Contents

Session 1

**General Aspects**

Chairman: F. Vogel

Genetic Predisposition for Cancer Risks in Man
D. G. Harnden ............................................................... 3

The Role of Epidemiology in the Detection and Reduction of Cancer Risks
R. Doll ................................................................. 14

Summary of Discussion: Session 1
L. Arab-Kohlmeier ...................................................... 24

Session 2

**Chemical Carcinogens: Risk Assessment**

Chairman: D. Neubert

Assessment of Cancer Risk from Chemicals
D. Henschler ............................................................... 27

Validity of Short-Term Tests to Detect Carcinogenic Chemicals
H. Greim, U. Andrae, W. Goggelmann, L. Schwarz, and K. H. Summer (With 5 Figures) ............... 33

Preneoplastic Lesions as Indicators of the Carcinogenic Risk Caused by Chemicals
P. Bannasch, H. Enzmann, and H. Zerban (With 6 Figures) ........................................... 47

Carcinogenic Risk Assessment:
Are Animals Good Surrogates for Man?
I. F. H. Purchase .......................................................... 65

Summary of Discussion: Session 2
R. Bass ................................................................. 80
Session 3  
**Chemical Carcinogens: Primary Prevention**  
Chairman: D. SCHMÄHL  

Possibilities of Primary Prevention Against Chemical Carcinogens  
R. PREUSSMANN (With 3 Figures)  

Primary Prevention Against Occupational Carcinogens  
P. J. LANDRIGAN and I. J. SELIKOFF  

Chemical Carcinogens in Tobacco  
D. HOFFMANN, E. L. WYNDER, S. S. HECHT, K. D. BRUNNEMANN,  
E. J. LAVOIE, and N. J. HALEY (With 4 Figures)  

Primary Prevention of Tobacco-Related Cancer  
E. L. WYNDER and M. A. ORLANDI (With 6 Figures)  

Summary of Discussion: Session 3  
H.-G. NEUMANN  

Session 4  
**Physical Carcinogens**  
Chairman: W. GÖSSNER  

Cancer Risk from Ultraviolet Radiation  
H. IPPEN  

Assessment of Cancer Risks Due to Ionizing Radiations  
A. M. KELLERER (With 1 Figure)  

Cancer Risk from Environmental Radioactivity  
W. JACOBI (With 5 Figures)  

Summary of Discussion: Session 4  
E. W. HAHN  

Session 5  
**Oncogenic Viruses**  
Chairman: E. WECKER  

Viruses in Human Tumors  
H. ZUR HAUSEN (With 1 Figure)  

Strategies in the Prevention of Infections by Oncogenic Viruses  
F. DEINHARDT (With 3 Figures)
Contents

Summary of Discussion: Session 5
G. HUNSMANN .................................................. 190

Summary of Round Table Discussion on Strategies
Against Tobacco Cancer
G. EISENBRAND .................................................. 192

Subject Index .................................................. 195
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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 4g 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 $8.5 \times 10^{-3}$ 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 $\alpha$-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 Casualty 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 spontaneous 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

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**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)

<table>
<thead>
<tr>
<th>Life-time mortality of cancer</th>
<th>Per Sievert</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemia</td>
<td>0.002</td>
</tr>
<tr>
<td>Mammary tumors</td>
<td>0.0025</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>0.002</td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>0.0005</td>
</tr>
<tr>
<td>Thyroid tumors</td>
<td>0.0005</td>
</tr>
<tr>
<td>Other organs</td>
<td>0.005</td>
</tr>
<tr>
<td>Severe hereditary damage</td>
<td>0.0125</td>
</tr>
</tbody>
</table>

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 representing the contribution of each organ to the risk of hereditary damage or mortality from radiation-induced tumors

<table>
<thead>
<tr>
<th>i</th>
<th>$w_i$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.25</td>
</tr>
<tr>
<td>2</td>
<td>0.15</td>
</tr>
<tr>
<td>3</td>
<td>0.12</td>
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<tr>
<td>4</td>
<td>0.12</td>
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<tr>
<td>5</td>
<td>0.03</td>
</tr>
<tr>
<td>6</td>
<td>0.03</td>
</tr>
<tr>
<td>7</td>
<td>0.30</td>
</tr>
</tbody>
</table>

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 $\gamma$-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 $\alpha$-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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Subject Index

across-species differences 81
actinic cheilitis 137
- keratoses 137
activation, metabolic 88
acute toxicity 70
African, black 138
AIDS 171, 184
ALARA principle 151
albinismus 140
alcohol consumption 191
aldrin epoxidase 134
Ames test 36
animal carcinogenesis 31, 80
- experiments 87
ankylosing spondylitis 144, 145, 150
antenatal diagnosis 9
antioxidants 92
antismoking programs 128
antitobacco propaganda 120
artificial light sources 138
asbestos 28
ataxia-telangiectasia (AT) 6, 24
atomic bomb 168
-- survivors 145
avoidance of exposure 89

background radiation 17
basal cell carcinoma 137
basophilic degeneration 137
benz[a]anthracene 34
benzo[a]pyrene 94
bioassay 32, 58, 80, 82
biological end-points 33
- markers 99
biomonitoring 32, 133
bis-(chloromethyl)ether 28
bladder carcinoma 76
blood group 8
breast cancer 150
bromodeoxyuridine (BrdUrd) 40
Burkitt’s lymphoma 173, 190

cancer, causes 66
- , - , nutritional 66
- of the bladder 76
- of the breast 150
- , carbohydrate metabolism and 52
- , cervical 172, 176, 190
- epidemiology 95
- families 8
- , gastric 21
- induction, monocausal 90
- , occupational 27, 28
- registries 20
- of the scrotum 94
- susceptibility 8
carcinogenesis, chemical 27, 87
carcinogenic risk 78, 81
carcinogenicity 33
carcinogens, occupational 30
case-cluster 20
cell-cell interaction 82
cellular heterogeneity 50
Celtic type 138
cervical cancer 18, 191
chemical carcinogenesis 27, 87
- , primary prevention of 87
- , theory of 88
- hazards 20
- substances, classification 80
chemoprevention 92
Chernobyl accident 167, 168
childhood leukemia 17
chlorodinitrobenzene (CDNB) 37
cholangiofibrosis 54
chromosomal abnormalities 7
chromosome breakage syndromes 6
- deletion 5
- rearrangements 6
chronic lung disease 133
cigarettes 117, 121, 124
- , average tar content 118
- , filter 116
- , less harmful 192
- , low yielding 116
cigarette smoking 114, 128, 130
- tar 14
classification of chemical substances 30, 80
- systems 28, 29
cocultivation experiments 82
continuous cell lines 34
Cotinine, elimination in active vs passive smokers 110
- as biological marker of exposure to tobacco 109, 110
cytochrome P448 34
- P450 34
deposition densities 160
detection, early 11
detoxifying processes 90
dexamethasone 34
diagnostic criteria 75
dial painters 144
displasias 190
DNA-adducts with tobacco-specific nitrosamines 108, 109
- amplification 171
DNA damage 33
- polymorphisms 9
- probes 9
- repair 40, 148
- process 91
dose 154
- collective 151, 152
- dependence of hepatic preneoplasia 56
- effective 148, 162
- equivalent 148, 157
- response relationships 80, 96
- virtually safe 73
Down’s syndrome 7
effective dose 148, 162
elastosis 137
electrons 149
environmental carcinogenesis 95, 96
- multicausal 90
enzyme-altered foci 56
- modulators 91
epidemiologic surveillance 98
epidemiology 24, 31, 71, 87, 133
Epstein-Barr Virus (EBV) 172, 173, 182, 190
ethoxyresorufin-O-deethylase 34
eumelanin 138
exposure 80
- avoidance 89
- reduction 89
extrapolation 81
filter cigarettes 116
flavones 91
foci 47, 56
- acidophilic cell 49
- of altered hepatocytes 50, 56, 58
- basophilic 51
gastric cancer 21
gene mutation 5
genetic/environmental interactions 3, 4
- counselling 11
- predisposition 3
- screening 10
- strategies 9
- susceptibility 14
glass fibers 133
glucuronosyltransferase 34
glutathione 37
glutathione-S transferase 37
glycogenesis 50
glycogen storage foci 51
gonadal dysgenesis 8
gray (Gy) 149
“hazard” 81
- assessment 31, 66
HBV (see hepatitis B virus)
health education 118, 126, 192
- passport 127, 128
hepatic neoplasia, dose-dependence 56
- preneoplasia 48
- dose-dependence 56
hepatitis B 181, 183
- immunoglobulin (HBIG) 185
- vaccine 186
- virus 17, 171–173, 191
- DNA 184
- vaccine 184–187
hepatocarcinogenesis 50
- models of 54
hepatocellular carcinoma (HCC) 17, 172, 183, 184, 191
hepatoma lines 39
herpes virus 181
high-risk groups 11
HLA 9
hormones 20
hormone balance 7
human carcinogenesis 80, 82
hydrogen peroxide 42
hydroxylase enzymes 6
IARC 28, 81
- list 28
immune deficiency syndromes 7
- response 7
Subject Index

immunization 18, 182
industrial hygiene 98
initiation, tumor 88
initiation-promotion protocol 55
interferon 181
intervention studies 133
iodine-131 150
ionizing radiations 16, 87, 143, 166, 167
keratoacanthoma 137
α-ketoacids 42
kidney 54

 latency period 190
latent tumor cell 88
LAV/HTLV III (HIV) 181
legal and administrative approaches 98
— measures 89
lentigo maligna 137
leukemia 24, 143, 147, 148
—, childhood 17
lifestyle 10
light-blocking agents 166
light-exposed skin areas 139
light habituation 141
light-induced callus 141
lip cancer 137
liver lesions, focal 56
—, preneoplastic focal 58
liver-specific-functions 39
— tumors 145
longevity 75
low-yield cigarettes 116
lung cancer 114, 115, 117, 130, 148, 167, 175

MAK values 81
malignant melanoma 137
mammary tumors 76, 148
mammography 151
“markers” of chemical exposure 99
mathematical models 31, 73
maximum tolerated doses 70
Mediterranean type 138
melanomas 18
Mendelian inheritance 7
metabolic activation 33, 38, 88
microdosimetry 148
modified production techniques 89
monocausal cancer induction 90
monoclonal tumors 190
monooxygenases 34
mouse hepatitis virus 191
multicausal environmental carcinogenesis 90
mutagenic effects 87
mutagenicity 33
mutations 147, 148

β-naphthylamine 94
neoplastic hepatic nodules 50, 53
neurological disorders 133
neutrons 149, 150
nicotine 118, 120, 121
— as a biological marker of exposure to tobacco 109, 110
— as a precursor to carcinogens 105, 108
—, in the particular phase of smoke 100
—, in the vapor phase of smoke 110
nitrates 21
nitrosamines (see also tobacco-specific nitrosamines) 193
— as human carcinogens 111
—, estimated human exposure 107
nucleophilic sulfur-containing compounds 91

occupational cancer 27, 28, 97
— carcinogens 30
— etiology of cancer 96
— exposure 96
oncogene expression 190
oncogenic viruses 87, 181
organ-specificity 82
osteosarcomas 144, 145, 148

papillomavirus 171–178
papovavirus 181, 183, 190
α-particles 149
parvoviruses 171
peer groups 192
personal measures 89
— protective equipment 98
pharmacokinetics 80
phenobarbital 34
pheomelanin 138
photo-augmentation 138
polycyclic enzymes 6
polyposis coli 11
population screening 10
potency 68, 82
predictivity figures 68
pregnenolone-16-β-carbonitrile 34
premarket screening 98
— toxicologic screening 97
preneoplastic focal lesions 47, 48, 53–59
prevention 14, 65
—, primary 87
—, secondary 97
—, tertiary 97
preventive oncology 130
primary hepatocyte cultures 33
progression 7
proto-oncogene 9
public intervention campaigns 121
radiation, background 17
- ionizing 87, 143
- ultraviolet 137
radionuclides 144
radon 167
"radon-daughter-exposure" 155
rat liver foci bioassay 54, 58
γ-rays 149, 150
reactive carcinogens, scavenging of 90
- oxygen species 34
reactor accident 151
rearrangement of genes 24
regression of lesions 82
- of foci of altered hepatocytes 57
regulations 80
relative risk models 150
repair 83
reproducibility 81
restriction of use 81
retinoblastoma 5
retinoids 92
retroviruses 182, 183
- reverse transcriptase 181
risk 14, 81
- assessment 59
- coefficients 145, 148, 150, 155
- evaluation 31
- management 66
Rn-concentration (EEC$_{Ra}$) 157
rodent liver cancer 76

S9 fraction 33
scavenging of reactive carcinogens 90
screening 11
- genetic 10
- population 10
secondary prevention 97
self-help programs 122
serum banks 21
short-term tests 33, 81, 87
sievert (Sv) 149
skin cancer 137
- tanners 139
skin-tanning agents 141
smoke cessation 124
- programs 133
- techniques 124
smokers 167
smoking, association with cancer 101, 178
- cessation of 104, 118, 125, 126
- habits 118
- nicotine delivery to nervous system 120
- relationship to lung cancer 115
- rooms 93
snuff, carcinogenicity of 101
snuff-dipping 101, 107
solariuums 139
squamous neoplasms 76
stop experiments 57
substitution 98
sulfotransferases 37
sunbathing 140
sunlight 166
sunscreens 139
tanning 139
target organs 68
TD50 68
terrestrial sunlight 138
tertiary prevention 97
thiourea 40
thorium-232 145
thorotrast 144, 145
threshold 143, 147, 148, 151
thyroid 150
- tumors 148
tobacco 14, 114, 115
- chewing 129
- smoke, aromatic amines 104, 105
-- bioassays of 101, 102
-- cocarcinogens in 102
-- organ-specific carcinogens in 104, 105
-- nitrosamines in (see tobacco-specific nitro-
samines)
--, particular matter of 101, 102, 105
--, polynuclear aromatic hydrocarbons in 102, 103
-- reduction of carcinogenicity 102, 103
--, tumorigenic potential of 103
--, tumor initiator 102
--, -- promoters in 102
--, vapor phase of 105
-- smoking 119, 122
tobacco-specific nitrosamines
--, biochemistry of 108
--, carcinogenicity of 106
--, DNA adducts of 108, 109
--, endogenous formation of 110
--, formation in tobacco and tobacco smoke 105
--, levels in commercial tobacco products 107
translocation of myc gene 190
tumor cell, latent 88
- initiation 88
- rates 152
tumors, liver 145
-- mammary 148
-- thyroid 148
ultraviolet A 138
– B 138
– C 138
– radiation 137, 166
“unscheduled DNA synthesis” (UDS) 40
uranium miners 167
urothelium 54
UV-blocking creams 166

ventilation 98
vinyl chloride 28
virus, EBV 171–173, 182, 190
–. HIV 181, 183
–. hepatitis B virus 171–173, 181, 183
–. herpes 171, 181
–. HTLV I 171, 173, 182
–. HTLV II 182
–. HTLV III (HIV) 182
–. hybrid 182
–. LAV/HTLV III 181
–. oncogenic 87, 171–178, 181
–. papilloma 171–178
–. papova 181, 183, 190
–. retrovirus 181
vitamin A 92

World Health Organization (WHO) 186

xenobiotics 34
xeroderma pigmentosum 24, 140
X-rays 143, 145, 149