

# Introduction to low-dose biological radiation effects

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Starting with the first observations by Pierre Curie and others of radiation injury at their own bodies, radiobiology has been developed over more than a century. But still today there is an enormous discrepancy between (a) the *observation* of radiation injury in the sense of *clinical symptoms* such as tissue damage or carcinogenesis, (b) the epidemiological approach, i.e. the *counting* of such effects in a population and the attempt of *correlating* them with presumable causes, (c) the experimental investigation of the underlying *radiobiological mechanisms*, including the influences of the defense barriers of the human organism, (d) the *high practical importance* of radiation protection at low doses with regard to radiation exposure in the course of professional exposure, medical diagnosis and by natural sources of ubiquitous occurrence such as radon in homes. Due to the *coincidence of high practical importance and existing incompleteness of the understanding* of causal relationships, low-dose radiation effects are a popular subject of debate, and it is not easy to regulate radiation protection in a rational way in the presence of partially limited knowledge. I will try to outline some categories of thinking which might be useful for you to find your way in this difficult field.

(1) Quantification of low-dose irradiation: A basic concept of quantifying the irradiation of a biological subject by ionizing radiation is the *absorbed dose*, i.e. the *expectation value* of the radiation energy absorbed per unit mass. In a given *radiation field*, due to *external or internal exposure*, the dose value depends on the chosen point of interest and may differ strongly between various parts of an irradiated body. The discontinuous nature of energy deposition by ionizing radiation along particle tracks causes *large stochastic variations* of the values of the *specific energy*, i.e. the *local values* of the absorbed radiation energy per unit mass. These variations, which increase as the absorbed dose decreases, are considered in the subdiscipline of *microdosimetry* by applying *track structure parameters* such as *LET*. Besides absorbed dose, another expectation value often used in high-LET work is the *particle fluence*, and the product of absorbed dose and a "radiation weighting factor" is called "*dose equivalent*". Low doses are loosely defined as lying below an absorbed dose of about 100 mGy, i.e. below the onset thresholds of the "deterministic effects" (see below). An important source of low doses is the natural radiation exposure, amounting to about 2 mSv/a at ground level in Germany.

(2) Clinically overt radiation injury: With regard to radiation injury it is important to distinguish between *deterministic* and *stochastic effects* (ICRP 103), as well as between *early* and *late* effects. A deterministic effect is an injury in a population of cells, characterized by a *threshold dose* and an *increase in the severity of the reaction as the dose is increased further*. It is also termed tissue reaction, which may be early or late. In some cases, deterministic effects are modifiable by post-irradiation procedures including biological response modifiers. A deterministic effect is, e.g., the *hemopoetic form of the acute radiation syndrome* which has a dose threshold at about 1 Gy and whose severity increases with dose up to its fatal outcome at doses beyond about 5 Gy. For *cataracts of the eye*, recent research results point to a threshold dose of about 0.5 Gy, much lower than assumed before. - The stochastic effects are malignant diseases and heritable effects for which *the severity is dose-independent*, but the *probability of occurrence is a function of dose*. The dose dependence of the stochastic effects is often regarded as *having no threshold*, but for carcinogenesis the existence or non-existence of a dose threshold is still a *matter of research*. If the same magnitude of biological effect in a given biological system is produced by two different types of radiation, the quotient of the absorbed doses needed to cause the effect is called the *relative biological effectiveness (RBE)*.

(3) Epidemiologic studies: Epidemiologic studies are linking pathologic disease classification, quantification of exposure parameters and statistical evaluations in order *to identify or reject statistical associations between clinically overt radiation effects and presumable causes*. A central concept is the *risk (= probability)* for a radiation-exposed person of developing a stochastic radiation effect. Well known examples are the lifelong study on radiation-induced cancer by the Radiation Effects Research Foundation of Hiroshima, the studies of lung cancer of uranium miners and in-door radon exposed persons in houses, the studies of breast cancer of women after medical X-ray exposure of the breast in the follow-up of tuberculosis treatment with pneumothorax, and the study of cancer incidence at nuclear shipyard workers. Many studies - although they have clear and important results in the higher dose range - are showing *large remaining uncertainties* about the *shape of the dose-risk relationship at low doses*; and *the existence of dose thresholds* for cancer risk at doses below some tens of millisieverts, i.e. in the realm of the normal natural radiation exposure, *can neither be proved nor be excluded*. In some epidemiologic studies, such as on the radium dial painters of New York and on the use of Thorotrast as an X-ray contrast medium, thresholds have been found, but, e.g., the international study on lung cancer by indoor radon exposure *did not result in clear evidence for or against the existence of a threshold*. ICRP 92 has concluded that, according to present knowledge, the extrapolation of cancer risk into the realm of low doses *cannot be solved by epidemiology*, and that the long and hard way of the radiobiological investigation of low-dose radiation effects is unavoidable. ICRP 103 has also recommended *not to calculate the "attributive risk"* (i.e. the expected number of cases in a population) if the risk is very low and therefore not adequately known whereas the exposed population is very large. However, this recommendation is not always followed, and attributive risk figures, *boldly extrapolated into the low-dose region*, are popular in public opinion-making.

(4) Low-dose radiobiological research: Modern radiobiology combines methods of radiation physics, molecular and cellular biology, genetics, cytology, histology, immunology, oncology and pathology. The visualization of, say, DNA and protein damage, chromosome aberrations and apoptotic cells, the measurement of mutations, signal pathways, cell cycle effects and immune responses, and the observation of changes of the life expectancy of irradiated organisms are among the most impressive. It is useful to distinguish between radiation effects on *isolated cells* in vitro, on *cell cultures* where single cells have some interaction between each other (the "*bystander effect*"), on *tissues*, on *whole organisms* and on *populations*. The concept of "*system biology*" has been introduced into radiobiology as a guiding mark in the sense that *the actions of radiations on molecules and isolated cells have to be distinguished from systemic effects*. This distinction is particularly useful in radiobiologic research concerning the dose-effect relationship for carcinogenesis at low doses: The development of cancer in an organism follows a *multi-step pattern* of initiation, promotion (accumulation of somatic mutations in cells, development of "genomic instability"), clonal expansion against the immune defense and finally tumor vascularisation and metastasis. Therefore it has to be clarified *which step(s) determine(s) the dose dependency of cancer risk*. The phenomenon that radiation carcinogenesis frequently follows the pattern of a "*multiplicative*" risk, i.e. the radiation-independent "base risk" is *multiplied* by a dose-dependent *factor* instead of being *accumulated* with a dose-dependent risk, points in the direction that *the dose dependence of low dose carcinogenesis is not determined in the initiation step*. Therefore the linear dose-effect relationships of simple molecular or cellular changes cannot be used to prove that the dose-effect relationship for carcinogenesis at low doses must be linear. Another quite general phenomenon and a further cause for nonlinear dose-effect relationships is that low doses are *activating defense mechanisms or "adaptive responses"* such as cellular DNA repair, cell cycle checkpoints, immune system reactions and even evolutionary effects in chronically exposed populations.

(5) The pragmatic approach of radiation protection at low doses: The situation, in which present radiation protection regulations have to be made can be compared to many situations in personal and public life: *A decision has to be made although not all relevant facts are known.* No doubt, a *precautionary principle* has to be followed, and the underestimation of danger has to be avoided. In acknowledgement of the inaccessibility to epidemiology of much of the low-dose region, and of the still incomplete understanding of radiobiological mechanisms at low doses, ICRP 103 has decided, for the time being, to make the *simplifying assumption* that the dose-effect relationship for cancer induction is *linear and has no threshold (the "LNT model")*. This model appears not to underestimate the risk for stochastic effects, i.e. corresponds to the *"precautionary principle"*, it makes practical radiation protection easier (e.g. gives *dose-independent RBE's* between types of radiation) and the *risk values can be easily derived* from higher dose levels where they had been determined by epidemiology. Of course, ICRP also knows of the disadvantages of this pragmatic approach, e.g. the possible misinterpretation of the LNT model as scientific knowledge ("there is no safe dose, each photon can kill you"), and the latent conflict with the evolutionary aspect that higher organic life has developed in the continuous presence of the natural radiation exposure. That is why commissions of specialists, e.g. the German Radiation Protection Commission (SSK), have clarified that they are using the LNT model for the precautionary estimation of radiation risk, but are aware of the inherent, numerically unknown inaccuracy of this practice and strongly encourage further radiobiological research at low doses.