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ASSESSMENT OF IONIZING RADIATION RISK ON HUMAN HEALTH

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ABSTRACT

Whenever ionizing radiation falls on human body, it produces ionization and excitation in the tissues and impairs the normal function of the cells. Thus human body will be subjected to biological damage and severity of this damage depends upon various factors mainly, nature and energy of the radiation, total dose & dose rate, the extent and part of the body exposed, age of the person exposed to radiation, radiation sensitivity of the organ exposed. The energy transmitted by radiation may act directly causing ionization of the biological molecule or may act indirectly through the free radicals resulting from the ionization of the water molecules that surround the cell. Risk refers to the potential for a radiation hazard to cause harm. Irradiation can cause two classes of harmful; deterministic and stochastic. Deterministic effects of radiation are those whose severity is dependent on the dose of radiation received. These effects can be acute, occurring within hours or days, or delayed for months or years. Stochastic radiation effects are those whose probability of occurring is related to dose, but whose severity when they do occur is not dependent on the initial dose of radiation. As quantifying radiation-induced cancer risks with radiological examinations is not an easy task, the ICRP proposed three different risk categories depending on effective dose to the subjects, and added a corresponding classification in terms of benefits.

KEYWORDS: Ionizing radiation, Free radicals, Deterministic effects, Stochastic effects.

INTRODUCTION

Ionizing radiation is produced by unstable atoms which differ from stable atoms by having an excess of energy, mass or both. Unstable atoms are radioactive. In order to reach stability, these atoms give off, or emit, the excess energy or mass. These emissions are called radiation. When the radiation interacts with other atoms, it ionizes the atoms altering their chemical properties.[1] Radiation may be electromagnetic or particulate. Light, gamma radiation and X-rays are examples of electromagnetic radiation while beta and alpha radiation are examples of particulate radiation. There is also natural background radiation exposure. It comes from cosmic rays and from radioactive materials in earth and in living things.

Ionizing radiation comprises four basic types.[2]

- Gamma rays and x-rays
- Beta particles
- Alpha particles
- Neutrons

These have different physical characteristics and biological effectiveness in causing tissue damage (table 1).

Table (1): Summary of types of ionizing radiation.[3]

Radiation	Range in air	Range in tissue	Hazard
Alpha	Few centimeters	50 microns	Internal
Beta	Few meters	Few mm	External and internal
Gamma	Many meters	Many cm	Mainly external
X-ray	Many meters	Many cm	Mainly external
Neutron	Many meters	Many cm	Mainly external

Radiation Quantities

Becquerel is a measure of radioactivity and contamination by radioactive material (1 Bq = 1 disintegration per second). The **absorbed dose** of radiation (the amount of energy absorbed by per unit mass of tissue) is measured in gray (Gy), where 1 Gy = 1 joule/kg of tissue.

Different types of radiation have different effects on human tissue (gray for gray, alpha particles and neutrons

are more damaging than beta particles, gamma rays or X-rays in terms of the risks of cancer or of heritable genetic defects), so the absorbed dose in tissue is multiplied by a radiation weighting factor to account for this. This gives the **equivalent dose** (to an organ or tissue), measured in Sievert (Sv). For X-rays, gamma rays, and beta particles, the weighting factor = 1.

The amount of damage caused by exposure to radiation depends on the efficiency with which it transfers energy into body tissues. Radiation comprised of particles with relatively high mass delivers a greater proportion of their energy into tissues than do electromagnetic radiation, such as x-rays and gamma-rays, which may pass through the body. Doses of different types of radiation are, therefore, converted into 'equivalent doses' using a weighting factor for each kind of radiation.[4]

Linear energy transfer (LET) is the amount of energy that an ionizing particle transfers to the material traversed per unit distance. It describes the action of radiation into matter. It depends on the nature of the radiation as well as on the material traversed.[5]

Tissues differ in their susceptibility to radiation for a given absorbed dose. Some organs are more radiosensitive than others (e.g. bone marrow is more sensitive than thyroid), and exposures are rarely uniform. Weighting the equivalent doses received by different organs and tissues during an exposure to allow for each organ's radio-sensitivity, and then summing the results, gives the **effective dose.** The "effective dose" is calculated by multiplying the absorbed dose by a tissue weighting factor which represents the sensitivity of each tissue to radiation.[6]

Radiation Exposure

Regardless of where or how an incident involving radiation happens, three types of radiation-induced injury can occur: external irradiation, contamination with radioactive materials, and incorporation of radioactive material into body cells, tissues, or organs.

- ***External irradiation*** is exposure to penetrating radiation from a radiation source. People exposed to a source of radiation can suffer radiation illness if their dose is high enough, but they do not become radioactive. For example, an x-ray machine is a source of radiation exposure. A person does not become radioactive or pose a risk to others following a chest x-ray. Irradiation occurs when all or part of the body is exposed to radiation from an unshielded source. External irradiation does not make a person radioactive.[7]

- ***Radioactive contamination*** occurs when material that contains radioactive atoms is deposited on skin, clothing, or any place where it is not desired. If is important to remember that radiation does not spread or get "on" or "in" people; rather it is radioactive contamination that can spread. A person contaminated with radioactive materials will be irradiated until the source of radiation (the radioactive material) is removed.[8]
  - A person is externally contaminated if radioactive material is on skin or clothing.
  - A person is internally contaminated if radioactive material is breathed in, swallowed, or absorbed through wounds.
  - The environment is contaminated if radioactive material is spread about or uncontained.

- ***Incorporation*** of radioactive material refers to the uptake of radioactive materials by body cells, tissues, and target organs such as bone, liver, thyroid, or kidney. In general, radioactive materials are distributed throughout the body based upon their chemical properties. Incorporation cannot occur unless contamination has occurred. These three types of exposures can happen in combination and can be complicated by physical injury or illness. In such a case, serious medical problems always have priority over concerns about radiation, such as radiation monitoring, contamination control, and decontamination.[9]

Overview of Radiation Injury

1. Background

Risk refers to the potential for a harmful event, a hazard, to have an adverse impact on health. Exposure to radiation poses a health hazard, but the amount of risk to a person depends on many individual and environmental factors.

In general an assessment of the risk posed by radiation exposure should comprise the following elements.[10]

1. ***Identify the hazard:*** the level of exposure and/or contamination which has occurred.
2. ***Identify the risk*:** estimate the potential health impacts of the amount of exposure and/or contamination which has occurred.
3. ***Communicate the risk:*** effectively communicate the potential health impacts of the exposure and/or contamination which have occurred.
4. ***Manage the risk:*** where possible reduce the impacts of the exposure and/or contamination which have occurred.

Identifying the hazard will generally involve the expert advice of a radiation physicist or other personnel able to measure and characterize the dose of radiation released from a source. Translating this into risk requires an assessment of individual factors which influence the probability a person will suffer injury from a given exposure. These include the timing of exposure, whether a whole or partial body dose of radiation was received, the age of the person and underlying physical illness. Risk communication is complex because there is no simple relationship between the perception of harm and the objective measurement of a hazard. It is, however, essential to communicate risk if measures to mitigate

harm like decontamination, administration of medical countermeasures or evacuation are to operate effectively.[11]

2. Identification of hazard

The hazard posed by irradiation is determined by several interacting factors:

a. Absorbed dose

Radiation can be absorbed by a person if they are exposed to a source without adequate protection, or if their body becomes contaminated with radioactive material. Absorbed dose is measured in Grays (Gy), where one Gray corresponds to one Joule of energy absorbed per kilo of tissue. One Gray is a large unit of radiation which may be associated with signs of acute radiation syndrome (ARS).

b. Type of radiation absorbed

The amount of damage caused by exposure to radiation depends on the efficiency with which it transfers energy into body tissues (table 2). Radiation comprised of particles with relatively high mass delivers a greater proportion of their energy into tissues than do electromagnetic radiation, such as x-rays and gamma-rays, which may pass through the body. Doses of different types of radiation are, therefore, converted into 'equivalent doses' using a weighting factor for each kind of radiation.[12]

Table (2): Weighting factors for ionizing radiation.

Radiation	Energy transfer	Weighting factor
Alpha particle	High	20
Neutron	High	5-20
Beta particle, electrons	Low	1
Gamma ray, X-ray	Low	1

Equivalent doses are measured in Sieverts (Sv), which is equal to the absorbed dose in Grays multiplied by the weighting factor. A dose of 1/100 Gray delivered entirely as alpha particles would, for example, equal 20/100 Sieverts.

c. Full or partial body irradiation

Only rarely will a person will be exposed to the same dose of radiation equally across their body. In general, accidental radiation exposures cause a person may receive the majority of a radiation dose to only part of their body. This may occur because of the orientation of the person in relation to the source, or because of partial shielding. Sometimes only one part of the body is sufficiently close to a radioactive source to be injured, as with a small radioactive fragment contaminating a wound or with inadvertent handling of an intact source injuring the fingers or hand. Alternately, radioactive material may be distributed to a particular part of the body if it is, for example, inhaled into the lungs or localizes to bone. In the case of partial body exposure the relevant dose is that absorbed by exposed tissue, not the dose averaged across the whole body.[13]

d. Tissue susceptibility

Tissues differ in their susceptibility to radiation and a given absorbed. The "effective dose" is calculated by multiplying the absorbed dose by a tissue weighting which represents the sensitivity of each tissue to radiation as shown in table 3.[14]

Table (3): Tissue weighting factors by organ.

Organ	Tissue weighting factor
Gonads	0.2
Colon	0.12
Bone marrow (red)	0.12
Lung	0.12
Stomach	0.12
Bladder	0.05
Chest	0.05
Liver	0.05
Thyroid gland	0.05
esophagus	0.05
Skin	0.01
Bone surface	0.01
Adrenals, brain, small intestine, kidney, muscle, pancreas, spleen, thymus, uterus	The weighting factor 0.05 is applied to the average dose of these organs

e. Rate at which dose is absorbed

The body has some capacity to repair the cellular and genetic damage caused by radiation exposure. This means that the amount of injury evident from radiation exposure will be less if the same dose is received

gradually over a period which allows some healing to occur rather than the dose being received rapidly.[15]

f. Presence or absence of contamination

A person may be irradiated by proximity to radioactive material with which they have no contact. In this case the person will cease to absorb radiation when they leave the vicinity of the radioactive material. If radioactive material enters the environment, however, this may contaminate the surface of a person's body (clothes, hair, and skin) or be absorbed into the body through ingestion, dermal absorption or inhalation. This may be the situation in an accidental or deliberate release of radioactive material as liquid, explosive debris or smoke. In this case irradiation will continue either until the radioactive source is removed from the person's body through decontamination and excretion, or the source decays. Contamination is, therefore, a hazard for ongoing exposure to radiation. If the type of radiation source, the location of a person while exposed, and the environment in which irradiation occurred are known then the dose of radiation a person is exposed to can be accurately reconstructed after the event. This is, however, only likely in controlled environments such as a nuclear reactor or laboratory and where small numbers of people are involved. If a deliberate release of radioactive material occurs, or large numbers of people are exposed to radiation, then reconstructing the dose received by each based on physics may be impossible. In this case the dose of radiation received may have to be estimated from the measurable effect of radiation after exposure has occurred.[16]

3. Assessment of risk

Risk refers to the potential for a radiation hazard to cause harm. Irradiation can cause two classes of harmful; deterministic and stochastic. Deterministic effects of radiation are those whose severity is dependent on the dose of radiation received. These effects can be acute, occurring within hours or days, or delayed for months or years. Stochastic radiation effects are those whose probability of occurring is related to dose, but whose severity when they do occur is not dependent on the initial dose of radiation. Cancer is highly unlikely to result from exposure to low-dose radiation, for example, but is a severe disease whenever it does occur. The main stochastic effect of concern is carcinogenesis.

The likelihood of a person suffering stochastic or deterministic effects of radiation exposure is modified by individual risk factors, including age, sex, exposure to other carcinogens, susceptibility to DNA damage, and nutritional and hormonal status. Because the impact of these factors has not been quantified, absolute risk cannot be assessed with certainty for most radiation exposures.[17]

4. Communication of risk

In most radiological incidents the majority of people are likely to be exposed to doses which do not cause immediate and severe physical effects. Although moderate and low doses of radiation can cause illness in some people, there are limited options for intervening to reduce this risk once irradiation has occurred. The main objective in most people is, therefore, to manage the psychological consequences of this risk and effective communication is a key aspect of this. Providing information about the magnitude and severity of health risks will help reduce distress and the inappropriate use of medical interventions which are potentially harmful. If mass casualties occur then managing the anxiety of people is particularly important to allow triage for appropriate management and prevent medical facilities being overwhelmed.[18]

The general objectives of risk communication are:

- To engender understanding of the probability and nature of adverse health effects faced by the person.
- To produce an understanding of the limitations of medical intervention in reducing this risk.
- To allow decisions to be made about the appropriate management of a person's risk.
- To reduce psychological distress by engendering trust in the validity of the risk assessment.

5. Assessment of radiation dose

(a) Physical measurement: Physical dosimetry can provide an estimate of individual dose, using a whole-body radiation dosimeter. Few whole-body dosimeters are available for rapid assessment of dose. Reconstruction of dose can be made with considerable sensitivity, using environmental measurements combined with time-integrated activity (19, 20). However, this is a time-consuming process that is impractical in an emergency situation, particularly when there are many potentially exposed persons. Estimation of the internal dose from the deposition of radioactive materials, such as alpha emitters (e.g., plutonium, americium, californium) and beta-gamma emitters (e.g., cesium, cobalt and iodine) into the lungs, gastrointestinal tract, and other tissues, requires detection with special instrumentation (such as ion chambers and spectroscopes). In this case, measurements are made on body fluids (blood, urine and saliva), nasal swipes, fecal samples, and/or expired air.[21]

(b) Biological and clinical markers: Currently, the three most clinically useful markers are the time to onset of emesis, lymphocyte depletion kinetics, and chromosomal aberrations. Monitoring the decrease in absolute lymphocyte count has been found to be the most practical method to assess the radiation dose within hours or days following a radiation exposure.[22] The time to emesis and lymphocyte depletion kinetics are dose-related and are amenable to quantitative analysis with respect to dose.[23] The rate of decline and nadir of the absolute lymphocyte count over the initial 12 h to 7 days after exposure is a function of cumulative dose. Lymphocyte depletion kinetics predict dose for a photon-equivalent dose range between 1 and 10 Gy with an

exposure resolution of approximately 2 Gy.[22,24] The three elements (i.e., time to onset of vomiting, lymphocyte depletion kinetics, and chromosome aberrations) should be sought for the most accurate assignment of prognosis and selection of therapy. As a practical matter, however, only the time of onset of vomiting and lymphocyte depletion may be available within the first 24 h following exposure (table 4, 5).

(c) Chromosomal changes: The frequency of chromosomal aberrations (e.g., dicentrics, chromosomal rings) in lymphocytes are correlated to radiation dose (25). A peripheral blood sample should be obtained at 24 h after exposure (or later) in accordance with the policies of a qualified radiation cytogenetic biodosimetry laboratory. Because of incubation times, results will not be available for 48–72 h after the sample has been submitted for analysis.[26]

Initial laboratory testing according to European consensus, within the first 48h are.[27]

- Repeated blood cell counts (lymphocites, granulocytes and platelets) if possible every 4–8 h for the first 24 h, then every 12–24 h (+reticulocytes).
- Chromosome aberration analysis on blood lymphocytes (biodosimetry).
- Red cell group typing.
- Store serum and cells for DNA for future analyses including human leukocytic antigen (HLA) typing upon request from clinical teams.
- Standard biochemical tests.

If there is suspicion of a neutron exposure, a blood sample of 20ml should be taken to measure the content of radioactive sodium.

- Urine and feces if radionuclide contamination is suspected.

The time of CBC collection must be carefully noted, because of important time-related changes in the lymphocyte count. Additional monitoring should be based on the whole-body dose, as the onset of neutropenia and its severity are dose dependent. Patients with low exposures may need a weekly or twice-weekly CBC for 4–6 weeks to document their WBC nadir and subsequent recovery. The various cytogenetics methods, including dicentric assay (DA) and fluorescence in situ hybridization (FISH) assay, offer high-accuracy exposure dose determination, yet require a long sample-processing time.

Table (4): Selected Methods for Estimating Radiation Dose.[28]

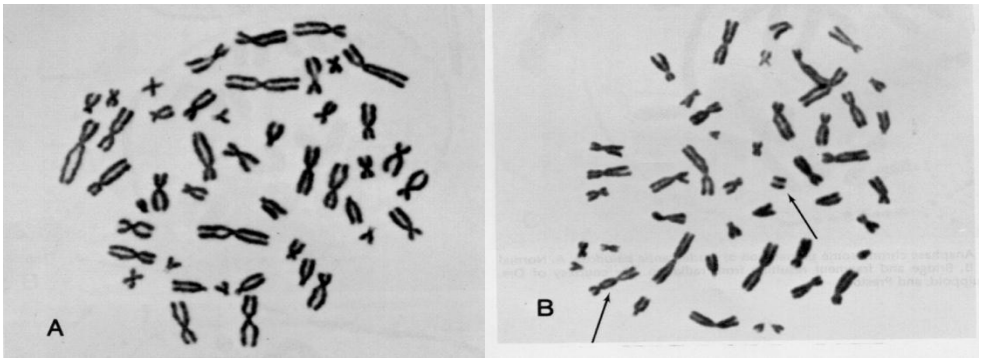
Dosimetry	Method	Utility
Biological	-Whole-body counting	Not generally available, impractical
	-Chromosomal aberrations (dicentrics, ring forms)	The "gold standard." Typically requires 4–5 days processing time
	-Lymphocyte depletion kinetics	Inexpensive but requires 2–4 days for decline at doses of 4–6 Gy and 4–6 days at 2–4 Gy
	Interphase aberrations (PCC, okadaic acid/kinase)	Under development
	Electron spin resonance (dental enamel)	Permanent record of exposure but requires removal of tooth
Clinical	Symptoms and signs	Practical but loses sensitivity at low doses.

Table (5): Whole-Body Dose Estimates Based on Absolute Lymphocyte Count.[29,30]

Absolute Lymphocyte Count, per mm3 (8–12 h postexposure)*	Absorbed Dose, Gy
1700–2500	1–5
1200–1700	5–9
<1000	>10

Dicentric Assay

Chromosomal dicentrics and ring forms are formed during cell division in cells affected by radiation. These can be identified during metaphase. The frequency of formation corresponds to the absorbed dose of radiation.



A. Undamaged cell **B. Damaged cell**

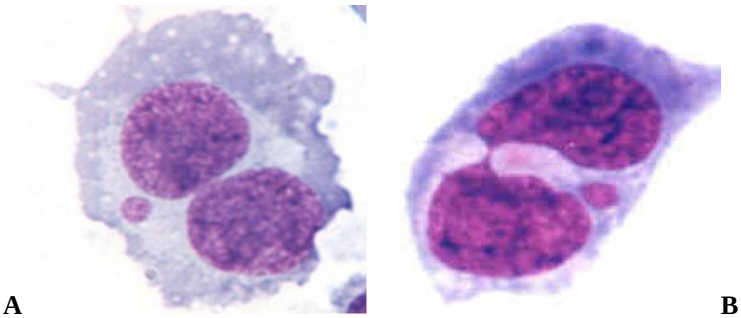
Figure 1: Dicentric and fragment.

This assay is the most specific and sensitive method for determining absorbed doses from recent (from within days up to six months) exposures to ionizing radiation. Dicentric and ring chromosomes are identified from slide preparations of activated lymphocytes arrested in metaphase as shown in figure 1.

Cytokinesis block micronucleus (CBMN) assay

Micronuclei are formed when acentric chromosomal fragments caused by exposure to ionizing radiation do not integrate into the nuclei of daughter cells during ex vivo division in cultured lymphocytes from peripheral blood. In this assay it is also possible to measure nucleoplasmic bridges that are formed from dicentric chromosomes induced by ionizing radiation (fig.2).

The sensitivity of this technique is limited to thresholds of 0.3 Gy, due to the presence of background micronuclei from other environmental causes. This is still sufficiently sensitive to identify persons needing medical intervention from those requiring continued surveillance.[31]



A **B**

Figure 2 (A): Bi-nucleated lymphocyte containing a micronucleus (MN); (B) Bi-nucleated cell containing a nucleoplasmic bridge (NPB) and a micronucleus (MN).

Fluorescence in situ hybridisation (FISH) assay

Stable chromosomal translocations caused by radiation can persist over decades, unlike dicentrics. These can be identified using fluorescent microscopy using chromosome-specific fluorescently-labelled DNA probes. This research tool is limited by availability, turnaround time, and cost. Additionally, translocations may occur due to other environmental factors, limiting accuracy without pre-event samples.[31]

6. Risk assessment framework for human exposure to ionizing radiation

Quantifying radiation-induced cancer risks with radiological examinations is not an easy task.[32] Here, effective dose has been particularly useful, as many countries use E in diagnostic reference levels.

In the context of biomedical research, ICRP 62.[33] focused on this topic and reviewed the risks and benefits of research involving exposure of humans to radiation, aiming to assist medical ethics committees in their evaluation of research proposals. Following the WHO, the ICRP proposed three different risk categories depending on effective dose to the subjects, and added a corresponding classification in terms of benefits.

ICRP103.[34] includes the exposure of volunteers in biomedical research under the category of medical exposure. Therefore, the present report follows ICRP 62 and ICRP 103 in using the same three risk categories providing a basis for a risk assessment framework for human exposure to ionizing radiation, both for clinical and research purposes. For additional guidance, categories II and III have been subdivided further in two subcategories.

Table (6): Effective dose with corresponding risk category and associated level of benefit.

Effective dose (mSv)[1)]	Risk Category[2)]	Level of Benefit
<0.1	I (10^{-6} or less)	Acquisition of knowledge
0.1 – 1	IIa (~10^{-5})	Acquisition of knowledge, resulting in health benefit
1- 10	IIb (~10^{-4})	Acquisition of knowledge, directly aimed at prevention or cure of disease
10 - 20	IIIa ($5{\cdot}10^{-3}$)	Acquisition of knowledge, directly aimed at prevention or cure of serious disease
>20	IIIb (>$5{\cdot}10^{-3}$)	Acquisition of knowledge, directly aimed at saving lives or mitigation of serious diseases

Notes

1) Effective doses apply to healthy adults. For children, elderly adults and patients with a short life expectancy, these numbers need to be adjusted.

2) The values between brackets represent the sum of the total probability of fatal cancers and the total weighted probability of non-fatal cancers.[35]

In Table 6 only a classification according to effective dose is given. It should be noted that in article 77 of the

Dutch legislation on radiation protection.[36] an effective dose of 20 mSv per year is in the same category as a lens equivalent dose of 150 mSv/year, a skin dose of 500 mSv per year (averaged per exposed cm^2) and effective doses to hand, feet and ankles of 500 mSv per year.

1. Risk categories for younger and elderly subjects

The classification in Table 6 relates to adults in the age range from 18 to 50 years. It is common practice to adjust the dose levels for both younger and older subjects. For example, if the effective dose for a certain study is 6 mSv, the applicable risk category for an adult is IIb. Clearly, in case of involvement of children, extra care should be taken. This can be accomplished by multiplying the estimated effective dose with a factor of 2 to 5 (before applying Table 6), depending on the actual age of the child, resulting in a higher risk category. In contrast, for elderly volunteers the estimated effective dose may be divided by a factor of 5 to 10, resulting in a lower category. Similarly, for patients with a short life expectancy (<10 years), estimated effective dose values may be divided by a factor of 100. Obviously, these global guidelines need to be fine-tuned for each protocol.

In addition, it should be noted that in patients who receive radiotherapy whole body exposure will be in the range of 500–700 mSv (i.e. 0.1% of the therapeutic dose), whilst the dose near the target volume (~10cm) can even be a factor 10 higher. For those patients, the additional risk from exposure to radiation as part of a research procedure will usually be negligible.

2. Interpreting risk categories (http://www.world-nuclear.org).

Category I

This is the lowest risk category with a statistical probability of less than one in a million to develop radiation-induced cancer, to be compared with the natural incidence of cancer, which is about 30%. The dose in this category is less than 0.1 mSv. Each member of the public in the Netherlands will receive this dose within a few weeks, just from natural background radiation. In addition, this dose is equivalent to that received during a transatlantic flight. Only a minor level of benefit is sufficient for approval of research in this category, including investigations that aim to increase knowledge.

- **Category IIa**

This category represents a very low level of risk. The range of 0.1 to 1 mSv corresponds with a maximum risk of one in hundred thousand and is less than the annual background dose. To justify these risks a research proposal should at least lead to potential health benefit for future patients. Examples are repeated mammography procedures or X-ray examinations of the thorax to gather data for prospective cohort studies.

- **Category IIb**

This category represents a low level of risk. The range of 1 to 10 mSv corresponds with a maximum risk of one in ten thousand, and is of the same order of magnitude as the annual natural background radiation in some parts of the world. In addition, it is not an uncommon for radiological workers to receive this dose on an annual basis.

To justify these risks a moderate benefit is required, which will be more directly aimed at the diagnosis, cure or prevention of diseases in the future. Examples are studies that use investigational or routine CT/PET/SPECT scans and those that are primarily intended for the development of novel imaging procedures, including the evaluation of new radiopharmaceuticals. Other examples are (mechanistic) studies in healthy controls. In the latter case potential benefits for future patients should be clearly indicated.

- **Category IIIa**

Category IIIa represents a moderate level of risk. The range of 10-20 mSv corresponds with a maximum risk of one in five thousand. To place this level into context, the maximum allowed dose for radiological workers is 20 mSv per year.

To justify research in this category, its benefit has to be related directly to prevention or cure of serious diseases. Examples are repeat CT/PET/SPECT scans and scans using tracers labeled with long lived radionuclides, such as ^{89}Zr labelled monoclonal antibodies.

- **Category IIIb**

Category IIIb exceeds the maximum allowed dose level that radiological workers may receive annually. To justify research in this category, the benefit will have to be directly related to saving lives or the mitigation of serious disease. For this category benefits also have to be weighed against possible deterministic effects that may be induced. These effects should be communicated explicitly to the subject, along with the stochastic effects. Examples are studies in cancer patients who receive radiotherapy, such as repetitive PET/CT scans during radiation treatment, and extensive PET/CT response monitoring scans (with or without ^{89}Zr labeled monoclonal antibodies) during experimental chemotherapy in terminal cancer patients who themselves may or may not benefit from the treatment.

Radiation Health Effects

Mechanism of action

Biological effects of ionizing radiation are a consequence of the ionization of atoms of biomolecules, which might cause chemical changes and alter or eradicate its functions. The energy transmitted by radiation may act directly causing ionization of the biological molecule or may act indirectly through the free radicals resulting from the ionization of the water molecules that surround the cell.

Due to ionization, proteins can lose the functionality of its amino groups and modify its behavior, thus increasing its chemical responsiveness; enzymes would be deactivated; lipids will suffer peroxidation; carbohydrates will dissociate; and nucleic acids chains will experiment ruptures and modifications of structure. But from all possible combined alterations, DNA is the primary target for radiation because it contain genes/chromosomes that hold information for cell functioning and reproduction that are critical to cell survival. As a result of radiolytic decomposition of water by ionization and excitation, hydrogen, and hydroxyl radicals could combine to form toxic substances as hydrogen peroxide (H2O2), which can also contribute to the destruction of cells.

The deposition of energy by ionizing radiation is a random process. Even at very low doses there is some probability that enough energy may be deposited into a critical volume within a cell to result in cellular changes or cell death. But thanks to the remarkable ability of cells to repair damage, enzymatic, and repair mechanisms would lead in many instances to the correct DNA repair and the cell will survive without any modification to its function or genetic structure. If the repair of DNA damage is incomplete, signaling pathways leading to cell death through apoptosis, terminal differentiation, and senescence are activated. Physical processes of energy absorption and induced ionization and excitation, as well as biochemical processes triggered by the living organism response, would occur within fraction of seconds.[37]

Repair of cellular damage, such as DNA repair, may from minutes to hours after exposure depending on the type of damage.

Another possible result is mutation. The cell will survive but with modification in the DNA sequence of the cell's genome. Mutated cells are capable of reproduction and thus perpetuate the mutation. If the mutated cell is a somatic cell, mutation could lead to a malignant tumor. If the mutated cell is a germ cell, it may cause a hereditary effect. These are stochastic effects and their consequences (cancer or hereditary effects) may be statistically observed long after exposure. If damage cannot be repaired cell death occurs. Cell death means the loss of a specific function for differentiated cells which do not replicate, such as nervous cells, muscle cells, or secretory cells. For proliferating cells, such as primary blood-forming (hematopoietic) cells or cell growing in a culture media (stem cells), cell death means the permanent loss of their proliferating capacity or the loss of their reproductive integrity. If many cells die, there will be tissue and organ damages which may cause a rapid, whole body response. Figure 3 shows both paths by which radiation may affect the whole body system.[37]

Cellular sensitivity to radiation has been better studied in proliferating cells. For proliferating cells, radiosensitivity depends on a number of factors of which the most important are cell proliferation capacity; cell differentiation degree; phase of the cell cycle at which the irradiation occurs; radiation quality; dose rate; and dose fractioning. In general, cellular sensitivity to radiation is directly proportional to the rate of cell division and inversely proportional to the degree of cell differentiation. This explains why tissues with a high turnover rate are more radiosensitive than those that do not have a continuously turnover. Related to the cell cycle, cells are more sensitive to radiation during mitosis (cell division) than through the preceding substages when the cells are not dividing and the mechanisms of repair. Some cells, like nerve cells, do not undergo much division. Most cells have a moderate cell rate division. For human organism, it might be considered that lymphocytes, stem cells in the bone marrow, cells of the lens of the eye, and epithelial cells of gastrointestinal tract are the most radiosensitive; surface of the stomach walls, esophagus, mouth, and skin are moderate radiosensitive; while muscle cells, bone cells and nerve cells are low radiosensitive. Ionizing radiation is more effective at producing biological damage when its LET (linear energy transfer) is high, the dose rate is high and the period of time between consecutive exposures is short.[38]

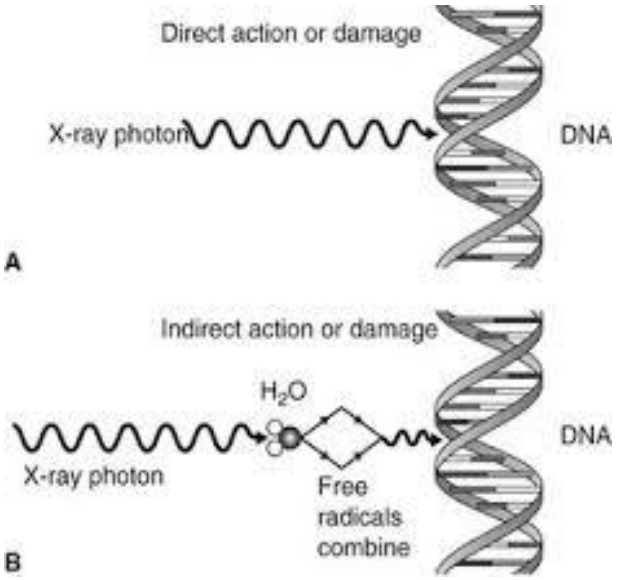


Figure (3): Mechanism of damage.

Radiobiological Effects

The harmful effects of the radiation fall into two categories, non- stochastic & stochastic effects as illustrated in figure 4.[39]

a) Non-Stochastic (deterministic) Effects

These effects are deterministic in nature and do not occur below a particular threshold radiation dose. Severity of these effects increases with increase in dose received. Now the term of non-stochastic effects has been replaced by 'deterministic effects'. Skin erythema, desquamation, necrosis, vomiting, hemorrhage and even death are some of the examples of non-stochastic effects.

b) Stochastic Effects

These effects do not have any threshold dose and are probabilistic in nature. Incidence of these effects increases with the dose received. Stochastic effects occur due to small exposure received over long period that may cause cancer (e.g. Leukemia, lymphoma, etc) and genetic effects by changing the coded genetic information which causes various deformations (e.g mental retardation, death of the offspring or many other damages).

The radiobiological effects may be further classified into two classes, namely somatic effects and genetic effects. The somatic effects arise from damage to cells in a particular irradiated tissue and affect the irradiated person only. The genetic effects are due to damage to germ cells which may manifest in the progeny of the irradiated person.

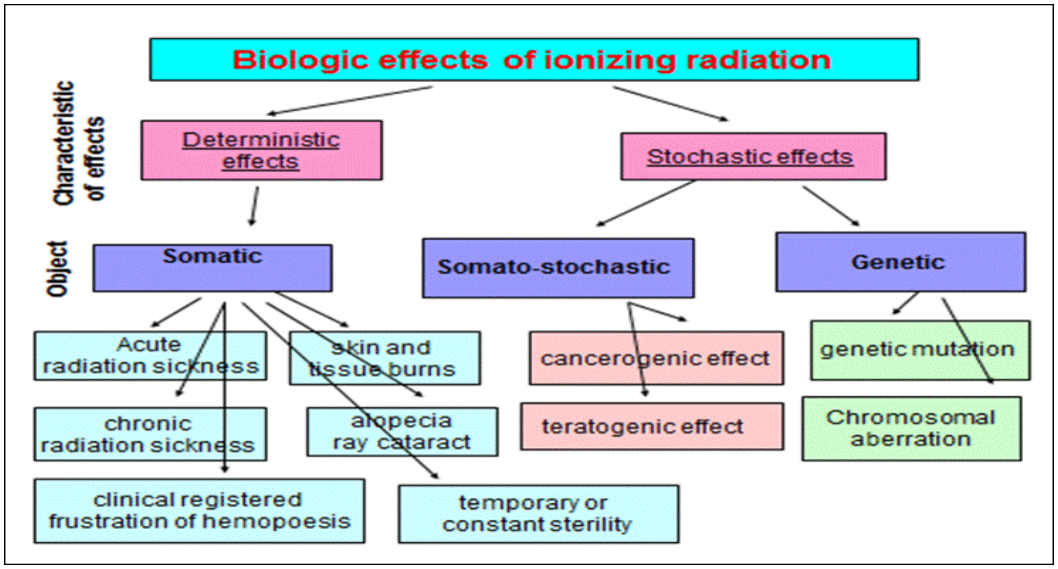


Figure (4): Biological effects of ionizing radiation.

Deterministic Effects

Deterministic effects are dose-related, acute health effects caused by exposure to high levels of radiation that cause large numbers of cells to die or lose their ability to replicate. Organs containing these cells then fail to function correctly. Such effects include nausea (radiation syndrome), reddening of the skin, cataracts, sterility and bone marrow failure. Each effect becomes apparent only above a threshold level and the severity of the effect depends on the level of exposure above its threshold. Below the threshold, the body can cope with the level of cell death by repair and replacement, when no explicit damage is seen (table 7).

Extreme doses of radiation to the whole body (around 10 sievert and above), received in a short period, cause so much damage to internal organs and tissues of the body that vital systems cease to function and death may result within days or weeks. Very high doses (between about 1 sievert and 10 sievert), received in a short period, kill large numbers of cells, which can impair the function of vital organs and systems. Acute health effects, such as nausea, vomiting, skin and deep tissue burns, and impairment of the body's ability to fight infection may result within hours, days or weeks. The extent of the damage increases with dose. However, 'deterministic' effects such as these are not observed at doses below certain thresholds. By limiting doses to levels below the thresholds, deterministic effects can be prevented entirely.

Doses below the thresholds for deterministic effects may cause cellular damage, but this does not necessarily lead to harm to the individual: the effects are probabilistic (occurring by chance) or 'stochastic' in nature.[39]

Table (7): Biological effects of acute total body irradiation.

Amount of Exposure	Effect
50 mSv	No detectable injury or symptoms
1 Sv	May cause nausea and vomiting for 1-2 days and temporary drop in production of new blood cells
3.5 Sv	Nausea and vomiting initially, followed by a period of apparent wellness. At 3-4 weeks, there is a potential for deficiency of white blood cells and platelets. Medical care is required.
Higher levels of exposure can be fatal. Medical care is required.	

Examples of deterministic health effects

1. Acute radiation syndrome
2. Chronic radiation syndrome
3. Teratogenesis
4. Late Noncancerous Effects:
5. Impaired Fertility and Temporary or Permanent Sterility
6. Loss of Pregnancy
7. Cataract

Stochastic Effects

Stochastic effects are those that occur by chance and consist primarily of cancer and genetic effects. Stochastic effects often show up years after exposure. As the dose to an individual increases, the probability that cancer or a genetic effect to occur also increases. However, at no time, even for high doses, it is certain that cancer or genetic damage will result. Similarly, for stochastic effects, there is no threshold dose below which it is relatively certain that an adverse effect cannot occur. In addition, because stochastic effects can occur in individuals that have not been exposed to radiation above background levels, it can never be determined for certain that an occurrence of cancer or genetic damage was due to a specific exposure.

For **stochastic radiation effects,** the risk of damage increases with the received dose. Especially important radiation health consequences are several types of cancer. No threshold for the risk of a health effect is known; therefore the **LNT-model (linear-no-threshold)** is the scientific model in use. Although much is known about the health effects after exposure to radiation at the 100 mGy–1 Gy dose range and high dose rates, the effects of **low-dose radiation** still leave many open questions. Debate continues about how to extrapolate radiation risks at low doses, the biological effectiveness of low-dose radiation, and the effects of dose rate and external versus internal exposure.[40]

Radiation-induced hereditary effects have not been observed in human populations, yet they have been demonstrated in animals. If the germ cells that are present in the ovaries and testes and are responsible for reproduction were modified by radiation, hereditary effects could occur in the progeny of the individual. Exposure of the embryo or fetus to ionizing radiation could increase the risk of leukemia in infants and, during certain periods in early pregnancy, may lead to mental retardation and congenital malformations if the amount of radiation is sufficiently high.[41]

1. Somato-stochastic effect

1.1 Carcinogenic effect

The mechanisms by which radiation may produce carcinogenic changes are postulated to include the induction of: (1) mutations, including alterations in the structure of single genes or chromosomes; (2) changes in gene expression, without mutations; and (3) oncogenic viruses, which, in turn, may cause neoplasia. Although controversy persists as to the relative importance of these hypothetical mechanisms in the induction of carcinogenesis, they are not mutually exclusive, since different mechanisms may be involved at successive stages in carcinogenesis.

Five cancers are presently prescribed in relation to ionizing radiation: leukemia (other than chronic lymphatic leukemia), and cancers of the bone, female breast, testis, and thyroid. The assessment of risks in relation to these tumors is technically complicated, as the doubling dose depends on multiple factors.

The five qualifying cancers were identified by the National Radiological Protection Board (NRPB) as ones which potentially might arise from occupational exposures during the course of ordinary employment and in the absence of an accidental over-exposure event.[42]

***The Doubling Dose Method*[43]**

The doubling dose method enables expressing of the expected increase in disease frequency per unit dose of radiation in terms of the baseline frequency of the disease class. The doubling dose (DD) is the amount of radiation required to produce in a generation as many mutations as those that arise spontaneously. Ideally, it is estimated as a ratio of the average rates of spontaneous and induced mutations in a given set of genes:

$$DD = \text{average spontaneous mutation rate/average induced mutation rate.}$$

The reciprocal of the DD (*i.e.*, 1/DD) is the relative mutation risk (RMR) per unit dose. Since RMR is the reciprocal of DD, the smaller the DD, the higher is the RMR and *vice versa*. With the doubling dose method, until recently, risk was estimated as a product of two quantities namely, the baseline disease frequency, *P*, and 1/DD:

$$\text{Risk per unit dose} = P \times (1/DD).$$

Table (8): Minimum Doubling Doses.[44]

Cancer	Minimum doubling dose estimated to double a person's risk of cancer (Sv)
Leukaemia	0.23
Bone	0.56
Female breast	0.74
Testis	0.81
Thyroid	0.51

1.2 Teratogenic effect

Prenatal radiation exposure can occur when the mother's abdomen is exposed to radiation from outside her body. Pregnant women may accidentally swallow or breathe in radioactive materials that have the ability to absorb into her bloodstream and the potential to cause prenatal radiation exposure. This occurs as the radioactive materials are able to cross the maternal blood and enter the fetal blood, or may pass through the umbilical cord exposing the fetus to radiation. The possibility of severe health effects depends on the gestational age of the neonate at the time of exposure as well as the amount of radiation it is exposed to. The most sensitive stage of pregnancy to radiation is during their early development between weeks 2-15 of gestation (the first trimester). Health consequences that may develop, even at radiation doses too low to make the mother ill include stunted growth, deformities, abnormal brain function or cancer that may develop later on in the child's life. Due to the fact that the fetus is protected by the mother's womb the fetus receives a lower dose of the radiation than the dose the mother receives.[45]

Investigation indicates that there is a relationship between X-ray exposure before birth and development of childhood cancer. The findings indicated that the most sensitive period of exposure for developing leukemia is about the seventh month of pregnancy, while for all other cancers it is the sixth month.[46] It is important to note that to develop congenital malformations the most crucial time is during the first four months, while to develop cancer is during the sixth and seventh month. Therefore there is no real 'safe' time to be exposed to radiation while pregnant, as there are possible health problems associated with the majority of the duration of pregnancy (table 9).

Table (9): Prenatal Radiobiological Effects.

Weeks	Post Conception Effect
0 - 1 (preimplantation)	Intrauterine death
2 - 7 (organogenesis)	Developmental abnormalities/ growth retardation/ cancer
8 - 40 (fetal stage)	Same as above with lower risk plus possible functional abnormalities

2. Genetic effects

The term genetic diseases refer to those that arise as a result of spontaneous mutations in germ cells and are transmitted to the progeny.

2 .1 Mendelian Diseases

Diseases caused by mutations in single genes are known as Mendelian diseases and are further divided into autosomal dominant, autosomal recessive, and X-linked, depending on the chromosomal location (autosomes or the X chromosome) and transmission patterns of the mutant genes. In an autosomal dominant disease, a single mutant gene (*i.e.*, in the heterozygous state) is sufficient to cause disease. Examples include achondroplasia, neurofibromatosis, Marfan syndrome, and myotonic dystrophy. Autosomal recessive diseases require homozygosity (*i.e.*, two mutant genes at the same locus, one from each parent) for disease manifestation. Examples include cystic fibrosis, phenylketonuria, hemochromatosis, Bloom's syndrome, and ataxia-telangietasia.

The X-linked recessive diseases are due to mutations in genes located on the X chromosome and include Duchenne's muscular dystrophy, Fabry's disease, steroid sulfatase deficiency, and ocular albinism. Some X-linked dominant diseases are known, but for most of them, no data on incidence estimates are currently available. Therefore, these diseases are not considered further in this report. The general point with respect to Mendelian diseases is that the relationship between mutation and disease is simple and predictable.[47]

2.2 *Chromosomal Diseases*

Historically, both UNSCEAR and the BEIR committees have always had an additional class of genetic diseases "chromosomal diseases" in their lists that included those that had long been known to arise as a result of gross (i.e., microscopically detectable), numerical (e.g., Down's syndrome, which is due to trisomy of chromosome 21), or structural abnormalities of chromosomes (e.g., cri du chat syndrome, due to deletion of part or the whole short arm of chromosome 5 [5p-]). As discussed later, this is really not an etiological category, and deletions (microscopically detectable or not) are now known to contribute to a number of constitutional genetic diseases grouped under autosomal dominant, autosomal recessive, and X-linked diseases.[48]

CONCLUSION

The use of ionizing radiation is increasing day by day in medicine, industry, research and other part of human life. Therefore, the number of involved professionals in radiation work is also substantially increasing. Strict guidelines are available for radiation professional for using radiation such that radiation exposure to staff and public remains within dose limits set by regulatory bodies, however, it has also been very difficult to detect adverse effects from low level radiation. This uncertainty highlights the importance of knowledge of deleterious effects of ionizing radiation. Biological damage due to radiation stems mainly from damage to DNA. Damage may by deterministic or stochastic. While working in radiation area, professionals are exposed to low levels of radiation. Therefore, stochastic effects are the most relevant, and can result in carcinogenesis or genetic defects. A better scientific understanding of biological

effects of radiation risks is crucial to the formulation of appropriate protective standards and, more broadly, to the achievement of a responsible balance in assessing the use of nuclear technologies in industry, medicine, and energy production.

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