5. Summary of Data Reported and Evaluation

5.1 Exposure data

The greatest exposure of the general population to X-rays and γ-rays comes from natural terrestrial radiation. The next most significant source is the use of X-rays and radiopharmaceuticals in various diagnostic and therapeutic procedures. Exposures from the atmospheric testing of nuclear weapons have diminished, and only small contributions to the collective human dose are made by the generation of electrical energy by nuclear reactors, by accidental releases from nuclear facilities and radioactive devices and by occupational exposure during medical uses, commercial nuclear fuel cycles, nuclear industrial sources, military activities and the clean-up of nuclear or radiation accidents. The latter contributions are important, however, as they can result in significant exposure of groups of individuals.

The most important exposures to X- and γ-rays from the point of view of the determination of cancer risk in humans are from the past use of atomic weapons and from the medical uses of radiation.

With regard to the overall exposure of the population, the variation in individual doses over time, place and conditions of exposure makes it difficult to summarize mean individual doses accurately, although some indications are possible. Most exposures are measured in units of absorbed dose (Gy) in individual organs, but they are compared in units of effective dose (Sv) in order to account for effects in all the organs, which differ in radiosensitivity (and for differences in radiation quality when appropriate). The average annual effective dose from X- and γ-rays from natural sources is about 0.5 mSv, with elevated values up to about 5 mSv. Medical procedures in developed countries result in an annual effective dose of about 1–2 mSv, of which about two-thirds comes from diagnostic radiography. Possible exposures in medicine vary widely, however, ranging from several hundred millisieverts from frequent diagnostic procedures to several sieverts from therapeutic procedures. The annual effective doses to monitored workers are commonly in the range of 1–10 mSv.

5.2 Human carcinogenicity data

The carcinogenic effects of ionizing radiation in human populations have been studied extensively. Evidence for causal associations comes primarily from epidemiological studies of survivors of the atomic bombings in Japan and patients exposed to radiation for medical reasons. Epidemiological studies of populations exposed to lower doses of radiation were considered but were determined not to be informative for this evaluation.

In epidemiology, associations between exposure and disease are most often accepted as causal when there is consistency across many studies conducted by different investigators using different methods; when the association is strong; and when
there is evidence of a dose–response gradient, with risk increasing as the level of exposure increases. These three important causal criteria are satisfied for exposure to radiation and the induction of cancer.

Perhaps most important is that the association between radiation and cancer has been found consistently in many different populations exposed at different times and in different countries throughout the world. Among survivors of the atomic bombings in Hiroshima and Nagasaki, who were exposed primarily to $\gamma$-rays, excess numbers of cases of leukaemia and other cancers have been observed up to 45 years after exposure. Excess numbers of cases of leukaemia and other cancers have also been observed among patients treated with X-rays or $\gamma$-rays for malignant or benign diseases. Important evidence comes from studies of women in 15 countries who were irradiated for cervical cancer and persons who were irradiated for ankylosing spondylitis in the United Kingdom. Excess risks for cancer were also found among children irradiated for an enlarged thymus gland in the USA, for ringworm of the scalp in Israel and for skin haemangioma in Sweden. Increased numbers of breast cancers have been observed in patients in Canada and the USA who received frequent chest fluoroscopic X-rays for tuberculosis. There are well over 100 studies of patient populations in which excess numbers of cancers have been linked to radiotherapy. Pioneering medical radiologists practising shortly after the discovery of X-rays in 1895 had increased rates of leukaemia and other cancers in studies conducted in the United Kingdom, the USA and, later, in China.

Strong associations between exposure to radiation and several types of cancer have been reported. Exposure to radiation at sufficiently high doses has increased the risk of developing leukaemia by over fivefold. Even higher relative risks have been reported for thyroid cancer following irradiation during childhood. Greater than two-fold increases in the risk for breast cancer have been seen after irradiation before the menopause.

Since in many studies the dose of radiation received by individuals was estimated with considerable accuracy, dose–response relationships could be evaluated. An increase in the risk for leukaemia with increasing dose was seen among atomic bomb survivors over a broad range of doses and among patients given radiotherapy for cervical cancer. Dose–response relationships for thyroid cancer have been demonstrated following irradiation in childhood for various conditions and among atomic bomb survivors. Dose–response relationships for breast cancer have been demonstrated among atomic bomb survivors, women treated for acute post-partum mastitis and benign breast conditions and patients who received many chest fluoroscopies. A dose–response relationship was also demonstrated for the combined category of all cancers among the survivors of the atomic bombings.

The level of cancer risk after exposure to X-rays or $\gamma$-rays is modified by a number of factors, in addition to radiation dose, including the age at which exposure occurs, the length of time over which the radiation is received and the sex of the exposed person. The level of cancer risk also varies with time since exposure. The sensitivity
of tissues to the carcinogenic effects of ionizing radiation differs widely. Cancers that appear to be readily inducible by X- and γ-rays include leukaemia, breast cancer in women exposed before the menopause, cancer of the thyroid gland among people exposed during childhood and some gastrointestinal tumours, including those of the stomach and colon. Some tissues in which cancer is induced only rarely or at relatively high doses include bone, soft tissue, uterus, skin and rectum. A number of cancers, such as chronic lymphocytic leukaemia, have not been linked to exposure to X- or γ-rays.

While there is some variation in the level of risk for specific cancers seen in epidemiological studies of populations exposed to X- and γ-rays, the consistency of the association, the strength of the association and the dose–response relationships all provide strong evidence that X-rays and γ-rays cause cancer in humans.

5.3 Animal carcinogenicity data

X-Rays and γ-rays have been tested for carcinogenicity at various doses and under various conditions in mice, rats, rabbits, dogs and rhesus monkeys. They have also been tested by exposure of mice and dogs in utero and by parental exposure of mice.

In adult animals, the incidences of leukaemia and of a variety of neoplasms including mammary, lung and thyroid tumours were increased in a dose-dependent manner with both types of radiation. When sufficient data were available over a range of doses and dose rates, the dose–response relationship was generally consistent with a linear–quadratic model, while lowering the dose rate resulted in a diminution of the quadratic portion of the curve. The effects of fractionation of the dose were highly dependent on fractionation size. Most importantly, low dose fractions were equivalent to low dose rates with respect to carcinogenic effectiveness.

Prenatal exposure of mice to X-rays in two studies and to 60Co γ-rays in one study and of dogs to 60Co γ-rays at late fetal stages resulted in significant increases in the incidences of lung and liver tumours in mice and malignant lymphoma, haemangiosarcoma and mammary carcinoma in dogs. Exposure at early fetal stages, however, did not increase the incidence of tumours in the offspring of either species. Parental effects in mice appear to depend on the strain tested. Parental exposure of mice of four strains to X-rays resulted in increased incidences of lung tumours and leukaemia in the offspring; however, studies with two other strains of mice showed no increase in the incidence of neoplasms.

5.4 Other relevant data

Exposure to radiation may result in effects on tissues and organs that are known as deterministic effects, which are distinct from cancer and genetic effects, known as stochastic effects. Deterministic effects increase in both incidence and severity with increasing dose and are not recognized below a threshold dose. The dose-dependent
increase in severity and the fact that the damage must reach a critical or threshold level to be detected distinguish deterministic effects from stochastic effects, for which, by convention for radiation protection purposes, there is no threshold and which do not increase in severity with increasing dose.

Deterministic effects, in general, result from cell killing. In the case of rapidly proliferating tissues, such as the gastrointestinal and haematopoietic systems, the effects may be early, occurring within a matter of days to a few weeks after high doses at high dose rates. Doses that kill critical numbers of clonogenic or stem cells may result in loss of the integrity of tissues and death. The loss of cells may be severe but not lethal, and in both cases the damage to these and other proliferating cell systems is reflected in clinical syndromes that result from impairment of organ function. Depending on the rates of cell renewal, radiation-induced damage is expressed at different times. In humans, death from damage to the gut may occur within about 10 days, whereas death from damage to the pulmonary system may occur only after six months. The information about deterministic effects comes from studies of humans exposed accidentally, to the atomic bombs or to radiotherapy. Much of the understanding of the underlying mechanisms and kinetics comes from studies in experimental animals. The need to understand deterministic effects led to studies of cell kinetics and the development of methods of studying cell survival and repair and the recovery of stem cells \textit{in vivo} in the major tissues. Tissues affected early after exposure to radiation may also show late effects months or years after irradiation. Other tissues, such as those of the central nervous system and kidney, do not show effects until quite late after irradiation. Clinically, the former class of tissues is called ‘early responding’ and the latter, ‘late responding’.

The damage that appears late may result from lesions incurred at the time of exposure but which are not expressed for many months. If the cells are renewed slowly and die only when attempting mitosis, the timing of the critical damage reflects the cell renewal rate. The function of some cell populations is affected indirectly by damage to blood vessels and by the fibrosis that replaces damaged tissue.

The success of radiotherapy depends on the differential between the killing of cancer cells and of cells of normal tissues. Recovery of normal tissues depends on repair of sublethal damage and repopulation. Fractionation of the dose increases the probability of recovery of the normal tissue more than recovery of the cancer cells. The total dose, the dose per fraction and the interval between fractions influence the effect of fractionation. The probability of late effects is determined mainly by the dose per fraction. Lowering the dose rate also reduces the effect. The degree and time of expression of injury vary among tissues and organs, depending on the radiosensitivity of the stem cells, which varies by a factor of about 2, and cell renewal rates, which vary many-fold. Cell survival is influenced by many genes, especially those concerned with repair of sublethal damage and also by \textit{p53}, a tumour suppressor gene. Data on cell survival are frequently fitted by the so-called linear–quadratic model.
In the two large populations that received total-body irradiation—the atomic bomb survivors and patients receiving bone-marrow transplantation—the rates of non-cancer adverse effects in a number of organs, including the lens, increased at about 1 Sv.

Radiation-induced deterministic effects were first reported in the skin, and effects such as erythema are still used as an indicator of individual patients’ response to radiation.

When the radiation field is restricted, as in the case of radiotherapy, and the doses are fractionated, many tissues can maintain their integrity and function even when receiving total doses up to 20–30 Gy; however, the gonads, the lens of the eye and the developing brain are highly radiosensitive.

Cellular hypersensitivity to radiation is shown in several (primarily two) rare, heritable cancer-prone disorders of DNA processing, but evidence that such individuals are prone to radiogenic cancer is lacking. Some normal members of the general population, including persons heterozygous for the *ATM* gene, can be made more sensitive to cell killing and induction of chromosomal damage by exposure to radiation. There is no evidence that they are at increased risk for radiogenic cancer. Individuals heterozygous for tumour suppressor gene mutations would be expected to be hypersensitive to both radiogenic and spontaneous cancer, and this hypothesis is borne out by the results of several studies in humans and experimental animals.

The induction of chromosomal aberrations, particularly dicentrics, in human lymphocytes has been well established *in vitro* and has been used as a biological dosimeter in a variety of situations of exposure in which induction of aberrations has occurred. The persons exposed include inhabitants of areas with a high background level of natural radiation, survivors of the atomic bombings, workers involved in cleaning-up after the accident at the Chernobyl nuclear reactor in Chernobyl, Ukraine, and people accidentally exposed to a discarded source of $^{137}$Cs in Goiânia, Brazil. An increase in the number of minisatellite mutations has been reported in the children of parents living in a region heavily polluted by the Chernobyl accident. The lack of availability of appropriate local controls and possible confounding by heavy metal pollution indicate that this result should be treated with some caution.

Most of the data available on effects in mammals come from experiments with mice. The effects of ionizing radiation can be divided into two categories: those in germ cells, which become visible in the offspring of exposed mice, and those in somatic cells, determined directly in the exposed animals. X- and $\gamma$-radiation induce dominant lethal mutations, recessive autosomal mutations and sex-linked recessive lethal mutations. The germ cells have been most extensively studied, and a clear picture is available of the sensitivity of the germ cells of male mice during the various stages of development. The rate of germ-cell minisatellite mutations in mice was increased after exposure to ionizing radiation, with a doubling dose comparable to that for other genetic end-points. Recessive coat-colour mutations were seen in mice when embryos were treated with X-rays *in utero* two and nine days after conception.
Mutations were also induced by ionizing radiation in somatic cells of exposed mice, both in endogenous genes (Hprr and Aprt) of T lymphocytes isolated from the spleen and in transgenic mice carrying a marker gene in which mutation rates can be determined in all cells of the body, provided enough DNA can be isolated from the organ or cell type of interest. Ionizing radiation was reported not to induce loss of heterozygosity at the Aprt locus in mice.

A number of in-vivo/in-vitro systems have been developed in which mammary, thyroid and tracheal cells are isolated and examined after exposure of the whole animal or are exposed in vitro and introduced into the whole animal. Studies with these systems have shown that: (i) X- and γ-radiation initiate many more cells than tumours develop; (ii) strain differences in susceptibility for radiation-induced mammary cancers are related to the sensitivity of the cells more than to host factors; and (iii) the late changes in chromosomes and multiple mutations in the p53 tumour suppressor gene associated with the development of neoplasms suggest that genomic instability is an early event induced by radiation.

Chromosomal aberrations, gene mutations and reduced plating efficiency have been shown to occur in various systems many cell generations after exposure to radiation, indicating the induction of persistent genomic instability.

Ionizing radiation induces neoplastic transformation in vitro in mammalian cells, including human cells. While this indicates a potential for carcinogenicity, it is not clear to what extent these observations made in vitro can be extrapolated to the situation in vivo.

Ionizing radiation induces gene mutations in a wide variety of cellular systems. The predominant mutations are deletions resulting in gene inactivation. Chromosomal aberrations are induced in all eukaryotic systems that have been examined.

Although ionizing radiation can give rise to many different types of nucleotide damage in DNA through the active oxygen species that it generates, double-stranded DNA breaks and more complex lesions are believed to be largely responsible for its biological effects.

5.5 Evaluation

There is sufficient evidence in humans for the carcinogenicity of X-radiation and γ-radiation.

There is sufficient evidence in experimental animals for the carcinogenicity of X-radiation and γ-radiation.

Overall evaluation

X-radiation and γ-radiation are carcinogenic to humans (Group 1).