Radiation Biology: A Handbook for Teachers and Students

Slide Series prepared in 2011 by J.H. Hendry. The IAEA officer responsible for this publication is J. Wondergem of the Division of Human Health, International Atomic Energy Agency.
4. Extra module for radiation protection personnel
Section 4.

Sources of additional illustrative material and slides.


• http://www.iaea.org/Publications/Training/Aso/register.html IAEA slide series of Modules in Radiobiology including Protection.

• http://rpop.iaea.org/RPOP/RPoP/Content/AdditionalResources/Training/1_TrainingMaterial/index.htm Slide sets on Medical Radiation Protection.

• http://lowdose.energy.gov/radiobio_slideshow.aspx Slide sets on Low Dose effects.
4.1 Introduction (1)

- The aim of Radiation Protection is to establish an appropriate level of protection for people and the environment against detrimental effects of radiation exposure without unduly limiting the desirable human actions that may be associated with such exposure.

- The first aim of radiation protection is to keep doses below the threshold value for tissue or organ reactions.

- These reactions are similar to the early and late side effects (morbidity) of radiotherapy in cancer patients, which occur only after high radiation doses and which show an increased severity with increasing radiation dose. They are not observed below a certain threshold dose.

- In the context of radiation protection these effects were previously called “deterministic radiation effects”.
4.1 Introduction (2)

- The main risks that radiation protection is concerned with are radiation-induced cancer and leukaemia, radiation-induced heritable damage and radiation-induced developmental damage to the developing embryo and foetus.

- The severity of both radiation-induced cancer and radiation-induced heritable diseases does not depend on radiation dose, but their frequency increases with increasing radiation dose. They are commonly called “stochastic radiation effects”.

- Recent epidemiological and radiobiological data do, however, blur the clear distinction between both types of effects which are dealt with in a radiation protection context.
4.2 Radiation accidents and environmental radiation exposure

• Accidents have happened infrequently in the history of radiology and nuclear research, and usually they have involved only small numbers of people.

• From those accidents, much has been learned about the health consequences and the appropriate medical management of radiation accidents.

• The Chernobyl accident in 1986 posed the greatest challenge to all radiation protection personnel involved in radiation accident management. The value of the experience gathered in previous accidents was shown after this event.

• Much more has been learned to be used in more recent accidents which involved even larger numbers of people such as in Brazil (abandoned radioactive source in Goiania), or which caused more severe bodily harm such as in Tokai-Mura, Japan.
4.2.1 Dose estimation (1)

- Radiation risks depend, above all, on the radiation dose received by the affected person(s). The risk increases with increasing radiation dose.
- Therefore, estimates of radiation risks have to be based on the careful evaluation of the individual radiation dose and the dose distribution in the body.
- Radiation exposure may come from external irradiation usually with γ-rays from radionuclides which may be natural or man-made, or it may come from internal irradiation, mostly with β-rays emitted by radionuclides from natural or man-made sources.
- It is in particular from naturally occurring radionuclides that also α-particles may be a problem in radiation protection from internal exposure.
4.2.1 Dose estimation (2)

- External radiation doses of occupationally exposed people, i.e. radiation workers, are routinely measured with personal dosemeters which are usually either based on film dosimetry or thermoluminescent (TLD) dosemeters.
- These dosemeters are designed to measure the accumulated exposure over a period of usually one month at the body site where the dosemeter is worn, but they also permit the measurement of the energy and penetration of the ionising radiation.
- Readings may be unreliable if exposure is very inhomogeneous.
- In order not to underestimate radiation exposure it is important that the dosemeters are worn at a suitable site of the body, usually the chest.
- Internal contamination of radiation workers is most often investigated by measuring the particular radionuclides in the urine.
4.2.1 Dose estimation (3)

• Whereas the determination of radiation doses of radiation workers is straightforward and follows a routine procedure, the determination of radiation doses in accident situations is much more complex and has to be especially designed to meet the individual scenarios.

• Retrospective determination of external and internal radiation doses after an accident has to be based on various measurements which then need to be fed into a complex model which takes account of the time-dependent changes of radioactive decay, transport of radioactivity in the environment and transfer in the human body.

• Prospective determination of external and internal radiation doses are needed to define the permitted releases of radioactivity from planned nuclear installations during normal operation and, more importantly, to estimate the potential radiation exposures of the population during accidents as the basis for decisions on required countermeasures.
4.2.1 Dose estimation (4)

- These estimates are entirely based on model calculations which use several models in sequence.
- The transport of radionuclides from the source (i.e. the site of the accident to the site of the population to be considered) is calculated using a meteorological model of transport of the aerosols to which radionuclides are attached and their deposition (either dry (fall-out) or wet (wash-out)) to the ground.
- These models are based on meteorological data and experiments, and may be quite detailed including e.g. translocation of deposited radionuclides by rainfall into the sewer system or resuspension of radionuclides attached to dust.
4.2.1 Dose estimation (5)

- The radionuclides deposited on the ground lead to external irradiation with $\gamma$-rays (which often is the most important contribution to the total dose), or to internal irradiation through direct contamination of food.

- The transfer of radionuclides deposited on the ground or in water (lakes or rivers) is determined with the use of radioecological models which describe the changes of activity concentration from one compartment to the next, e.g. from ground surface to plant roots, from there to the edible parts of the plants and from there to the actual food.

- The calculation of radiation doses requires also knowledge or estimates of food intake (how much and when). The distribution of radioactivity which has been incorporated by eating (ingestion) or breathing (inhalation) is determined with the biokinetic model which relates the uptake with a dose factor which defines the committed dose per Bq incorporated radionuclide in the different organs of the body.
4.2.1 Dose estimation (6)

• The determination of external radiation exposure immediately after accidental releases of radionuclides usually is relatively straightforward, and often can be performed on the basis of direct measurements, e.g. the dose rate at 1 m height above the ground from radionuclides deposited on the ground.

• On the other hand, the determination of internal radiation exposure usually requires many measurements in the food chain and complex modelling.

• Retrospective dose estimation has to be performed for past exposures in order to estimate radiation risks. This has been done, e.g. for A-bomb survivors (see below), for populations exposed from the Chernobyl accident, for populations exposed in Siberia from the radioactive pollution of the Techa River, and from contamination of large areas from nuclear weapons test, e.g. in the Marshall Islands and near the Semipalatinsk test site.
4.2.1 Dose estimation (7)

• The radioecological methods have been developed in major international cooperative research projects and have reached a high degree of reliability.

• However, there is often the need to determine individual radiation doses which can best be performed by biological dosimetry techniques, e.g. in the liquidators after the Chernobyl accident.

• The determination of radiation dose from accidental exposure in the first few weeks after the accident is commonly done by a combination of physical reconstruction of exposure scenarios and calculation of organ doses and total body doses, as well as by biological dosimetry.

• The preferred method of biological dosimetry which has proven its value in many accidents is the determination of the frequency of unstable chromosome aberrations in stimulated blood lymphocytes. The method has been well standardised.
4.2.1 Dose estimation (8)

• Phytohaemagglutinin is added to 5 – 10 ml heparinised blood to stimulate resting lymphocytes into proliferation.

• After incubation for 48 hours at 37 °C, cells entering mitosis are arrested in metaphase by adding colchicine. It is important to arrest cells in their first mitosis since many of the severe chromosome aberrations are eliminated in the first cell division.

• As a general rule, the number of dicentric chromosomes is counted in 500 arrested metaphases. If there are 25 dicentrics among 500 metaphases, a total body dose of 0.3 Gy can be assumed. After 3 Gy, there is, on average, one dicentric chromosome per metaphase.

• After homogeneous total body irradiation, the number of dicentric chromosomes per cell follows a Poisson distribution. Marked deviations from a Poisson distribution are an indicator of very inhomogeneous dose distribution which may have consequences for the prognosis.
4.2.1 Dose estimation (9)

- The determination of radiation doses from accidental exposures many months and years after irradiation is based on the measurement of stable chromosome aberrations, such as balanced translocations which can be visualised using fluorescence in situ hybridisation (FISH).

- Biological dosimetry based on cytogenetics requires time-consuming investigations by highly trained staff, and thus can usually not be performed on large numbers of accident victims.

- For this reason, alternative methods which can be automated to some degree such as micronuclei in peripheral lymphocytes and glycophorin A (GPA) mutations in erythrocytes have been developed and used, e.g. in clean-up workers and affected populations of the Chernobyl accident. However, they have not found the same degree of general acceptance.
4.3 Diagnosis and medical management of radiation syndromes
4.3.1 LD-50 (Lethal dose 50%) (1)

• The dramatic experience of the deaths and long term morbidity of thousands of people in Hiroshima and Nagasaki and the prospect of a nuclear war, initiated in the 1950s a large scale research programme into the acute radiation lethality of a wide range of mammalian animals ranging from mice to large animals such as goats and dogs.

• The death rates and the latency to death after different radiation doses given to the whole body were determined in laboratories around the world. The experiments with total body irradiation of mice in particular defined our understanding of the causes of death and of the lethal radiation doses.

• Lethality increased with increasing dose following a sigmoid dose response curve. Usually, radiosensitivity was defined in the steepest part of the dose response curve as the dose resulting in lethality in 50% of subjects (LD50) in a specified period after radiation exposure, most commonly in 30 days.
4.3.1 LD-50 (Lethal dose 50%) (2)

- Significant differences in the LD50/30 were found between different animals, and there was a trend for decreasing LD50/30 with increasing body mass. Whereas in mice the LD50/30 usually is about 7 Gy, in some large animals it is as small as 3 Gy.

- From the experience of some radiation accidents and of some groups of atom bomb victims who did not suffer from extensive burns or wounds but still had received high radiation doses, the LD50 of humans within 60 days was estimated to be 3 - 4.5 Gy.

- Lethality after total body irradiation depends also on factors such as co-morbidity and the quality of medical care. The Medical Research Council of the United Kingdom defined three dose ranges with different prognoses: survival very likely, survival possible with adequate medical care, survival unlikely despite adequate medical care. For these prognostic categories, doses of ≤ 2 Gy, 2-8 Gy, ≥8 Gy were estimated.
4.3.2 Radiation syndromes (1)

- Experiments in mice demonstrated that increasing the dose from 5 to 12 Gy, the survival time gradually decreased from about 2-3 weeks to about 4 days.
- Further increase of total body dose up to >30 Gy did not lead to further shortening of the latency to death in mice, however, even higher doses caused death within a few days and very high doses, even within hours.
- Three different radiation syndromes were associated with these three categories based on the latency to death: the haemopoietic syndrome after doses < 12 Gy, the gastrointestinal syndrome after doses of 12 to 30 Gy, and the cerebrovascular syndrome after even higher doses.
4.3.2 Radiation syndromes (2)

- The different latencies of the haemopoietic and the gastrointestinal syndrome were explained by the different cell turnover rates of the critical cell lineages in the tissues in which severe lethal hypoplasia occurred lead to death of the animal, i.e. the granulocyte cell production lineage in the bone marrow and the epithelial mucosal cell lineage in the small bowel.

- Death in the haemopoietic or bone marrow syndrome was associated with septic infection due to agranulocytosis; death in the gastrointestinal syndrome was associated with complete denudation of the small bowel surface leading to profuse diarrhoea and hypovolumic shock.

- Since the 1970s, few additional experimental studies on radiation syndromes have been performed – although extensive research using similar methods has been directed at the development of total body irradiation with subsequent stem cell transfusion in the treatment of leukaemia and some other malignant diseases.
4.3.2 Radiation syndromes (3)

- Some results of this research certainly had also been used in the further refinement of treatment protocols of affected accident victims.
- The present understanding of the nature and the pathogenetic development of human radiation injury after whole body irradiation is also based on careful clinical evaluation of human accident victims, from the Oak Ridge accident in 1958 to the Chernobyl disaster in 1986 and the Tokai-Mura accident in 1999.
- It became apparent that the simple classification of radiation syndromes based on latency and critical cell lineages is not appropriate to describe the complexity of the clinical features of human accident victims.
- In 2001, a manual of MEdical TREatment ProtocOLs (METREPOL) was published by a European consortium of expert scientists, as the results of a comprehensive evaluation of all existing data on radiation accident victims.
4.3.3 Medical management of radiation accidents

• The METREPOL system of radiation accident management defined response criteria for four separate organ systems, each of which is involved together in the development of signs and symptoms of health damage after accidental radiation exposure.

• These four organ systems are the neurovascular system, the haematopoietic system, the cutaneous system, and the gastrointestinal system. The basic idea behind this concept is to unravel the complexity of the acute radiation syndrome.

• The first step is to divide it into more accessible elements, i.e. those clinical signs and symptoms that characterise the extent of damage to the four early reacting organ systems under concern (N, H, C, G) and defining their severity in four grades (mild = spontaneous recovery certain; moderate = recovery with possible deficit; severe = recovery possible with intensive medical care but probable deficit; fatal).
4.3.1 The Neurovascular syndrome (N) (1)

- Irradiation may cause both cerebrovascular disorders and nervous tissue injury.
- Although electrophysiological studies after total body irradiation with doses >6Gy have demonstrated significant changes at the synaptic level in brain tissue consistent with a state of increased brain excitability, the clinical symptoms are most likely linked to cerebral oedema with an increase in intracranial pressure.
- Along with early oedema, acute inflammatory reactions occur as well as decrease of the blood-brain barrier. The onset and duration of the different phases of the neurovascular syndrome depend on radiation dose.
- Symptoms such as nausea, vomiting and anorexia characterise the prodromal phase. Although the symptoms are expressed by the gastrointestinal system, the control site is located in the brain.
4.3.1 The Neurovascular syndrome (N) (2)

- After high radiation doses, the severity of symptoms gradually increases and results in a fatigue syndrome, associated often by hypotension and dizziness.

- With increasing severity of the neurovascular syndrome, survivors have a high risk of developing late effects, in particular impairment of cognitive functions and neurological deficits.

- Grade N1 is defined by late onset of mild prodromal symptoms and symptoms of mild fatigue which may persist for several weeks. Anti-emetic treatment on an outpatient basis is usually sufficient.

- N2 is defined by episodes of vomiting in the prodromal phase and moderate fatigue lasting several weeks. These patients need anti-emetic treatment and regular clinical monitoring in hospitals.

- N3 is defined by severe nausea and vomiting within the first hour after exposure lasting for about 2 days.
4.3.3.1 The Neurovascular syndrome (N) (3)

- Symptoms recur after a symptom-free interval and persist for about 2 weeks, leading to electrolyte imbalance. Patients also suffer from headaches and severe fatigue syndrome, hypotension and fever.

- Hospitalization of these patients is obligatory, medical management has to include intravenous glucocorticoids, electrolyte and fluid replacement and analgesics.

- N4 is characterised by rapid incapacitation by severe nausea, vomiting, headaches, fever, erythema and drowsiness within the first hour after exposure. Recovery is unlikely and mostly primary symptoms continue intermittently.

- Only sufficient fluid and electrolyte replacement, analgesic medication and the application of intravenous glucocorticoids and mannitol infusion to reduce intracranial pressure, will increase the patient’s chance of survival.
4.3.3.2 The Haematopoietic syndrome (H) (1)

- Signs and symptoms of the haematopoietic syndrome are directly related to reduction of concentration of specific cell types in the blood. Radiation-induced cytopenia is strongly related to dose.
- Radiation does not decrease life span or function of blood cells but it blocks in a dose dependent way the production of new cells.
- Normal human erythrocytes have a life span of about 120 days. Therefore, even after complete cessation of all erythropoiesis, the decline of red blood cell concentration is less than 1% per day and anaemia is not a clinical problem unless there is additional damage which causes increased loss such as haemorrhage from wounds or thrombopenia, or haemolysis which is frequently observed after severe burns.
- Radiation damage to erythropoiesis can be monitored by measuring the concentration of reticulocytes in the blood.
4.3.3.2 The Haematopoietic syndrome (H) (2)

• Granulocytopenia is the main cause of critical health effects after total body irradiation leading to increased risk of systemic bacterial infections (sepsis).

• Granulopoietic cells originate from bone marrow stem cells which undergo proliferation and differentiation into the mature granulocytes of the peripheral blood.

• The transit time for cells from the myeloblast to the first non-dividing cell, the metamyelocyte in the bone marrow is about 6 days, and another 3–4 days are required. Granulocytes disappear from the blood randomly with a half time of 6-7 hours. Their overall life span is approximately 30 hours.

• Thrombocytes (platelets) are produced by megakaryocytes. The total transit time from the most immature megakaryocytes in the bone marrow to the release of platelets is 8-10 days, and the life span of platelets in the blood is on average 8-10 days.
4.3.3.2 The Haematopoietic syndrome (H) (3)

- Radiation-induced cytopenia of the blood cells is the consequence of inhibition of cell production in the proliferative precursor cells.

- Regeneration, however, depends on the survival of a sufficient number of bone marrow stem cells. Stem cells in the circulation can be assessed by characteristic surface markers. However, grading of the haematopoietic syndromes is based on the response patterns of blood cells (Fliedner reference, page 24).

- H1 is defined as cell counts at just below the normal range. No treatment is necessary because spontaneous regeneration will occur.

- H2 is a lymphocyte count on day 2 of 500 -1500 / μl, by transient granulocytosis within the first few days, followed by a decrease to the lower end of the normal level until day 10, followed by a second, abortive rise. Then the clinically important granulocytopenia occurs between days 12 and 20 with a value < 1000 granulocytes / μl which may result in general infection in some patients.
4.3.3.2 The Haematopoietic syndrome (H) (4)

- Regeneration starts after day 30.
- Platelets decrease gradually during the first three weeks to a value around 50,000/μl which, in some patients may cause haemorrhage, particularly into the bowels. Only those patients who develop infection or haemorrhage need to be treated with antibiotics or platelet transfusion.
- H3 is defined by a rapid decrease of lymphocytes to 250-500/μl and by transient granulocytosis during days 1-3. This is followed after day 5 by a steady decrease to a plateau of about 500/μl around days 10–15 with regeneration starting around day 30. Platelets decrease steadily to a nadir in the third week which may be well below 50,000/μl.
- Treatment options are similar as for H2 patients, however, stimulation of haematopoiesis with growth factors should be considered as soon as possible. Platelet transfusions should be given to maintain stable values in the blood of >20,000/μl.
4.3.3.2 The Haematopoietic syndrome (H) (5)

- Treatment with granulocyte colony-stimulating factor (G-CSF) is commonly performed in medical oncology to treat drug-induced cytopenia with daily subcutaneous injection of 10μg/kg for 2 weeks. An addition of a single i.v. injection of 5μg/kg thrombopoietin may increase the effectiveness of growth factor treatment. A clinical response of should be apparent 10 – 14 days after initiation of treatment, and prolonged treatment is not indicated.

- H4 is defined by very rapid decrease of all blood cells to very low values; lymphocytes to < 250/μl on day 2, granulocytes to < 500/μl at the end of the first week after exposure, and platelets to 0 at day 10.

- The only real option for therapeutic intervention into an otherwise lethal progress of the haematopoietic syndrome H4 is stem cell transplantation. The procedure of stem cell transplantation is presently used most frequently for the treatment of leukaemias. If no HLA (human leukocyte antigen) identical sibling is available, the best option might be umbilical cord blood stem cells.
4.3.3.3 The Cutaneous syndrome (C) (1)

- The experience from the Chernobyl accident showed for the first time that radiation damage to the skin from beta particles emitted by radionuclides deposited on the skin could be a major clinical problem.

- In the special case of the firefighters of Chernobyl, the main cause of death might have been from grade 4 cutaneous syndrome.

- Signs and symptoms of the cutaneous syndrome are the consequence of radiation damage to the proliferating and the stem cells in the epidermis and a pronounced inflammatory response in the dermis. They follow a distinct time pattern which is determined by the proliferative organisation of the epidermis.

- C1 is defined by an early transient erythema (reddening) of the skin which subsides within 36 hours. A second wave of erythema appears 5 days after exposure, 3 to 4 weeks after exposure the skin will appear dry due to the loss of sebaceous glands. This may be associated with mild pain, discomfort and itching. Treatment is symptomatic with anti-inflammatory lotions or powder.
4.3.3.3 The Cutaneous syndrome (C) (2)

- C2 is defined by erythema progressing to oedema and blistering 5 to 10 days after exposure, covering no more than 10% of the body surface. Transient loss of hair may develop at around 14 days after exposure. Treatment with topical glucocorticoids, linoleic acid creams and systemic antihistamines is usually required.

- C3 is defined by the same signs and symptoms but covering 10 to 40% of the body surface. There is a risk of deeper ulceration which is influenced and complicated by the concomitant haematopoietic syndrome. Systemic treatment with glucocorticoids and analgesics should be used.

- C4 is defined by the same signs and symptoms but covering >40% of the body surface and involving deeper underlying tissues of the skin and subcutis. Intensive care treatment is essential to deal with the multitude of symptoms such as pain, infection, and necrosis, but even if the patient survives, long term skin damage is likely to persist.
4.3.3.4 The Gastrointestinal syndrome (G) (1)

- Prodromal symptoms which are secondary to the neurovascular changes described above, such as nausea, vomiting and anorexia.

- Symptoms of the gastrointestinal syndrome, which usually start in the second week after radiation exposure, are mainly abdominal cramps and diarrhoea. After high radiation doses, the loss of the mucosal covering of the bowels, which if associated with thrombocytopenia, may also lead to bloody diarrhoea and to entry of enteric pathogenic and non-pathogenic bacteria.

- Signs and symptoms of radiation damage occur earlier in the small bowel than in the large bowel.

- Symptoms of the gastrointestinal syndrome are very much affected by functional changes in the neural and immune cells in the bowel wall. This is particularly obvious in the stomach in which, even after low doses of 1 to 2 Gy, functional changes such as decreased gastric motility, decreased production of gastric juice and inflammation (gastritis) have been observed.
4.3.3.4 The Gastrointestinal syndrome (G) (2)

- G1 is defined by a few episodes of altered stool consistency and frequency with associated abdominal pain. Treatment is usually not necessary.

- G2 is defined by changes in frequency and consistency and blood in stool together with abdominal cramps. Spontaneous recovery is certain however treatment of diarrhoea with Loperamide is indicated.

- G3 is defined by a higher frequency of these events, with several episodes per day over several days and weeks. Spontaneous recovery is likely but may be incomplete with recurring episodes of diarrhoea alternating with constipation.

- To prevent electrolyte imbalance, the individuals should be carefully monitored and replacement therapy given. In addition, antibiotics, anti-inflammatory drugs and analgesics may be necessary as indicated by the clinical symptoms.
4.3.3.4 The Gastrointestinal syndrome (G) (2)

- G4 is defined by rapid onset of diarrhoea which may be explosive. This is more due to functional disturbances than to mucosal damage. Frequent episodes of severe diarrhoea will lead to severe fluid and electrolyte imbalance and will be accompanied by severe painful abdominal cramps.

- Septicaemia is also very likely due to the simultaneously occurring granulocytopenia. Treatment is purely symptomatic with the main emphasis on fluid and electrolyte replacement, systemic antibiotics and analgesics.

- The signs and symptoms of the four radiation-induced acute syndromes, their diagnosis, classification into severity grades and their treatment reflects the complexity of the pathogenesis, symptomatology and treatment options. The Manual on the Acute Radiation Syndrome prepared by the Concerted Action METREPOL gives a full account of all aspects of the medical management of radiation accidents.
4.3.3.4 The Gastrointestinal syndrome (G) (3)

- The Tokai-Mura accident in Japan in 1999 demonstrated that acute exposure to very high radiation doses leads to a new type of radiation syndrome described by the term Multi-Organ Involvement.
- 3 workers poured uranium fuel from a bucket into a larger vessel where a critical mass led to non-uniform radiation high exposure.
- The haematological grading was H4. Umbilical cord stem cell transplantation in one patient led to transient restoration of haematopoiesis after 10 days which was complete after 50 days.
- The patient died 210 days after the accident. Failure of several organs was diagnosed. Most critical was the nearly complete loss of immunological responsiveness leading to the activation of cytomegalovirus infection (which was successfully treated with gancyclovir).
- Reactivation of skin burns and loss of mucosal barriers plus a multitude of other delayed damage finally caused his death.
4.3.4 Methods of triage for treatment after a radiation accident (1)

- In major accidents such as at Chernobyl, the decision on the need for treatment and prognosis of the individual accident victim cannot be based on dose estimates, which are time consuming, uncertain and with little impact on the medical response.
- Rather, these decisions have to be based on clinical criteria which are simple, early and permit the reliable identification of accident victims who do not need special treatment.
- It is more important not to miss any victim who may need treatment than to identify only those who will certainly need treatment.
- Such criteria have been established for many decades and they proved their usefulness particularly in the acute aftermath of the Chernobyl accident, when the members of the rescue teams had to be assessed as to who would need which treatment and when
### 4.3.4 TRIAGE CRITERIA USED AFTER THE CHERNOBYL ACCIDENT

<table>
<thead>
<tr>
<th>Severity</th>
<th>Vomiting time</th>
<th>Lymphocytes per µl</th>
<th>Hair loss within 2 weeks</th>
<th>Cytogenetic radiation dose</th>
<th>Lethality including skin burns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>no</td>
<td>&gt;600</td>
<td>no</td>
<td>&lt; 2Gy</td>
<td>0/105</td>
</tr>
<tr>
<td>Intermediate</td>
<td>after 1-2 h</td>
<td>300-600</td>
<td>no</td>
<td>2 – 4 Gy</td>
<td>0/53</td>
</tr>
<tr>
<td>Severe</td>
<td>after 30-60 min 100-300</td>
<td>yes</td>
<td>4 – 6 Gy</td>
<td></td>
<td>6/23</td>
</tr>
<tr>
<td>Very severe</td>
<td>immediate</td>
<td>&lt;100</td>
<td>yes</td>
<td>6 – 16 Gy</td>
<td>19/22</td>
</tr>
</tbody>
</table>
4.4 Radiation carcinogenesis
4.4.1 Mechanisms of carcinogenesis (1)

- The development of cancer in tissues is assumed to be a multi-stage process that can be sub-divided into four phases: neoplastic initiation, promotion, conversion and progression.
- Neoplastic initiation of normal cells creates the potential for unlimited proliferative capacity.
- This event results from one or more mutations in a single cell which is the basis of the clonal evolution of the cancer.
- Further neoplastic development of initiated cells depends on promotional events which involves intercellular communication, e.g. by growth factors, hormones or environmental agents.
- This results in the proliferation of the initiated pre-neoplastic cells in a semi-autonomous manner.
4.4.1 Mechanisms of carcinogenesis (2)

- During the process of conversion of the pre-neoplastic cells into fully malignant cells, additional mutations in other genes are accumulated, probably facilitated by increasing loss of genomic stability.

- The subsequent progression into an invasive cancer depends on still more mutations in the unstable genome.

- Two classes of cancer-associated genes have been identified. Proto-oncogenes are normal genes involved in growth regulation. Mutations e.g. by the translocation of a promoter, may result in an increased rate of proliferation.

- Proto-oncogene mutations to oncogenes are thus classified as gain-of-function mutations.

- Tumour suppressor genes are involved in growth regulation of normal cells, and they prevent excessive cell proliferation.
4.4.1 Mechanisms of carcinogenesis (3)

• The critical mutation in these genes are loss-of-function mutations which may be the result of partial or complete loss of the gene structure, e.g. by deletions.

• Because radiation-induced DNA damage preferentially causes deletions, it is generally assumed that the inactivating mutation of tumour suppressor genes is the most probably mechanism of the induction of cancer by radiation.

• Most cancers are the clonal descendants of a single neoplastic cell, and a single DSB may, although with an extremely low probability, cause a deletion in a specific DNA sequence, e.g. of a tumour suppressor gene.

• Hence, it has been argued that, in principle, a single mutational event in a critical gene in a single target cell in vivo can create the potential for neoplastic development.
4.4.1 Mechanisms of carcinogenesis (4)

- A single radiation track traversing the nucleus of an appropriate target cell has a finite probability, albeit very small, of generating the specific damage of DNA that results in the initiating mutation.

- This argument would strengthen the hypothesis that the risk of radiation induced cancer increases progressively with increasing dose with no threshold.

- Although these basic facts are generally accepted, the conclusion that they necessarily exclude the possibility of a dose threshold has been debated extensively.

- So far, no agreement has been reached about the role of the influence of a range of other biological mechanisms on the dependence of radiation-induced cancer rates on dose at very low doses, such as are the object of radiation protection regulations.
4.4.1 Mechanisms of carcinogenesis (5)

- The mechanisms range from low-dose hypersensitivity, which may eliminate specifically cells harbouring DNA damage after very low radiation doses, non-targeted radiation effects such as radiation-induced genomic instability, and effects related to intercellular communication including bystander effects and immunological surveillance mechanisms.

- The report of the Académie Nationale de Médecine in Paris stressed that “cell responses are based on a complex network of intra- and intercellular signalling, and may be expressed in several ways, including the repair of damage, apoptosis, delayed death or prolonged quiescence of initiated cells. The modalities of the response are adapted to the context and vary according to the dose, fractionation, dose rate, LET, cellular redox state, cell status before irradiation, the presence of signals emitted from neighbouring cells and, possibly, of other toxic agents.”
4.4.1 Mechanisms of carcinogenesis (6)

• The respective roles of direct radiation-induced initiating, transforming mutations in normal target cells on the one hand, and of the complex mechanisms which may respond to those initial processes as listed above, continue to be the subject of continuing radiobiological research.

• A better understanding of these processes may permit a science-based judgement on the existence or not of a dose threshold below which the risk of radiation-induced cancer is zero.

• ICRP 2007, § 65 draws the conclusion from this controversy that biological and epidemiological information that would unambiguously verify the Linear Non-Threshold (LNT) model is unlikely to be forthcoming. “Because of this uncertainty … it is not appropriate … to calculate the hypothetical number of cases of cancer or heritable diseases that might be associated with very small radiation doses received by large numbers of people over very long periods of time.”
4.4.2. Epidemiological evidence for radiation carcinogenesis (1)

• The assessment of radiation risks in exposed populations can use either of two epidemiological methods, which differ in their workload, in the information they can provide, and in their duration and costs.

• Cohort studies define, usually soon after exposure, a cohort of often many thousand people who were exposed to different radiation doses. Individual or group doses have to be determined for all members of the study cohort.

• Health effects are subsequently collected as the cohort is ageing for as long as possible, ideally life-long. The best example of a cohort study of radiation effects is the Life Span Study (LSS) of the Japanese atomic bomb survivors.
4.4.2. Epidemiological evidence for radiation carcinogenesis (2)

- Case-control studies define patients, who suffer from the disease to be investigated. These patients are called “cases”.

- For each case, 1 to 5 control patients are selected who have a different disease but matched to the individual case, e.g. regarding age, sex, socioeconomic status.

- The radiation risk is estimated by comparing the radiation doses of the cases versus the controls. The best examples of case-control studies in radiation epidemiology are the radon-in-homes studies.

- Cohort studies permit the evaluation of different risks from the same exposure such as for cancer, cardiovascular diseases, stroke etc. in the Life Span Study. The identification of other risk factors is usually difficult and may require nested case-control studies.
4.4.3. The A-bomb survivor Life-span Study, cancer mortality and cancer incidence (1)

- The experience of the people of Hiroshima and Nagasaki in 1945 was the initiator for a proposal by the National Academy of Sciences of the USA to develop a programme for life-long follow-up of all A-bomb survivors.

- This programme, started in 1949 by the US Atomic Bomb Casualty Commission (ABCC) and, since 1975, continued by US-Japanese cooperation in the Radiation Effects Research Foundation (RERF), is arguably the largest, most comprehensive and most detailed epidemiological study ever performed – and it has been decided that even now, more than 60 years after exposure, follow-up will continue.

- The results of this study are the most important source of information on which the rules and regulations of radiation protection are based. No other epidemiological study has comparable influence.
4.4.3. The A-bomb survivor Life-span Study, cancer mortality and cancer incidence (2)

- Animal experiments and in vitro studies may provide mechanistic information, but the RERF studies are the “gold standard” against which all other epidemiological and radiobiological studies on the long-term effects of radiations on man have to be judged.

- The reason for this outstanding role is that in this study a large normal and healthy population of all ages and both sexes who were exposed to a wide range of radiation doses to all organs of the body.

- Most important is that through a massive effort, the radiation doses to all critical organs of each member of the cohort has been individually assessed by various methods of retrospective dosimetry.
4.4.3. The A-bomb survivor Life-span Study, cancer mortality and cancer incidence (3)

- The Life Span Study comprises 120,321 people including about 54,000 atomic bomb survivors who were within 2.5 km of the hypocentre and about 40,000 survivors between 2.5 and 10 km.
- Also, about 26,580 people are included who were not in Hiroshima or Nagasaki at the time of the bomb explosions, or at > 10 km.
- On 1.1.1999, 52% of the study population was still alive, and this includes >85% of the ~50,000 individuals <20 years of age in August 1945. For >90% of the total study population, detailed information was collected by Japanese interviewers in the early 1950s on their exact location at the moment of bomb explosion, to permit precise evaluation of shielding parameters.
4.4.3. The A-bomb survivor Life-span Study, cancer mortality and cancer incidence (4)

- In the early dose assessments, data from test explosions with regard to kerma in free air were the basis of analyses, grossly corrected for shielding in the houses.

- Later analyses (DS86) were based on Monte Carlo calculations of track passage from the source in the exploding bomb through the air (allowing for pronounced attenuation of neutrons by the high humidity), through the building structures to the human body, finally calculating mean organ doses for different critical organs.

- In 2002, a refined dosimetric system (DS02) was published took into account the products of interaction of neutrons with materials such as bronze statues. With each dosimetric system the neutron contribution to the total dose became less. However, differences between the DS86 and DS02 are small and have little influence on risk estimates.
4.4.3. The A-bomb survivor Life-span Study, cancer mortality and cancer incidence (5)

- The most important and significant long-term health damage observed in the LSS of the A-bomb survivors is a dose dependent increased mortality from cancer. In 2003, among 44,771 deceased members of the life span cohort with detailed dosimetric information, there were 9,335 deaths from solid cancers and 582 deaths from leukaemia.

- By analysing the relationship with radiation exposure, it was concluded that until 1997 approximately 440 solid-cancer deaths (4%) and nearly 100 leukaemia deaths (15%) could be attributed to radiation exposure from the bomb in 1945.

- Significant relationships with radiation exposure were found for the following types of malignant disease (in decreasing probability of cancer mortality): stomach, colon, lung, leukaemia, breast, oesophagus, bladder, ovary, liver.
4.4.3. The A-bomb survivor Life-span Study, cancer mortality and cancer incidence (6)

- Since 50% were still alive at the last evaluation time, it is not possible to make well-founded statements on the life-time risk of dying from radiation-induced cancer for young people at the time of exposure.

- The mortality data have the advantage of near 100% coverage due to the unique “koseki” system of registration in Japan. These advantages may be outweighed by the greater precision of cancer diagnosis and the inclusion of non-fatal cancer diseases which are possible in epidemiological studies on cancer incidence.

- Cancer registries were established in 1957 and managed by RERF in Hiroshima and Nagasaki. Most cancer patients in Japan are treated in large hospitals, so few tumours are missed. The RERF cohorts are routinely linked with the cancer registries. Study members treated for cancer outside these catchment areas are not included.
4.4.3. The A-bomb survivor Life-span Study, cancer mortality and cancer incidence (7)


- The number of cancer cases increased since the last analysis by 50% to 17,448 cases of solid cancer over a period of forty years, and nearly 90% were verified by histology, endoscopy or surgery.

- These data permit comprehensive evaluation of radiation risks for fatal and non-fatal malignancies, and risks associated with histological types. More importantly, the number of cases was high enough to investigate in great detail temporal patterns, gender differences, birth cohort and age at exposure patterns.
4.4.3. The A-bomb survivor Life-span Study, cancer mortality and cancer incidence (8)

- The main results are briefly as follows. Of the 17,448 cancer cases observed in this study, 7,851 occurred in individuals who had received a dose of > 0.005 Gy.

- 853 of these, (11%) were attributable to the radiation exposure, but of the 645 cancer observed in individuals exposed to more than 1 Gy, 307 (48%) were attributable to radiation.

- For a person aged 70 who was exposed to the radiations from the bomb at age 30, the excess relative risk (ERR) per Gy was 0.47 for all cancers combined. This ERR was 0.58 for females and thus higher than the 0.35 for men.

- There was strong evidence for a linear increase of excess cancer incidence with increasing dose. 156 of the estimated excess cancers occurred among individuals in the dose range of 5 – 200 mGy.
4.4.3. The A-bomb survivor Life-span Study, cancer mortality and cancer incidence (9)

- The 10,000 cancer cases in non-exposed controls permitted analysis of the dependence of age-specific cancer rates on birth cohort.

- These trends complicate the interpretation of the effects of age at exposure on the excess risk, particularly for the ERR.

- The apparent strong dependence of the relative risk of radiation-induced breast cancer in the Life Span Study turned out to be due nearly entirely to the birth cohort effect, since baseline breast cancer rates increased dramatically in more recent birth cohorts, yet excess absolute risk still showed a significant age-at-exposure effect.

- Similarly, the increase in ERR of lung cancer with increasing age at exposure is largely a consequence of the large smoking-related birth cohort effect on lung cancer baseline rates.
4.4.3. The A-bomb survivor Life-span Study, cancer mortality and cancer incidence (10)

- The major conclusions of the 2007 study on cancer incidence in the LSS are that cancer incidence was well described by a no-threshold linear dose response relationship down to doses of <0.2 Gy.

- The longer follow-up of the new study demonstrated that the oesophagus and the bladder are particular radiosensitive with regard to radiation-induced cancer which has, however, already been taken into account adequately in the tissue weighting factors based on the older mortality data.

- The new recommendations of the International Commission on Radiological Protection (ICRP) in 2007 are based, for the first time, on the cancer incidence data described above whereas until now, recommendations by ICRP were always based on cancer mortality data.
4.4.4 The Chernobyl accident (1)

- The Chernobyl accident in 1986 was the most severe accident in the civil use of nuclear energy, so far. It was caused by careless manipulation of safety systems in a nuclear power plant which lead to a core melt-down resulting in the release of a large proportion of accumulated fission products over a period of 10 days.

- Many thousands of people were evacuated from the nearby town of Pripjat, and more people were relocated later.

- The radioactive cloud changed direction several times during the long period of release and distributed radioactivity, in particular caesium and iodine all over Europe as far as England, Finland and also to Turkey.

- Several hundred acute emergency personnel were exposed when they worked to contain the accident.
4.4.4 The Chernobyl accident (2)

- The severity of exposure was determined using the triage criteria (Table 1). The most severely affected were treated in Moscow, the others in Kiev.

- In some of the most severely affected, bone marrow transplantation was attempted but the benefit of this heroic treatment was not convincing.

- Of the 134 confirmed exposed emergency workers, 28 died in 1986 from acute radiation syndrome, most of them having multi-organ involvement.

- There were particular problems posed by extensive radiation damage to the skin from smoke particles from the burning graphite which were loaded with beta-rays emitting radionuclides, and these became attached to the wet clothing of the fire-fighters.
4.4.4 The Chernobyl accident (3)

- Many 1000 people in the former Soviet Union, rescue workers (liquidators), as well as relocated people who had lived close to the reactor, were concerned about possible health damage from the radiation.

- It was impossible to set up a comprehensive research programme such as after the Hiroshima and Nagasaki bomb explosions.

- Several epidemiological studies have been initiated to provide information on health consequences which complement the LSS e.g. the studies performed in the liquidator registers in Russia, Estonia, Ukraine and Belarus.

- More important is the comprehensive programme of monitoring and treating thyroid cancer in the general populations of Belarus and Ukraine. The results of these studies have been summarised recently by the World Health Organisation (WHO).
4.4.4 The Chernobyl accident (4)

• Among the 192,000 Russian emergency workers, individual radiation doses were determined for 72,000. The mean dose was ~0.1 Gy from external irradiation, and internal radiation doses are assumed not to contribute much.

• There was no increase in overall or cancer-specific mortality compared to the general population up to 1998, although more recent data point to a possible increase in the incidence rates of leukaemia.

• WHO in 2006 suggested that 4.6% of all fatalities that occurred during 1 year after the accident can be attributed, to radiation exposure-associated diseases, comprising 2.3% to cancer, 2% to cardiovascular diseases and 0.3% to leukaemia.

• The liquidator studies are certain to provide much important information in the future on radiation risks from low dose rate radiation exposure.
4.4.4 The Chernobyl accident (5)

• Most important was the epidemic of thyroid cancer which, until 2002, had affected nearly 5000 people under age 17 in 1986.

• The data could be well-fitted to a no-threshold linear dose response relationship with an eight-fold increase of risk after 1 Gy thyroid dose. The highest rate was in those who were children under 4 years of age at the time of the accident. In young adults, the risk may be lower by nearly one order of magnitude.

• More information is being collected in an on-going cohort study on >25,000 subjects with individual dose estimates who are regularly screened for thyroid disease every two years. There is still uncertainty on the shape of the dose response relationship at different ages, in particular how long the increased risk of thyroid cancer will remain high, and whether it may follow a relative risk model which would mean that the numbers might continue to increase until 2040.
4.4.4 The Chernobyl accident (6)

- Great effort went into the estimation of individual radiation doses to the thyroid in the children of Belarus and Ukraine.

- The most important contribution to those doses came from iodine-131 in milk from cows which were grazing on contaminated meadows. Several weeks after the accident, nearly 350,000 people were assessed for radioactivity in the neck region in order to estimate possible uptake of iodine-131 in their thyroids.

- For individuals not directly measured, estimates of thyroid doses were made based on radio-ecological models of iodine deposition, milk consumption etc, with individual factors being included in the calculations based on interviews and measurements of ground contamination of Cs. However, the deposition of caesium did not follow closely the deposition of iodine since maximal release took place at different times.
4.4.4 The Chernobyl accident (7)

- Most thyroid cancers in patients exposed in childhood were papillary cancers. Extensive international pathology review programmes were established to validate each diagnosis.

- A large molecular programme looked for fingerprint mutations specific for radiation-induced papillary thyroid cancer. More than 90% of cancers occurring in those born between 1980 and 1986 were radiation-induced whereas only <10% of those occurring in those born after 1987 were radiation-induced.

- No convincing difference in the frequency of different molecular changes, in particular ret-PTC (rearranged in transformation/Papillary Thyroid Carcinomas) translocations have been observed if data are corrected for age at diagnosis.
4.4.4 The Chernobyl accident (8)

- The largest group of 741 patients with thyroid cancer who were children at the time of the accident was treated in Minsk.

- Most were treated by total thyroidectomy (426), the others by less radical surgery. 464 received treatment with iodine-131 for residual cancer or distant metastases.

- Recurrences were diagnosed in 27% of the cases. So far, few of the patients died from thyroid cancer or treatment related complications, the overall prognosis of these people who are young adults now, appears good.
4.4.5 Patients treated for benign diseases (1)

- Up to the 1960s, more patients were treated with radiotherapy for non-cancer diseases than for cancer.
- The most successful indications were painful degenerative joint disorders such as osteoarthritis, frozen shoulder, tennis elbow, autoimmune diseases such as ankylosing spondylitis, Dupuytren contracture, endocrine orbitopathy related to hyperthyroidism, and bacterial infections such as mastitis or sweat gland abscesses.
- Radiation doses were only <10 % of the doses typically given to treat cancer. Most of these treatments are obsolete today, mainly because pharmacological treatment options are available, and some of these treatments were associated with a significantly increased risk of later induction of leukaemia and cancer.
4.4.5 Patients treated for benign diseases (2)

- Court-Brown and Doll in 1957 analysed the mortality of 14,554 patients who had been irradiated for ankylosing spondylitis between 1935 and 1954 at any one of 87 radiotherapy centres in Great Britain and Northern Ireland.

- Among the 1,582 recorded deaths, the most striking finding was a tenfold increase in death from leukaemia, 52 patients compared to the 5 expected from the general population. This excess occurred from the first years up to about 15 years after irradiation.

- Besides the LSS of the Japanese bomb survivors, this study remains the most important source of information about radiation-induced leukaemia. In a later study irradiated patients were compared to ankylosing spondylitis patients who were managed conservatively without radiotherapy, and the radiation risk estimates were confirmed.
4.4.5 Patients treated for benign diseases (3)

- An increase in leukaemia risk was also found in nearly 10,000 women treated between 1925 and 1965 with intrauterine radium or external X rays for bleeding from the uterus, compared to women with comparable clinical diagnosis but not irradiated (64 leukaemia deaths vs 37 expected).

- Other patients found to have a twofold increased leukaemia risk were treated for peptic ulcer or tinea capitis.

- Radiation-induced leukaemia may become manifest already after a few years, however risk remains increased for at least 25 years. Children are more sensitive by about a factor of two and have a shorter latency time than adults.

- The latency of the different leukaemia subtypes shows significant differences, with chronic myeloid leukaemia (CML) having the shortest mean latency of approximately five years.
4.4.5 Patients treated for benign diseases (4)

- In the past, post-partum mastitis has been one of the most successful indications for low-dose radiotherapy. In its early stages, 1-2 0.5 Gy doses would abolish the inflammation within a day or two, no abscess would develop, no antibiotics or surgery would be required and breast feeding could be resumed quickly.

- This indication for radiotherapy was abandoned when the high radiosensitivity of the young breast to cancer induction became apparent.

- 601 American women irradiated between 1940 and 1957 for acute post-partum mastitis using a median dose ~3.5 Gy, were followed-up for ~30 years. 56 developed breast cancer compared to only 32 expected from the patients’ sisters.

- The dose response curve was indicative of a proportional increase of cancer risk with increasing dose.
4.4.5 Patients treated for benign diseases (5)

- Mattson et al. studied 1216 Swedish women who received radiotherapy between 1925 and 1954 for acute or chronic mastitis or for fibroadenomatoses with doses from <1 Gy to 50 Gy (mean 5.8 Gy). They were compared with 1874 of similar age, same diagnosis, but were not irradiated.

- 198 irradiated women developed breast cancer compared with 101 controls. The incidence rate ratio decreased from 25 years but was still increased at 40 years postirradiation. There was a clear dose response relationship within this group of patients.

- Irradiation of very young girls for haemangioma, increases the risk of developing breast cancer later in life. There was a linear dose response relationship, and 12% of all breast cancers (8 cases) in this group were attributable to irradiation.
4.4.6. Radon exposure of hard rock miners or in homes (1)

- The publication of a report in 1879 on lung disease among the miners in Schneeberg in Saxony was a milestone in the history of occupational medicine.

- The report was written by a young doctor and a mining engineer who were working in a small town in the ore mountains (Erzgebirge) in Eastern Germany, where silver and semi-precious metal such as cobalt and bismuth had been mined since the Middle Ages.

- It had been known for centuries that the miners there tended to die early from a lung disease called the “Schneeberg mountain illness”.

4.4.6. Radon exposure of hard rock miners or in homes (1)

- Härting and Hesse (1879) showed: (1) the mountain illness was “lymphosarcoma” of the lung, today called small cell lung cancer,

- (2) only miners working underground developed the disease, usually after about 20 years working underground

- (3) every miner not dying prematurely from other diseases or accidents, died from lung cancer

- (4) induction of lung cancer in the miners was related to toxic substances in the dusty air which contained e.g. arsenic

- (5) cleaning the air by the introduction of wet drilling and forced ventilation reduced the lung cancer rate significantly within 10 years.

- This was the first study to describe the carcinogenic effects of radiation, but published more than 15 years before the detection of radioactivity by Becquerel in 1896.
4.4.6. Radon exposure of hard rock miners or in homes (2)

- The disease was ascribed to the exposure of the miners to radon, but only in the 1950s was it recognised that the cause of radon-induced lung cancer was the radioactive decay products of the radon gas.

- These are heavy metal atoms such as lead and bismuth, which attach to aerosols in the mine air and are inhaled and deposited on the bronchial epithelium causing irradiation of the epithelial stem cells with $\alpha$-particles.

- Several large cohort studies of uranium miners, e.g. the USA (Colorado Plateau), Czech Republic (Jachymov, close to Schneeberg), confirmed the findings in Schneeberg.

- Radon progeny potential alpha energy exposure was defined as the product of radon concentration corrected for the decay product equilibrium in the mine and exposure time. This measure of exposure was given the name working level months (WLM).
4.4.6. Radon exposure of hard rock miners or in homes (3)

- Based on modelling and size distribution of the aerosols which determines the site of aerosol deposition, radiation doses in Gy have been calculated.

- With increasing radiation dose there is a proportional increase of the risk of lung cancer. All types of lung cancer have been found to be increased in the uranium miners, with small cell lung cancer the most prevalent.

- There is a supra-additive interaction between exposure to radon and cigarette smoking.

- The most important conclusion from these studies is the possibility of lung cancer risk for the general population from exposure to radon and its decay products in houses.
4.4.6. Radon exposure of hard rock miners or in homes (4)

- Extensive measuring programmes have demonstrated that radon concentrations vary by orders of magnitude between houses in the same country.

- In several European countries and in China large case-cohort studies on the contribution of radon exposure to the lung cancer risk have been performed.

- In the large German study (Wichmann et al. 2005), nearly 3000 cases of lung cancer and 4,200 controls were investigated.

- In addition to a structured questionnaire about demographic characteristics, residence history, life-time active/passive smoking and occupational history, radon concentration measurements were performed in the current homes and in the previous homes, going back 5-35 years using alpha-track detectors.
4.4.6. Radon exposure of hard rock miners or in homes (5)

- The most important risk factor for lung cancer is cigarette smoking: >95% of the lung cancer patients were current smokers or ex-smokers while among the controls this number was ~60%.

- There was a strong relationship between the number of packs smoked and relative risk, reaching 46-fold increase in relative risk for heavy smokers (>20 cigarettes per day for more than 30 years).

- Despite this strong influence of smoking, a dependence of relative risk on radon concentration in the homes was observed, as was the case in most other studies e.g. in Finland, Sweden and the United Kingdom. The overall excess lung cancer risk at a radon concentration of 100 Bq/m³ was 10%.

- The excess risk from radon was found for smokers as well as for non-smokers, and risks interacted in a multiplicative way.
4.5. Heritable radiation effects (1)

• In the public perception, the most dangerous long-term risk of environmental, occupational, or medical radiation exposure may be the risk of heritable damage to children and future generations.

• Up to the 1970s, rules and dose limits in radiation protection were mainly concerned with heritable radiation effects.

• Radiation exposure of the general population from diagnostic procedures in medicine and from atmospheric atom-bomb test explosions were generally recorded and reported as genetically significant radiation doses.

• These were calculated as radiation doses to the gonads corrected for the age and sex dependent probability of having children.

• Since then, a complete re-evaluation of the risks of heritable radiation damage has taken place.
4.5. Heritable radiation effects (2)

- No significant increase in heritable diseases was found in a study on 70,000 children of Japanese A-bomb survivors whose parent had received a conjoint radiation dose to their gonads of approximately 0.15 Gy on average. No dose dependent increase in the frequency of biochemical mutations was found. A few studies on children of radiotherapy patients confirmed this conclusion.

- The present concepts of the risks radiation-induced heritable diseases combine experimental data on the dose dependence of mutation rates in the various stages of germ cell development with epidemiological data on the spontaneous frequency of naturally-occurring genetic diseases with different patterns of inheritance.

- Mathematical models developed in population genetics research are used to describe the equilibrium between mutation and selection and the dynamics of mutant genes in populations.
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4.5. Heritable radiation effects (4)

- Mutation rates after irradiation of inbred strains of mice have been determined in large breeding experiments using the 7-locus method.

- Mouse strains were bred which are homozygous for seven different genes with recessive Mendelian inheritance. Each gene produces, in the homozygous situation, phenotypes which can be identified easily even in the early weeks of life of the affected animal.

- The experiment involves irradiation of wild-type animals and their subsequent mating with homozygous partners. With no radiation-induced mutation, all progeny of the mating are wild-type.

- However, if a mutation in a germ cell is induced, the phenotype typical for the respective mutation will be visible in the progeny.

- The results of the experiment with low dose rate irradiation are given in Table 2.
### 4.5 Heritable radiation effects (5)

**TABLE 2. MUTATION RATES AFTER LOW DOSE RATE IRRADIATION IN THE SEVEN LOCUS TEST**

<table>
<thead>
<tr>
<th>Dose</th>
<th>Number of offspring</th>
<th>Number of mutations</th>
<th>Mutation rate per locus per million gametes</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9 Gy</td>
<td>-</td>
<td>-</td>
<td>8</td>
</tr>
<tr>
<td>0.9 Gy</td>
<td>59,810</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>3 Gy</td>
<td>108,026</td>
<td>25</td>
<td>33</td>
</tr>
<tr>
<td>6 Gy</td>
<td>59,711</td>
<td>23</td>
<td>55</td>
</tr>
<tr>
<td>8.6 Gy</td>
<td>24,281</td>
<td>12</td>
<td>71</td>
</tr>
</tbody>
</table>
4.5. Heritable radiation effects (5)

- These results indicate an increase in the mean mutation rate per locus which is proportional to dose. The spontaneous mutation rate of approximately 1 in 100,000 is doubled by approximately 1 Gy. This is called the doubling dose at low dose rates.

- Other experimental models have also been used to determine the mutation rates after irradiation such as skeletal disorders with dominant inheritance, cataracts with dominant inheritance, recessive lethal mutations, dominant lethal mutations, mutations coding for enzymes and chromosome translocations.

- The spontaneous mutation rate per gene is similar in mice and men. There is no good reason to assume that in humans, the doubling dose may differ significantly from that in mice.
4.5. Heritable radiation effects (6)

• However, the mutation doubling dose alone does not give any useful information on the risk of heritable disease.

• The relationship between and increase of mutation rate and increase of frequency of heritable diseases is complex, and depends on the specific phenotype and its influence on the health of the affected person, on the pattern of inheritance, and the interaction of the mutated gene with other factors in multifactorial diseases.

• Therefore, the mouse doubling dose is combined with information derived from human population genetics to estimate the risk of heritable disease in the progeny of irradiated people.
4.5. Heritable radiation effects (7)

- Heritable diseases may occur as direct result of a mutation in a single gene (single gene disorders). Inheritance of these diseases follows the rules established by Mendel, and may be autosomal dominant, autosomal recessive or sex-linked recessive.

- For these “Mendelian” diseases, there is a straightforward relationship between mutation and disease and the pattern of transmission is simple and predictable.

- The overall frequency of Mendelian diseases in the population is 2.4% (1.5% autosomal dominant, e.g. Huntington’s disease, 0.75% autosomal recessive e.g. phenylketonuria, and 0.15% sex-linked recessive, e.g. haemophilia).

- A new mutation in a gene with dominant inheritance following the Mendel rules of single gene inheritance, will directly lead to the respective phenotype.
4.5. Heritable radiation effects (8)

- In most instances this mutation will be passed on to later generations, if the impact on the health of the affected is low, in particular in the first few decades of life.

- The mutation may be transmitted through many generations since its influence on the Darwinian selection will be small.

- The mutation will be eliminated in the first generation if it causes death before the affected have any chance to have children.
4.5. Heritable radiation effects (9)

- The balance between mutation and selection is the basis of population genetics theory.

- The relationship is described by the mutational component which mathematically describes the ratio of increase in mutation rate to increase in disease rate.

- For the known heritable diseases with dominant inheritance, the mean mutational component is 0.3, which means that, on average, new dominant mutations stay in the population for 3 generations.

- For recessive mutations, the mutational component is close to 0.
4.5. Heritable radiation effects (10)

- In addition to single gene disorders which have a frequency at birth of 3.3%, approximately 6% of live births are affected by a congenital abnormality with some genetic component.

- 65% of the population will develop, later in life, chronic disease with some genetic component as well, although environmental factors play a much bigger role.

- These are called multifactorial diseases and comprise common diseases such as diabetes, essential hypertension and coronary heart disease.

- This complexity of heritable diseases is incorporated in the present method of estimating the heritable risk among the progeny of irradiated people.
4.5. Heritable radiation effects (11)

• The equation to calculate genetic risk combines population genetic data in humans and radiation genetic data in mice as follows:

Risk = Prevalence x 1/Doubling Dose x Mutation Component x PRCF

• Risk is the probability that an offspring of the exposed person will develop heritable disease of one of the groups described above (Mendelian or multifactorial). The prevalence data are given above.

• For protracted irradiation, the accumulated dose in the gonads before conception is divided by 1.

• The mutation component is a factor which describes the relationship between the increase in the mutation rate and the rate of additional disease. Even for dominant diseases this factor is not 1, since the majority of existing mutations are inherited from parents and grandparents, often through many generations.
4.5. Heritable radiation effects (12)

• A cautious estimate suggests that doubling of the rate of new dominant mutations will cause only a 30% increase of diseases with dominant inheritance in the first generation and 15% in the second generation.

• The same value of the Mutation Component is allocated to sex-linked recessive diseases.

• Since the development of single gene disease with recessive inheritance requires mutations in both alleles of the same gene, the relationship between a mutation and disease is very remote and the mutation component is therefore assumed to be close to zero.

• For multifactorial diseases, the relationship between mutation and disease is also not very close, and presently the mutation component is assumed to be 0.01.
4.5. Heritable radiation effects (13)

- The potential recoverability correction factor (PRCF) has been introduced to account for the fact that the molecular structure of radiation-induced mutations differs markedly from the molecular structure of “spontaneous” mutations.

- Most spontaneous mutations are point mutations with a single base pair altered or a minute deletion, whereas radiation-induced mutations are mostly large deletions, often affecting whole genes.

- Depending on the gene affected, these mutations may not be compatible with inter-uterine development, and most will lead to premature termination of pregnancy.

- A cautious estimate is that 30% of radiation-induced mutations are not leading to intrauterine death and thus may be “recovered” at birth.

- Thus, the value of PRCF suggested today is 0.15 to 0.3.
4.5. Heritable radiation effects (14)

- Using this equation for estimating the risk of heritable diseases of a young man who had been exposed to a radiation dose of 1 Gy from radiotherapy e.g. of pelvic lymph nodes in Hodgkin’s disease, the risk of radiation-induced dominant and sex-linked heritable disease would be:

  \[
  \text{Risk} = 0.0165 \times 1 \times 0.3 \times 0.3 \times 0.5
  \]

- The last factor of 0.5 has been introduced to account for the fact that only the father was irradiated. The result is a risk of less than 0.1%.

- The risk of multifactorial disease is similar at < 0.1% and the risk for radiation-induced recessive disease among the children is essentially zero.
4.5. Heritable radiation effects (15)

- In addition to single gene disorders and multifactorial diseases, another class of heritable damage which is rare in the general population with a spontaneous frequency of 0.2%, but which may be particularly important after radiation exposure to the gonads, is developmental injury. Such developmental defects may affect multiple organs.

- The genetic consequences of radiation exposure are mainly related to micro-deletions, i.e. deletions of multiple, functionally unrelated, yet physically contiguous genes that are compatible with survival of the individual receiving them.

- Such micro-deletions are known to cause multi-system congenital abnormalities which share some common features such as mental retardation, growth retardation, and various malformations.
4.5. Heritable radiation effects (16)

- Unlike the majority of congenital abnormalities which are typical multifactorial disorders, these abnormalities would show the same inheritance pattern as autosomal single gene diseases. These diseases are rare.

- The estimation of the risk of multi-systems congenital abnormalities resulting from radiation-induced micro-deletions does not use the "doubling dose method", but rather uses experimental data on radiation-induced skeletal mutations and cataract mutations with dominant inheritance in mice, for which such a molecular mechanism of mutation induction is likely.

- The estimated risk for multi-system developmental abnormalities is similar as for heritable diseases caused by single gene mutations (approximately 0.1% per Gy or Sv to one parent).
4.5. Heritable radiation effects (17)

- The risks of radiation-induced heritable diseases have been estimated indirectly on the basis of mouse data on induced mutation rates, so far.

- The progress of molecular radiation genetics and closer understanding of the molecular basis of the different heritable diseases in humans, offer the prospect to determine the effects of radiation exposure of humans on the risk of heritable diseases in the progeny directly.

- The assumption underlying all previous risk estimates was that radiation would equally cause all different classes of heritable diseases. It has become clear in recent years that radiation-induced heritable diseases are most likely to be genomic disorders rather than single gene disorders.
4.5. Heritable radiation effects (18)

• Genomic disorders are multi-system developmental abnormalities, most often associated with mental retardation and other neurological defects, and are caused by deletions or gene duplications.

• These occur spontaneously, predominantly by non-allelic homologous recombination in meiosis, in particular in oocytes.

• Similar effects are likely to occur as a consequence of repair of radiation-induced DNA double strand breaks in specific stages of meiosis.

• This would lead to genomic changes which might be specific for radiation induction, permitting their direct identification against the huge background of heritable diseases caused by spontaneous mutations.
4.6. Effects on the developing embryo (1)

- More than 1,500 children born between September 1945 and March 1946 in Hiroshima and Nagasaki were investigated at regular intervals between 1948 and 1964 to study the effects of radiation doses between 0.01 and >1 Gy on intra-uterine development at different stages of pregnancy.

- This study remains the only reliable source of information on the radiosensitivity of the unborn human.

- No malformations were found increased in a dose dependent way. However, there were 18 children who presented with micro-cephaly and severe mental retardation.

- The mothers of 15 affected children had been exposed to radiations from the bomb explosions at close distance from the hypocentre when they were in week 8 to 15 of pregnancy, while 3 affected children were exposed in later stages of pregnancy.
4.6. Effects on the developing embryo (2)

- Findings of dystopic grey matter by MRI investigations of some of those severely retarded people are in accordance with the results of experimental studies on the effects of radiation doses < 1Gy given to pregnant mice in late pregnancy.

- These experiments demonstrated that migration and maturation of immature neural cells during the development of the forebrain was severely disturbed. The result of this disturbance of migration was severe disorganisation of the structure of the synaptic network in the brain.

- The development of the mammalian brain is very radiosensitive over long periods of pregnancy due to the prolonged duration of cell formation and maturation processes. Throughout the process of brain development, damage and compensation processes occur side by side leading to a very complex pattern of radiation response.
4.6. Effects on the developing embryo (3)

• Cortical cell formation is radiosensitive and associated with extensive migration of cells formed in the ventricular regions towards the surface which determines the later organisation of the neuronal network.

• Even radiation doses as low as 0.1 Gy cause significant disorientation of the cytoarchitecture and the neuronal network.

• Neurophysiological alterations appear to be related to those structural defects from radiation doses of <0.2 Gy, which affect neuronal cell migration, branching, apoptosis of individual cells causing failure of anchoring of neuronal synapses and axon process formation.
4.6. Effects on the developing embryo (4)

- In animal experiments, radiation doses of <0.3 Gy given in the period of enhanced radiosensitivity i.e. in the period of corticogenesis, may lead to neurofunctional damage such as changes in the electroencephalogram (EEG) patterns, behavioural changes, deficiency in learning and memory and seizures.

- Similar radiation effects are likely to occur in the human brain, although the plasticity and capacity for compensation is so pronounced that clinical damage may not be obvious unless radiation doses exceed a certain threshold.
4.6. Effects on the developing embryo (5)

- Damage to intrauterine development was found in none of the experimental studies in mice after doses < 0.1 Gy. Also in the studies of the Hiroshima children there was evidence for a threshold dose of >0.1 Gy.

- The risk of severe mental retardation increases to 40% at 1 Gy. In later stages of pregnancy, the threshold dose may be higher.

- All children aged 10, exposed in utero to radiation from the A-bomb explosions, had an IQ test. There was a dose dependent decrease of the mean IQs and the mean school performance scores of those children who were exposed in weeks 8-15 and 16-25 to >0.1 Gy.

- No decrease of intellectual development was recorded if irradiation had occurred before week 8 or after week 25, even if radiation doses were >0.5 Gy.
4.6. Effects on the developing embryo (6)

- Embryos in the pre-implantation stage are very radiosensitive. However, the radiation damage inevitably will lead to death of the embryo and early abortion. Those embryos which survive develop normally.

- In human embryos in the first few weeks after implantation, during the period of major organogenesis, a comparable all-or-nothing effect is likely i.e. either an early, spontaneous abortion or normal development.

- The results of these studies as well as of some follow-up studies and anecdotal reports after medical exposures demonstrate the high radiosensitivity of the developing embryo and foetus, in particular during the time of brain development.
4.6. Effects on the developing embryo (7)

- The findings of a probable threshold of 0.1 Gy will influence the advice to be given to pregnant women after a diagnostic radiology procedure.

- In particular after abdominal CT investigations, careful analysis of radiation doses in the uterus has to be performed.

- A recommendation of termination of pregnancy because of possible radiation injury is very unlikely in most cases of women exposed in diagnostic radiology procedures.

- This is either because radiation did not occur in weeks 8 to 15, or because radiation doses to the uterus from most radiological procedures was well below 0.1 Gy.
4.7. The system for radiation protection (1)

• There is clear need to have a system that affords appropriate levels of radiation protection in situations where radiation is being used or is present.

• The United Nations Scientific Committee on the Effects of Atomic Radiations (UNSCEAR) closely monitors the progress of radiation research and publishes extensive, critical and authoritative reviews at regular intervals on the sources and levels of global radiation exposure, and on the biological effects of ionising radiation.

• The International Commission on Radiological Protection (ICRP), an independent charity, issues recommendations on radiation protection, based primarily on the scientific foundation provided by the UNSCEAR reports.

• The advice of ICRP is aimed at authorities, bodies and individuals that have responsibility for radiological protection but it does not provide regulatory texts. In essence the ICRP develops policy.
4.7. The system for radiation protection (2)

- the International Atomic Energy Agency (IAEA), a member of the UN family, uses the ICRP recommendations as the basis for developing regulatory-style radiation protection requirements.

- These IAEA Safety Standards, comprised of Safety Fundamentals, Safety Requirements and Safety Guides, provide the basis for the regulation of radiation protection in many countries of the world, especially in the so-called developing world.

- The IAEA also assists its Member States in the application of these Safety Standards.
4.7. The system for radiation protection (3)

- In its 2007 Recommendations, the ICRP introduced 3 types of exposure situations to cover all conceivable circumstances.

- "Planned exposure situations" are situations involving the deliberate introduction and operation of sources. Planned exposure situations may give rise both to exposures that are anticipated to occur (normal exposures) and to exposures that are not anticipated to occur (potential exposures).

- "Emergency exposure situations" are situations that may occur during the operation of a planned situation, or from a malicious act, or from any other unexpected situation, and require urgent action in order to avoid or reduce undesirable consequences.

- "Existing exposure situations" are exposure situations that already exist when a decision on control has to be taken, including prolonged exposure situations after emergencies.
4.7. The system for radiation protection (4)

- The ICRP also distinguishes between 3 categories of exposures: occupational exposures, incurred by workers; medical exposures, incurred by patients for the purpose of diagnosis or treatment; and public exposure from sources in any planned exposure situation, existing exposure situation, or emergency exposure situation.

- The ICRP has long espoused three principles of radiation protection – the principles of justification, of optimisation and of application of dose limits.

- The principle of justification aims to ensure that decisions that alters the radiation exposure situation should do more good than harm.

- The principle of optimisation of protection is that the likelihood of incurring exposures, the number of people exposed, and the magnitude of their individual doses should all be kept as low as reasonably achievable, taking into account economic and societal factors.
4.7. The system for radiation protection (5)

• The first two principles apply to all exposure situations – planned, existing and emergency.

• The third principle of application of dose limits applies only to planned exposure situations, and in effect is a "safety net" applied after the first two principles have been implemented.

• Dose limitation means that the total dose to any individual from all planned exposure situations, other than medical exposure to patients, should not exceed the appropriate limits specified by the ICRP.
4.7.1. The derivation of risk coefficients and organ weighting factors from epidemiological data (1)

• Radiation exposure can lead to many harmful health effects. Such effects were classified by ICRP in 1990 into deterministic and stochastic effects, and both categories of effect are considered by the ICRP in establishing dose limits in their recommendations.

• Radiological protection aims at avoiding tissue reactions (previously called deterministic effects) by setting dose limits below the threshold at which they start to occur.

• Cancer and heritable effects (stochastic effects) are believed to occur even at the lowest doses and therefore have to be taken into account whatever is the radiation dose. With this understanding, the dose limits cannot prevent such stochastic effects, but instead aim to reduce their likelihood to acceptably low levels.
4.7.1. The derivation of risk coefficients and organ weighting factors from epidemiological data (1)

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4.7.1. The derivation of risk coefficients and organ weighting factors from epidemiological data (2)

- The term “detriment” was introduced by the ICRP as a measure of the harmful health effects to individuals or descendants of the exposed individual that could occur as a result of radiation exposure at low doses.

- In general, the detriment in a population is defined as the mathematical expectation of the induction of cancer and hereditary damage caused by an exposure to radiation.

- Detriment is a complex concept combining the probability, severity and time of expression of radiation harm.

- Detriment is assessed by the calculation of the “effective dose” which takes into account the total risk attributable to the exposure of all tissues irradiated.
4.7.1. The derivation of risk coefficients and organ weighting factors from epidemiological data (3)

- The fundamental dosimetric quantity in radiological protection is the absorbed dose.

- The detriment depends not only on the absorbed dose but also on the type and energy of the radiation causing the dose, in particular the LET of the radiation.

- This is taken into account by weighting the absorbed dose by a factor related to the quality of radiation. The radiation weighting factor is selected for the type and energy of the radiation incident on the body of, in case of sources within the body, emitted by the source.

- The weighted absorbed dose is the product of the absorbed dose averaged over the respective tissue or organ and is called the “equivalent dose”.
4.7.1. The derivation of risk coefficients and organ weighting factors from epidemiological data (4)

- The “effective dose” is derived by weighting the equivalent doses of the different tissues and organs by a factor which represents the sensitivity of the respective tissues and organs to stochastic effects, primarily radiation-induced cancer.

- Thus, the detriment for all radiations is expressed as effective dose $E$ which is measured in sieverts (Sv).

- The values of the radiation weighting factors for a specified type and energy of radiation has been selected to be representative for values of the relative biological effectiveness (RBE) in inducing stochastic effects at low radiation doses.

- The radiation weighting factors recommended by ICRP in 2007 are shown in Table 4.3.
4.7.1. The derivation of risk coefficients and organ weighting factors from epidemiological data (5)

**TABLE 4.3 RADIATION WEIGHTING FACTORS (ICRP 2007)**

<table>
<thead>
<tr>
<th>Radiation type</th>
<th>Radiation weighting factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Photons and electrons, all energies</td>
<td>1</td>
</tr>
<tr>
<td>Protons and charged pions</td>
<td>2</td>
</tr>
<tr>
<td>Alpha particles, fission fragments, heavy ions</td>
<td>20</td>
</tr>
<tr>
<td>Neutrons*</td>
<td></td>
</tr>
<tr>
<td>$E_n &lt; 1 \text{ MeV}$</td>
<td>$2.5 + 18.2 e^{[-\ln E_n]2/6}$</td>
</tr>
<tr>
<td>$1 \text{ MeV} \leq E_n \leq 50 \text{ MeV}$</td>
<td>$5.0 + 17.0 e^{[-\ln 2E_n]2/6}$</td>
</tr>
<tr>
<td>$E_n &gt; 50 \text{ MeV}$</td>
<td>$2.5 + 3.25 e^{[-\ln 0.04E_n]2/6}$</td>
</tr>
</tbody>
</table>

*) these values have replaced the following step values that were recommended in 1990: $< 10 \text{ keV}$, 5; $10 \text{ keV}$ to $100 \text{ keV}$, 10; $100 \text{ keV}$ to $2 \text{ MeV}$, 20; $2 \text{ MeV}$ to $20 \text{ MeV}$, 10; $>20 \text{ MeV}$, 5.
4.7.1. The derivation of risk coefficients and organ weighting factors from epidemiological data (6)

- The tissue weighting factors were intended to ensure that a weighted tissue equivalent dose would produce the same degree of detriment irrespective of the tissue or organ involved.

- They are representative values averaged over age at exposure and sex and, besides the risk for fatal cancer in the respective organs, also make allowance for different losses of life span, for the morbidity resulting from the induction of non-fatal cancers and for the risk of serious hereditary diseases in the first two generations of descendants of the irradiated individual.

- On the other hand, any possible health damage arising from developmental damage in utero such as severe mental retardation is not included in the tissue weighting factors.
4.7.1. The derivation of risk coefficients and organ weighting factors from epidemiological data (7)

- The period of observation of exposed populations does not extend to a full life time in any of the major epidemiological studies.

- Therefore, it is necessary to project the probability of cancer induction or mortality from the period of observation to the full lifetime of the exposed population.

- This is done using two alternative projection models: (1) the absolute or additive risk model predicts a constant excess of induced cancers throughout a life-time unrelated to the spontaneous cancer rate.

- (2) the relative or multiplicative model predicts that the excess of induced cancers increases as a constant multiple of the age-dependent spontaneous rate.
4.7.1. The derivation of risk coefficients and organ weighting factors from epidemiological data (8)

- By averaging the results of the dependence of risk on age, sex, projection model, and their influence on the base-line cancer risks in different populations e.g. those of Japan, United States of America, United Kingdom and China, the relative probabilities of cancer after irradiation of different for a nominal world population of all ages were derived.

- These form the basis for the tissue weighting factors, taking also into account the expected number of years of life lost due to the different types of radiation-induced cancer. This is highest for leukaemia and breast cancer (since both have a high mortality and early onset) while lung, stomach and colon have a lower value due to their appearance later in life, despite having similar lethality.
4.7.1. The derivation of risk coefficients and organ weighting factors from epidemiological data (9)

- In 2007, ICRP recalculated its nominal risk, taking into account the latest development in genetic risk estimation and the results of the cancer incidence data from the Japanese Life Span Study.

- From the cancer incidence data, sex-averaged nominal risk coefficients for cancer were calculated which are adjusted for lethality and quality of life.

- ICRP proposed nominal risk coefficients for detriment-adjusted cancer risk as 5.5% per Sv for the whole population and 4.1% per Sv for adult workers. For hereditary effects, the detriment adjusted nominal risk in the whole population is estimated at 0.2% per Sv, and in adult workers as 0.1% per Sv (Table 3.4).

- The most significant change from 1990 is the 6-8 fold reduction in the nominal risk coefficient for hereditary effects as a result of the considerations described above.
4.7.1. The derivation of risk coefficients and organ weighting factors from epidemiological data (10)

TABLE 4.4 DETRIMENT ADJUSTED NOMINAL RISK COEFFICIENTS (% PER SV) FOR CANCER AND HEREDITARY EFFECTS (ICRP, 2007).

<table>
<thead>
<tr>
<th>Exposed population</th>
<th>Cancer</th>
<th>Hereditary effects</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole</td>
<td>5.5</td>
<td>6.0</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>6.0</td>
<td>7.3</td>
<td></td>
</tr>
<tr>
<td>Workers</td>
<td>4.1</td>
<td>4.8</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>4.0</td>
<td>5.6</td>
<td></td>
</tr>
</tbody>
</table>

Based on these values ICRP in 2007 confirmed that their previous overall fatal risk coefficient of 5% per Sv continues to be appropriate for radiation protection purposes. While the overall fatal risk coefficient has not changed compared to 1990, the value of some of tissue weighting factors was significantly altered as shown in Table 4.5.
4.7.1. The derivation of risk coefficients and organ weighting factors from epidemiological data (11)

TABLE 4.5 RECOMMENDED TISSUE WEIGHTING FACTORS

<table>
<thead>
<tr>
<th>Tissue</th>
<th>ICRP 2007</th>
<th>ICRP 1990</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone marrow, colon, lung, stomach,</td>
<td>0.12</td>
<td>0.12</td>
</tr>
<tr>
<td>Breast</td>
<td>0.12</td>
<td>0.05</td>
</tr>
<tr>
<td>Remainder *)</td>
<td>0.12</td>
<td>0.05</td>
</tr>
<tr>
<td>Gonads</td>
<td>0.08</td>
<td>0.2</td>
</tr>
<tr>
<td>Bladder, oesophagus, liver, thyroid</td>
<td>0.04</td>
<td>0.05</td>
</tr>
<tr>
<td>Bone surface, skin</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Salivary glands, brain</td>
<td>0.01</td>
<td>part of remainder*)</td>
</tr>
</tbody>
</table>

*Remainder tissues: adrenals, gall bladder, heart, kidneys, lymphatic nodes, muscle, oral mucosa, pancreas, prostate, small intestine, spleen, thymus, uterus, extrathoracic region. The tissue weighting factor for the remainder tissues applies to the weighted mean doses of the 13 listed organs which are added up to be multiplied by the tissue weighting factor of 0.12.
4.7.1. The derivation of risk coefficients and organ weighting factors from epidemiological data (12)

• Below 100 mSv per year, the increase in the incidence of stochastic effects is assumed by ICRP to occur with a small probability, and in proportion to the increase in radiation dose above background.

• Use of this so-called linear, non-threshold (LNT) model is considered by ICRP to be the best practical approach to managing risk from radiation exposure and a prudent basis for radiological protection.

• Effective dose and tissue weighting factors are to be used for prospective dose assessment for planning and optimisation of protection of the general population or for working populations, but not for calculating risks for individuals or specific populations such as young women.
4.7.1. The derivation of risk coefficients and organ weighting factors from epidemiological data (13)

- An important statement about effective dose in ICRP 2007, § 157, is the following:

- “Effective dose is intended for use as a protection quantity on the basis of reference values and therefore is not recommended for epidemiological evaluations, nor should it be used for detailed specific retrospective investigations of human exposure and risk. This is especially important in cases of individual doses exceeding dose limits”.
4.7.2. Dose limits (1)

- Implementation of the third ICRP principle of application of dose limits for planned exposure situations (excluding medical exposures) requires the setting of values for the dose limits.

- The values of the dose limits should ensure the avoidance of deterministic effects or reduce the risk of stochastic effects to acceptable levels, as relevant. Despite the changes in the nominal risk coefficients underpinning the dose limits, the values given in ICRP 103 in 2007 are mostly the same as those given previously in ICRP 60, except for the eye lens.

- In planned exposure situations, for occupational exposure the Commission recommended in 2011 an equivalent annual dose limit for the eye lens of 20 mSv, averaged over defined periods of 5 years, with no single year exceeding 50 mSv. For public exposure the equivalent dose limit is 10 mSv in a year. Recommendations on other dose limits remain unchanged.
4.7.2. Dose limits (2)

- For occupational or public exposure, arising from planned exposure situations, an individual may be exposed from several sources.

- Hence, an assessment of the total exposure has to be attempted which includes all sources causing exposure to the individual.

- The doses from this total exposure are compared with the appropriate dose limits.

- Table 4.6 shows the dose limits for planned exposure situations to the public and to radiation workers.
4.7.2. Dose limits (3)

<table>
<thead>
<tr>
<th>Type of limit</th>
<th>Occupational</th>
<th>Public</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effective dose</td>
<td>20 mSv per year *)</td>
<td>1 mSv per year **)</td>
</tr>
<tr>
<td>Annual equivalent dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In lens of the eye (revised 2011)</td>
<td>20 mSv</td>
<td>15 mSv</td>
</tr>
<tr>
<td>Skin ***</td>
<td>500 mSv</td>
<td>50 mSv</td>
</tr>
<tr>
<td>Hands and feet</td>
<td>500 mSv</td>
<td>--</td>
</tr>
</tbody>
</table>

*) the 20 mSv value applies to the average value over a period of 5 years with the additional provision that in any one year the dose should not exceed 50 mSv. Moreover, once a woman has notified pregnancy to the employer, her exposure for the remainder of the pregnancy should not exceed 1 mSv since the embryo/foetus is considered the same as the public.
4.7.3. Risk-benefit considerations in breast cancer screening using mammography (1)

• In medical uses of radiation, all exposures should be, as a result of medical indications, for the patient’s diagnosis or treatment.

• This means that both the risk and the benefit apply to the same person.

• Moreover, radiation risks are usually negligible compared to the benefit of the individual.

• In any case, radiation protection for the patient is afforded through the application of the principles of justification and optimisation.
4.7.3. Risk-benefit considerations in breast cancer screening using mammography (2)

- The situation is very different in radiological screening programmes for early diagnosis of specific diseases such as cancer.
- For each person who will be identified by the screening exposure at an early stage of disease and who might therefore have a better chance of cure, there will be hundreds or thousands of healthy people exposed to radiation who do not have the disease and who will not benefit directly from the radiation exposure.
- The most important example is mammography screening for early breast cancer too small to be found using clinical examination.
4.7.3. Risk-benefit considerations in breast cancer screening using mammography (3)

- Breast cancer is the second leading cause of cancer death for all women, and the leading cause of death in women between the ages of 30 and 55 years.

- Age standardised breast cancer rates vary markedly between countries, the lowest rates are reported from China and Japan (20 to 35 per 100,000), the highest rates in white American and some European women (75-100 per 100,000).

- The probability of cure depends critically on the risk of the primary cancer having already spread to lymph nodes and distant sites. If the primary cancer is smaller than 1 cm, the risk of distant metastasis which would preclude cure is less than 10%, while if the primary is larger than 4 cm the risk of distant metastasis would be over 50%.

- Therefore, the smaller the primary tumour at diagnosis the greater is the chance of cure.
4.7.3. Risk-benefit considerations in breast cancer screening using mammography (4)

- Clinical methods such as palpation are not reliable detecting tumours smaller than 1 cm, while mammography is very capable of doing this.

- In each mammographic investigation with state-of-the-art methods, the breast is exposed to a dose of 4 mGy, which varies much between women depending on the size of the breast.

- Since the breast is one of the most sensitive organs of the body with regard to radiation-induced cancer, the radiation doses from mammography have to be kept as low as compatible with the diagnostic aims and be justified by the expected decrease in breast cancer mortality.

- Elevated breast cancer risk following radiation exposure has been demonstrated both in the Life Span Study of A-bomb survivors and in different cohorts of medically exposed women.
4.7.3. Risk-benefit considerations in breast cancer screening using mammography (5)

4.7.3. Risk-benefit considerations in breast cancer screening using mammography (5)

• Among the 29,700 women of the Life Span cohort of the A-bomb survivors who had received a dose of >5 mGy to the breast, 173 died from breast cancer by 1997.

• Analysis of the dose dependence of risk provided strong evidence for a linear dose response relationship and a strong dependence on age at exposure with decrease of risk with increasing age, the risk becoming insignificant if exposure occurred at ages over 50.

• Both the relative risk model and the absolute risk model fitted the data equally well. Altogether 24% of the 173 cases were attributable to the radiation exposure, the excess relative risk per Gy was 0.79 (with 90% confidence limits of 0.29 to 1.5), and the excess absolute risk was 1.6 per 10,000 person-years.
4.7.3. Risk-benefit considerations in breast cancer screening using mammography (6)

- The most important epidemiological data from radiation exposure of the breast come from studies in tuberculosis (TB) patients treated with pneumothorax under fluoroscopic control, and from women given radiotherapy for bacterial infection of the breast after giving birth (postpartum mastitis).

- In the biggest TB study, there were 349 breast cancer deaths in 13,078 women (compared to 237 deaths expected), and in the most important mastitis study, there were 210 breast cancers in 3,034 women.

- All studies confirmed that radiation-induced breast cancer occurs at ages similar to those at which breast cancers are seen in the absence of exposure, that the excess risk increases linearly with radiation dose, and that age at exposure and attained age both have a great influence on the risk of radiation-induced breast cancer.
4.7.3. Risk-benefit considerations in breast cancer screening using mammography (7)

- There are also other risks of mammography screening which may be even more important than radiation-induced breast cancer such as:

- (1) false negative mammograms which may give inappropriate reassurance, and diagnosis of breast cancer and treatment may be delayed. Up to 25% of invasive breast cancers are not detected by mammography in 40-49 year old women compared to only 10% in women older than 60.

- (2) false positive mammograms, more common in younger women, cause unnecessary interventions such as biopsies and psychological stress.

- (3) overtreatment e.g. of ductal carcinoma in situ, which is frequently diagnosed by mammography especially in younger women, but some ductal carcinoma will not progress to invasive cancer.
### 4.7.3. Risk-benefit considerations in breast cancer screening using mammography (8)

- Since the radiation risks of breast cancer induction are lower after age 50 years, and the rate of false negatives/positives is reduced in older women, it has been recommended to perform mammography screening for breast cancer only in women aged 50 and older.

- In several large epidemiological studies, in particular in Sweden, a reduction of mortality from breast cancer due to mammography screening of over 20% was determined.

- Depending on the assumptions of radiation risks, improvement of therapeutic outcome and breast cancer incidence, different ratios of benefit versus risk have been calculated but for women over 50, all estimates have been very positive with a benefit to risk ratio ranging from 20 to >100.

- These results were the basis of mammography screening programmes on a national basis in many countries.
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