986). This is likely to be a controversial topic in radiation protection in the years to come, and it is a question closely linked to the remaining uncertainties of risk assessment and to the lack of human data for the effects of neutrons.

When the body is exposed uniformly, the meaning of the dose or the dose equivalent is clear. When the body is exposed nonuniformly, or when certain organs only are exposed, more complicated specifications of dose are required. To provide a single quantity which can adequately express the resulting overall level of exposure, one has introduced the effective dose equivalent (ICRP 1977), which is now usually called the effective dose. It is a weighted average of all the organ doses. The weighting factor for each organ represents its fractional contribution to the total somatic and genetic risk (see Table 2). The notion may appear artificial, but it is, in fact, a

[1] The former units rad (1 rad = 0.01 Gy) and rem (1 rem = 0.01 Sv) are still widely used

natural matter, if one assumes proportionality to dose at low doses for radiation-induced tumors.

For clarification and illustration one may use an example familiar from the discussion after the reactor accident. The weighting factor for the thyroid is 0.03. If a child consumes a liter of milk contaminated with 1000 Bq of iodine-131, about half of the activity may be collected in the thyroid and it produces there a dose equivalent of roughly 3 mSv. Multiplication by the weighting factor results in an effective dose of roughly 0.1 mSv. For the purposes of radiation protection it is assumed that the exposure of the thyroid to 3 mSv causes a risk of the same magnitude as a whole body exposure of 0.1 mSv which may be caused, for example, by external γ-irradiation or by incorporation of cesium-137.

Validity of the Risk Estimates and Applicability of the Assessment System

One can ask two questions. First, how reliable are the risk coefficients? Second, how useful are they? An adequate answer to either question is outside the scope of the present survey. However, a brief summary can be given.

There has been occasion, in recent years, to doubt the validity of the risk estimates. The reason is that the dosimetry for the atomic bomb explosions has turned out to be incorrect (Loewe and Mendelsohn 1981). Some years ago it was thought that the larger part of the radiation effects in Hiroshima were due to neutrons emitted by the uranium bomb (Rossi and Kellerer 1974; Rossi and Mays 1978). In Nagasaki there were hardly any neutrons, because the plutonium bomb was surrounded by tons of conventional explosives, which shielded the emitted neutrons effectively. The revision of the dosimetry, while not finally concluded, has now led to the consensus that even in Hiroshima there were few neutrons. It was argued then, that effects earlier ascribed to neutrons must now be assigned to γ-rays, with a resulting increase of the risk estimates. However, the revised dosimetry has led to increased γ-doses in Hiroshima (Ellett et al. 1985), and this balances largely the disappearance of neutrons. Any resulting change of the risk estimates due to the revision of the Japanese dosimetry would appear to be less than a factor of 2.

A more substantial change of the risk estimates may arise if the excess rates of mammary tumors, thyroid tumors, lung tumors, and of intestinal tumors persist, and if they follow the increases of the spontaneous rates in the aging collective of exposed persons. The term relative risk model refers to such a persistence and age-dependent increase of excess tumor rates. The Japanese data appear to be in line with a relative risk model, and this appearance is underscored by the occurrence of breast cancer in recent years in a number of women who were very young girls at the time of the bombing. However, recent data on the British ankylosing spondylitis patients (Darby et al. 1985) point in the opposite direction. It is therefore indicated to reserve judgement on the applicability of the relative risk model and to continue the two important studies. Whatever the final conclusion may be, it is important to note, that present risk estimates are based on an observation period of about 30 years only and that an extension to longer times at risk could increase their values.

Are the risk estimates useful? They are hypothetical, because one can, at present, merely surmise but not prove that tumors are caused by small doses of ionizing radiations. In spite of this uncertainty, the risk estimates remain suitable for the pragmatic purposes of radiation protection. For hereditary damage and also for somatic mutations, the linear hypothesis is valid and it is therefore prudent and practicable to make a corresponding assumption also for radiation-induced tumors. The important consequence for radiation protection is, to replace the former concept of dose limits by the principle to keep radiation doses as low as reasonably achievable (ALARA).

The International Commission for Radiological Protection has attempted to formalize the ALARA principle and to develop it into a cost-benefit assessment. Some have gone to the point of assigning a monetary cost to a man sievert, which is the unit of collective dose, i.e., the sum of doses to individuals in a collective. In practice such formalistic approaches are likely to fail. The ALARA principle itself has, however, become a useful tool to reduce undesirable exposures, both in nuclear technology and in medical applications. When exposure limits are considered as ultimate ceilings, not as permissible levels, and when unnecessary exposures are avoided, average dose levels in controlled groups will stay far below the limits. This has, indeed, been achieved in nuclear industry. In medicine, similar efforts have been made, and data are now available which facilitate the optimization of diagnostic equipment and the cost-benefit assessment of diagnostic screening procedures. The controversy, in recent years, on mammography as a screening procedure exemplified the potential of the cost-benefit approach, and it has largely contributed to the reduction of the doses and to better definition of the indications for mammography. The prudent assumption of no dose threshold for somatic late effects has also helped to advance the use of modalities other than ionizing radiations.

Need for a Balanced View of Risks

The merits of the assessment system are less obvious, when it is misused, and when a philosophy is embraced which aims at total avoidance of radiation exposures or, at any rate, the complete avoidance of any "nonnatural" radiation exposure. The computation of hypothetical numbers of cancer deaths, usually in large collectives but without reference to their size, is then an effective means to generate confusion and even panic.

These problems became evident when the recent reactor accident produced contaminations in several European countries which exceeded levels legally set for the routine practice of radiation protection. Limits or derived limits were then erroneously interpreted as thresholds that separate harmless exposures from dangerous doses. On the other hand, the assumption of linearity and the risk coefficients were used to compute absolute numbers of expected cancer deaths. Even if they are formally correct, such computations can be highly misleading, when they are not related to spontaneous rates and their fluctuations due to various other factors.

For example, in a recent discussion, the claim was made that about 1000 cancer deaths would result from the collective dose of 75000 man sievert which results from the emission of $5.3 \cdot 10^{14}$ Bq of ^{14}C during the 40 years of projected operation of a

reprocessing plant. The computation of the collective dose is correct. However, the statement omits the fact that more than 99.9% of this collective dose is caused after the global dispersion of ^{14}C, and over a period of several thousand years. In fact, the computed number of deaths relates to 200 generations of all of mankind. It is therefore hardly conceivable how the number 1000 could be meaningful.

Computations of assumed numbers of cancer deaths may be less widely removed from reality when applied to the consequences of large-scale radioactive contaminations from the reactor catastrophe. But they are grossly misleading when employed to induce personal anxieties. Possible increases of tumor rates in Western Europe are far smaller than the existing rates and than their fluctuations due to various controllable and uncontrollable factors. The absence of a personal thread is due to the dilution of the risk within a population of many millions. On the other hand, such dilution is no reason to disregard the possible detriments and to omit suitable measures. It is essential to distinguish between a tangible personal threat and an undesirable addition to the pool of existing detriments. To neglect risks to large populations, unless they break through the threshold of epidemiological ascertainment, would be a fatal counterposition against unfounded anxieties. Reasonable administrative measures to reduce doses, for example, from iodine-131 in milk, were therefore justified and were in line with the ALARA principle.

A more balanced view of risks and their numerical values is required. Further efforts will be needed to achieve such a view, and to have it take the place of prevailing misconceptions and collective anxieties.

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