DEFINITION

1. **The leukaemias** are a group of diseases affecting the lymphatic and reticulo-endothelial systems, including the bone marrow, resulting in over production of abnormal leucocytes, with or without an increase in these cells in the circulating blood, and infiltration of various structures. Leukaemias are neoplastic diseases and may be regarded as cancers of the haemopoietic organs. They account for 2% of all cancers and of cancer deaths world-wide and 3% of all new malignancies in the UK.

NORMAL BLOOD AND BONE MARROW

2. Normal blood contains three main groups of cells: red cells, leucocytes and platelets. The cyclic process of their production, circulation, removal and renewal is not yet fully understood. In health, a balance is maintained and the numbers of these formed elements is remarkably constant.

3. All mature blood cells derive from stem cells, which are few in number, but have the capacity to proliferate and persist throughout life. The stem cells arise during embryonic development and migrate from the yolk sac to the foetal liver and thence to the bone marrow. After birth, the marrow is the major site of blood cell production.

4. White cells, red cells and platelets are all derived from a single cell type. The number of peripheral blood cells far exceeds the number of stem cells, so the haemopoietic process must involve progenitor cells. The stem cells are initially pluripotent but, under a variety of stimuli, become increasingly differentiated or committed to specific mature peripheral blood cells.

5. Blood cells have a limited life span and haematopoiesis continues throughout life. Mature blood cells thus undergo controlled removal and replacement, a process regulated by feedback factors. One of those is growth factor, which is involved in the proliferation and differentiation of the stem cells.

6. Normal haematopoiesis depends on feedback loops. Factors affecting these loops are both endogenous and exogenous. In their complex interaction patterns there is opportunity for error, with abnormal haematopoiesis leading to leukaemia.

7. **The leucocytes** form the cellular basis of host defence against pathogens and foreign proteins. They can be divided into phagocytic cells which include neutrophils, eosinophils and monocytes, and non-phagocytic cells which include basophils and lymphocytes. Granulocytes (polymorphonuclear leucocytes) are classified into three types, according to the histological staining characteristics of their nuclei.

8. **Functional classification of leucocytes:**

    8.1. Phagocytic leucocytes ingest and digest cellular and non-cellular debris as well as exogenous particles.

    8.2. Neutrophils, in addition to their phagocytic function, provide immunity against bacteria and fungi.

8.3. Eosinophils are far less numerous, comprising 1-6% of leucocytes. They are phagocytic, but less so than neutrophils, and release substances at sites of inflammation. These substances include basic proteins which are helminthotoxic and defend against parasitic, as well as activating mast cells.

8.4. Basophils comprise less than 0.2% of leucocytes and are non-phagocytic. They release a wide range of substances, some of which are anti-parasitic while others are involved in immunoregulation and hypersensitivity.

8.5. Monocytes are phagocytic and have properties similar to neutrophils (macrophages, which are derivatives of monocytes, are the most potent phagocytes). They also produce many immunomodulatory substances including interferon, tumour necrosis factor (TNF) and reactive intermediaries which interact to form substances toxic to intracellular organisms. Cytokines produced by macrophages act both locally and by hormonal effect to cause fever, acute-phase protein synthesis and tissue catabolism.

8.6. Lymphocytes comprise about 20% of leucocytes, and are of two main types. B-cells and T-cells, which are specialised for antigen recognition. B-cells develop in the marrow, and are involved in humoral immune responses, whereas T-cells migrate to the thymus and are processed there before colonising all lymphoid tissues as mature T-lymphocytes. They are responsible for cell-mediated responses. A third population of lymphocytes includes antigen-presenting cells and natural killer (NK) cells.

CLASSIFICATION OF LEUKAEMIAS

9. The leukaemias are conventionally described by their kinetic behaviour (whether acute or chronic in their untreated course) and by their pattern of cellular differentiation as myeloid or lymphoid (lymphatic).

10. **Acute leukaemias,** which occur mainly in children and in older adults, are malignancies with little evidence of differentiation. Their characteristic cells are immature blasts and accurate classification may depend on identification of immunophenotypes by using monoclonal antibodies.

10.1. **Acute myeloid leukaemia** (AML, acute myelocytic or myeloblastic) and **acute monocytic leukaemia** are the principal forms of acute leukaemia in adults

10.2. **Acute lymphatic leukaemia** (ALL, acute lymphocytic or lymphoblastic) occurs in children and adults. It is the most frequent type in childhood and the commonest childhood cancer.

11. **Chronic leukaemias** are principally diseases of adults. There are two major variants:

11.1. **Chronic myeloid leukaemia** (CML or chronic granulocytic leukaemia) occurs in two forms, a rare atypical juvenile form found in children below the age of five and more commonly, the adult type found mainly in middle age. It is characterised by the uncontrolled proliferation of myeloid cells.

11.2. **Chronic lymphatic leukaemia** (CLL or chronic lymphocytic leukaemia) differs in many respects from the other leukaemias and has common features with some forms of non-Hodgkin's lymphoma. Its inclusion as a type of leukaemia is based on the demonstration of bone marrow infiltration, and invasion of the blood by small, immature, immunologically incompetent lymphocytes. Immunophenotyping shows that most of the lymphocytes in chronic lymphatic leukaemia are of B-cell origin. Hairy cell leukaemia and prolymphocytic leukaemia are related to chronic lymphatic leukaemia.

CLINICAL MANIFESTATIONS

Acute leukaemia

12. This has bimodal distribution with peak incidence in children aged 5-14 and in adults of the 60-75 age group.

13. Failure of the normal differentiation and maturation of white cell precursors in an accumulation in the bone marrow of abnormal white cell precursors and the failure of normal bone marrow function. Anaemia, neutropenia and thrombocytopenia result and are responsible for the clinical manifestations.

14. The onset of **AML** is usually abrupt, either with vague symptoms such as lethargy, weakness and malaise or with more specific problems. Bleeding tendency may cause epistaxis, bruising, purpura, menorrhagia, post-extraction dental haemorrhage, fundal or even cerebral haemorrhage. There may be bone pain or atypical skin lesions which fail to heal. Infective lesions may occur in the lungs, pharynx or perianal areas and septicaemia may ensue. Splenomegaly may be found. Rarely, AML presents with appendicitis.

15. **ALL** may present acutely or insidiously. The more common signs and symptoms are lethargy, malaise, pallor, fever, bone and joint pain, bleeding tendency, hepatosplenomegaly, lymphadenopathy (usually generalised and painless) nerve root problems or a mediastinal mass. Skin infiltration and gum hypertrophy are characteristic of **monocytic** leukaemia.

Chronic myeloid leukaemia (CML)

16. Until recent years, the usual presentation was with symptoms resulting from anaemia and/or splenomegaly. In Western Europe about 50% of cases are now discovered on routine blood screening.

17. The onset is usually insidious. Early symptoms may include fatigue, lassitude, weight loss, dyspnoea, pallor and hyperhidrosis. The symptoms are related to anaemia, splenomegaly and hypermetabolism. Both the spleen (in up to 80% of cases) and the liver may be palpable. Patients with very high leucocyte counts may have retinal vein engorgement and pulmonary insufficiency due to leucostasis. Pruritis may be a prominent symptom. Gout or priapism may occur. By the time the symptomatic patient seeks medical advice, the disease is often fully established and has probably existed for over a year. In the early phase, granulocyte function is not impaired and susceptibility to infection is not increased. Fever may occur early but is more frequent in the later stages. Patients presenting at a later stage will have a variety of the above symptoms, together with signs of infection, lymphadenopathy and bone and joint pains, often with sternal tenderness.

18. The chronic phase is of variable duration and is followed by an accelerated phase or by transformation into acute leukaemia (the blast phase), either myeloid or lymphoid. Rarely, there is gradual progression to myelofibrosis.

Chronic lymphatic leukaemia (CLL)

19. About a third of cases are discovered by chance, with lymphocytosis and no specific symptoms or signs. Others tend to present with lymphadenopathy or symptoms of anaemia, such as fatigue or malaise. Less than half of these have some systemic symptoms such as weight loss or night sweating. Fever usually indicates infection.

20. There may be no physical signs but when present these may include lymphadenopathy, petechiae, purpura, or skin infiltration with atypical skin lesions. Splenomegaly is found in 50% of cases, but hepatomegaly is less common.

21. Later in the disease, petechiae, bruises or bleeding from mucous membranes may occur. Herpes zoster is a frequent complication. Chest symptoms and massive lymphadenopathy may occur. There may be leukaemic infiltration of the small bowel, stomach or kidney. This infiltration may be clinically silent or may result in ulceration, bleeding, malabsorption or obstructive nephropathy. Central nervous system involvement is rare. Because of immunoglobulin depletion, patients are prone to infection, which may be bacterial, fungal or viral, and haemolytic anaemia occurs in about 5% of cases. The course of the disease is variable.

22. An association has been recognised between chronic lymphatic leukaemia and some other malignancies, including skin tumours, and carcinoma of the lung and colon. These carcinomas may precede the chronic lymphatic leukaemia. The association probably reflects a deficiency of immunocompetence in these patients, rather than a common external cause.

AETIOLOGY

General risk factors for all cancers

23. Clinical cancer is the end of a multistage process involving initiating and promoting agents. If the carcinogen is an initiating agent, eg asbestos – rather than a substance influencing a later stage nearer clinical manifestation, eg cigarette smoking – cancer incidence in the population may continue to rise, albeit more slowly, for a considerable time after exposure to the carcinogen has ceased.

Risk factors in the individual case of all cancers

24. The main factors that determine whether a particular individual develops cancer relate to constitution and exposure to environmental factors.

Genetics

25. The close connection between certain chromosomal abnormalities associated with recognised clinical syndromes and subsequent tumour development, eg polyposis coli and cancer of the large bowel and xeroderma pigmentosum and skin tumours, confirms that an individual's genetic make-up has an effect on his susceptibility to cancer.

26. Many studies have looked at cancer rate in the families of individuals with the disease. There appears to be no material tendency for cancer in general to cluster in families and no genes have been identified that increase the risk of cancer in all tissues. However, all common cancers do cluster in families to some extent – the risk of a sibling of a patient developing a tumour at the same site is twice normal. This might be due to genetic susceptibility but could equally well reflect lifestyle, eg diet or hygiene or a common legacy of infections in early life.

Environmental factors

27. Our knowledge of the environmental causes of cancer relies on animal laboratory investigation and human epidemiology, with the two approaches complementing each other. Since there are features common to most cancers, there are factors which can cause cancer at all or many sites. Present evidence confirms the importance of life style factors in cancer causation.

Tobacco smoke

28. Cigarette smoking is thought to cause 30% of all cancer deaths and has been conclusively linked to cancer of the lung, upper respiratory tract, oesophagus, bladder, stomach, liver, kidney and chronic myeloid leukaemia. It may also cause cancer of the colon and the rectum. Relevant factors include number of cigarettes smoked, tar content, age at smoking onset and duration of habit.

Diet

29. There is good evidence that some common cancers would be less common if diet were modified. Animal fat consumption, particularly red meat, high salt intake and ingestion of very hot beverages and food have all been linked to specific cancers. Similarly what is **not** in the diet may be important. Low consumption of vegetables and fruit in the presence of high calorie intake is associated with several different tumour types, eg childhood obesity and cancer of the breast and prostate, adult obesity and endometrial cancer. Consumption of alcohol (particularly along with cigarettes) increases the risk of cancer of the upper respiratory and digestive tracts. There is evidence that as little as two units a day may contribute to breast, colon and rectal cancer. In total, diet is considered to account for 30% of all cancer mortality in developed countries, alcohol for a further 3% and salt for 1%.

Radiation

30. Radiation is difficult to avoid and, in total, radiation of all types causes 2% of all cancer deaths. Most of these deaths result from natural sources, particularly sunlight, UVB. UVB radiation causes 90% of all skin cancers, including basal cell cancers, malignant melanoma and squamous cell carcinoma.

- **Electromagnetic radiation** as a cause of cancer has been the subject of several recent studies. The results are confusing and inconsistent and reported associations may not be causal. It is of two main types:

  i. **Extremely low frequency fields,** eg power lines and household appliances. Basic science confirms that these radiations are of too low frequency to initiate cancer-causing genetic mutation as they are of insufficient energy to ionize molecules.

  ii. **Radiofrequency electromagnetic radiation,** eg cellular telephones, microwaves and living creatures. Although more energetic than i., they are still unable to cause molecular ionization. In conclusion, at this date there is no good scientific evidence that electromagnetic radiation causes cancer. Any possible association remains hypothesis.

- **Ionising radiation**
  Ionising radiation can penetrate animal tissue and damage DNA and theoretically has the power to produce cancer in most tissues. The actual risk due to exposure to ionising radiation may, however, be different. It is often overestimated and not evidence-based. Amongst Japanese residents of Hiroshima and Nagasaki who survived more than a year after detonation, only 1% have died of tumours.

  Studies of humans exposed to high dosage of ionising radiation eg the Japanese atomic bomb survivors or individuals medically irradiated for tumours, have shown an increased incidence of cancer due to that exposure. There is, however, no firm evidence from human low-dose epidemiological studies, which unequivocally demonstrates an increase in cancer incidence. This may be due to the very large size of study population, which would be needed to demonstrate an increased incidence.

  For radiation protection purposes it is, therefore, accepted that there is no threshold level below which no carcinogenic effect is produced, and the risk of a cancer developing is extrapolated on a dose-proportional basis from high to low doses and dose rates.

  All humans are constantly exposed to ionising radiation, from both the natural environment and man-made products. The natural sources include cosmic radiation from space, radiation from the ground, and from inhaled and ingested materials. Air travel and mining both increase exposure to background radiation. Radiation originating in the body comes mainly from potassium, while lungs are exposed through radon in inhaled air. Man-made radiation comes from medical uses, past atomic tests, man-made products and radioactive waste.

Natural radiation differs depending on location. In the UK the average annual dose is less than 2,000 microsieverts. There is, however, a considerable range; it may rise to 8,000 microsieverts in some areas and to 100,000 in some homes. The UK average annual dose from man-made sources in total is less than 300 microsieverts and, again, there may be variation.

From 1952 to 1958 the UK carried 21 atmospheric nuclear tests in the Pacific Ocean. The locations were chosen because of their isolation and low natural radiation level. On average the Christmas Island annual background radiation is less than 700 microsieverts.

Therapeutic drugs

31. About 20 agents, not all of which are in current use, are known to cause cancer. Potential carcinogens may still be used if the hazard is judged to be less than the chance of saving a life, eg certain cancer drugs. Close scrutiny is kept on drug hazards and the position of oestrogens in hormone replacement therapy (HRT), known to cause endometrial cancer, and of the oral contraceptive pills, which have been associated with carcinoma of the cervix, breast and hepatoma, is closely monitored. Together, prescribed drugs are held responsible for less than 1% of all fatal cancers.

Occupation

32. Historically, study of occupational exposures has identified many important carcinogens. Material or process modification and, latterly, health and safety statute have removed many potential hazards in the developed world. However, the long latent period of cancer means that a considerable time will be required for the effects of industrial carcinogens to be eliminated and, equally, that new hazards may remain unsuspected for a long time. At present overall, occupation is considered responsible for 2-3% of all fatal cancers in developed countries. Particularly important occupational carcinogens are asbestos dust exposure, exposure to combustion products of fossil fuels, and ionising radiation.

Pollution

33. Investigation of the relation between environmental pollution – air, soil and water – and cancer is difficult because of the widespread nature of pollution and similar risk to people over a wide geographical area. It is generally accepted that, in the UK at the beginning of the last century, air pollution via combustion may have contributed to a few per cent of lung cancers. Over the last 30 years with increasing statute on pollution reduction this has become much less common. Advances in chemical analysis have allowed recent interest in pollution of soil and water as possible cancer risks.

34. Another complicating factor in accurately attributing risk of cancer to individual external agents is **interaction.** Some carcinogenic agents act together to produce effects much greater than the sum of the separate individual effects, eg smoking and asbestos in relation to cancer of the lung: smoking and alcohol in relation to carcinoma of the oesophagus, and aflatoxin and hepatitis B infection in cancer of the liver.

Specific risk factors for leukaemias

35. The aetiology of the leukaemias includes constitutional (genetic) and environmental factors. In the majority of cases of acute leukaemia, there is no identifiable underlying cause.

Epidemiology

36. The leukaemias account for about 2% of all malignancies. The sex ratio M/F is about 1.7/1 overall. The age incidence per 100,000 in early infancy is about 6(M) and 5(F), falling to about 2(M) and 1.5(F) in the early twenties, then rising exponentially to about 75(M) and 40(F) at the age of 75 years.

    36.1. **AML** occurs at all ages, becoming progressively more common from childhood, and is the most common type in young adult life.

    36.2. **ALL,** with a peak incidence at 2-3 years of age, is the commonest childhood cancer.

    36.3. **CML** is rare in youth, but more common than AML by late middle age.

    36.4. **CLL** increases progressively with age and there are marked geographical variations in its incidence.

Genetic factors

37. There is firm evidence that genetic factors are important in the aetiology of various types of leukaemia.

    37.1. In families where a child develops acute leukaemia, the risk to other family members is doubled.

    37.2. There is a four-fold risk that a sibling of a child with ALL will develop the disease. The risk is much higher in monozygotic twins, with a concordance rate approaching 100% in infancy.

    37.3. Down's syndrome and genetically determined immunodeficiency syndromes are associated with an increased incidence of leukaemia. Such conditions include Fanconi's anaemia, ataxia telangiectasia, Wiskott-Aldrich and Bloom's syndromes. In Down's syndrome, there is a 20-fold increase in risk of leukaemia, with a tendency to develop ALL in childhood at a later stage.

    37.4. Down's syndrome and the immune deficiency states listed above are associated with chromosomal damage. Evidence is accumulating that this may be involved in the pathogenesis of the malignant transformation process. Beta cell lymphomas characteristically show an 8:14 translocation and 9:22 translocation is pathognomonic of chronic myeloid leukaemia. In both of these situations, oncogenes are located on one of the translocated segments. The chromosomal rearrangement itself is possibly a trigger for the transformation process.

37.5. There is an increased incidence in leukaemia in patients with non-melanotic skin cancer, which is independent of any known risk factor other than genetically determined susceptibility.

37.6. In nearly all cases of CML and some cases of AML, the peripheral blood granulocytes, platelets and erythrocytes contain the Philadelphia (Ph) chromosome, an acquired cytogenetic abnormality resulting from reciprocal translocation between chromosomes 9 and 22. Acute-phase Ph-positive leukaemia is exceptionally resistant to conventional treatments and patients are candidates for marrow transplantation.

Ionising and non-ionising radiation

38. There is a clear association between exposure to excess ionising radiation and development of the leukaemias (especially acute myeloid) and chronic myeloid leukaemia, over a period 2-10 years after acute exposure. The magnitude of risk is proportional to the total radiation dose received. Chronic lymphatic leukaemia is **not** associated with radiation exposure.

39. Evidence of a causal link:

39.1. Prior to safety legislation, there was a high incidence of acute leukaemias in radiologists.

39.2. Patients treated with radiotherapy for other malignancies have an increased risk of leukaemia, with a peak incidence 4-5 years later. Radiotherapy for ankylosing spondylitis has been abandoned because of significant risk. Those receiving repeated, large exposures for diagnostic purposes are at increased risk.

39.3. An increased incidence of acute and chronic myeloid leukaemia was found among people exposed to excess ionising radiation from the nuclear bombing of Hiroshima and Nagasaki, with a peak incidence 6 years after exposure. Incidence declined with distance from the detonation.

39.4. Results from the UK National Registry for Radiation Workers show that, although this worker population has a lower leukaemia incidence rate than the general public, there is a significant connection between magnitude of occupational radiation exposure and leukaemia incidence. A dose of the order of a few tens of rads doubles the natural incidence of leukaemia.

40. Paradoxically, there is lowered overall incidence of cancers, including leukaemias, in patients treated with radioiodine for hyperthyroidism.

41. There is an increased incidence of leukaemia among children whose fathers are radiation workers, and it was suggested that this was due to the fathers' pre-conception exposure to radiation (the Gardner hypothesis). However more recent and extensive studies have shown that there is **no** dose-response relationship. Indeed, the association was greatest for those with exposure **below** the detectable level. Infections and the genetic effect of population mixing in the vicinity of nuclear facilities are now thought to be the factors responsible for the cluster of leukaemias near the Sellafield nuclear reprocessing plant in the UK.

42. Public concern has been raised by reports of an apparent link between exposure to electromagnetic fields, eg from high voltage power lines, and leukaemia, especially childhood leukaemia. These reports have been inconsistent, lacking accurate measures of exposure, and unsupported by animal experiments or plausible biological mechanisms. In particular, such fields do not release enough energy to damage DNA. There is no convincing evidence of a causal link.

43. **Chemical agents**

43.1. Occupational exposure studies showed an increased incidence of acute myeloid leukaemia in the adhesive and rubber film industries prior to appropriate safety legislation. The specific chemical involved was benzene. Exposure to toluene carries a similar risk.

43.2. Other chemicals associated with an increased risk of AML include paint solvents, embalming fluids, ethylene oxide, herbicides and tobacco.

43.3. Treatment of neoplastic conditions, in particular the lymphomas and multiple myeloma, by chemotherapy is associated with a subsequent increased incidence of secondary malignancies including leukaemias, in particular AML. Substances known to be implicated include adriamycin, melphalan, busulphan, procarbazine, razoxane, interferon and cisplatin. The risk is higher in patients who have received radiotherapy.

43.4. The same risk is associated with the use of some of these chemotherapeutic drugs for immunosuppression, eg in transplant patients. In all cases clinically, the leukaemogenic risk is outweighed by the potential benefit.

Infection

44. Leukaemia in animals may be caused by retroviruses, but there is no evidence of this in humans.

CONCLUSION

45. The leukaemias are a diverse group of malignant conditions of the white blood cells. Diagnosis is made by blood count and marrow biopsy. Constitutional (genetic) and environmental factors mentioned above play major parts in their aetiology.

46. There is no evidence that leukaemia is caused by climatic extremes, trauma, physical or mental stress or lowered resistance arising from hardship or other diseases. The course of leukaemia is unaffected by environmental factors other than those involved in their treatment and the treatment of their consequent infections.

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Annex A

Radiation dose

1. The first definition of a unit of radiation dose was made in 1928 by the International Congress of Radiology. The roentgen (R) was defined as that quantity of radiation which produces in 1 cm of air one unit of charge of either sign, thus defining a unit of exposure. Units of **absorbed dose**, the actual energy absorbed in the tissue being irradiated are now used. The radiation absorbed dose or **rad** is now cited in SI (Systeme Internationale) units – joules per kg – of absorbing material. The fundamental unit, 1 joule/kg, is 1 gray (1 Gy), equivalent to 100 rads (R).

2. Different radiation types have greater or lesser effect per unit dose, so they are all expressed relative to the effects of X-rays, ie. a unit equivalent dose is used. To calculate the roentgen equivalent in man (**rem**), the absorbed radiation dose is multiplied by a radiation weighting factor, dependent on type and energy of the radiation. The current SI unit of equivalent dose is the **Sievert**. For X-rays and gamma rays the equivalent dose in sieverts and the absorbed radiation dose in grays are the same. The relationship between the different dose units is:-

   1 gray (Gy) = 1 joule/kg = 100 rads (R) = 100 rems (r) = 1 sievert (Sv) = 1,000 millisieverts (mSv) = 1,000,000 microsieverts (microSv). Typical doses of radiation include:

   Chest X-ray – 0.02 mSv
   Brain scan – 7 mSv
   Bone scan – 4 mSv
   Average annual UK dose from cosmic rays – 0.26 mSv
   Average annual UK dose from gamma rays – 0.35 mSv
   Average annual UK dose from natural background radiation – 2.2 mSv

3. **Effects of total body irradiation**

Equivalent dose (Sv)	**Effect**
Sub lethal to man 0.0001 (0.1 mSv)	Around 2 weeks' natural background radiation, no detectable effect
0.001 (1 mSv)	Around 6 months' natural background radiation, no detectable effect
0.01 (10 mSv)	No detectable effect
0.1 (100 mSv)	Minimal decrease in peripheral lymphocyte count, no clinical effect
1 (1000 mSv)	Mild acute radiation sickness in some individuals (nausea, possible vomiting), no acute deaths, early decrease in peripheral lymphocyte count, decrease in all WBC and platelets at 2-3 weeks, increase in late risk of leukaemia, solid tumours

Equivalent dose (Sv)	Effect
Lethal to man 10 (10,000 mSv)	Severe acute radiation sickness, severe vomiting, diarrhoea, death within 30 days of all exposed individuals. Severe depression of blood cell and platelet production, damage to gastrointestinal mucosa.
100 (100,000 mSv)	Immediate severe vomiting, disorientation, coma, death within hours
1000 (1,000,000 mSv)	Death of some micro-organisms, some insects within hours
10,000 (10,000,000 mSv)	Death of most bacteria, some viruses
100,000 (100,000,000 mSv)	Death of all living organisms, denaturation of proteins

Radiation dose limits

4. Since the days of Marie Curie it has been appreciated that ionising radiation exposure may be hazardous to health. Radiation dose limits were first recommended for ionising radiation exposure in 1928. The statutory limit on the amount of radiation to which the general public may be exposed in excess of natural background radiation and excluding medical exposure is set, from 1 January 2000, at 1 mSv per annum.

5. The most important source of man-made exposure is medical investigation which accounts for 90% of man-made exposure. Average natural background radiation is raised to 2.6 mSv by all man-made exposure. UK estimated exposure, excluding medical investigation, is 0.04 mSv. Other statutory limits include occupational dose limits. From 1 January 2000, these are 20 mSv per annum for classified workers and 6 mSv per annum for unclassified workers.

January 2000