SECTION A

GENERAL INTRODUCTION
Biological effects of radiation from the interaction of radiation with matter comprising all levels of biological organization. The interaction causes subtle and obvious “changes” in various components of cells, tissues and organism. The effected living system usually “responds” to the “changes”. The living system is normally endowed with ways and means of variable magnitude and types to counter such “changes”. Consequently and depending on the quality and quantity of the changes, some such changes are reverted or repaired. The remaining component or “changes” are likely to effect the process of life and are commonly referred to as “damages”. The outcome of these intricately balanced and, to a great extent not clearly understood, processes culminate into cancer, heritable changes and cell death.

The damages include a variety of changes in the genetic material, which, among others, includes base changes, mutations, strand breaks and transformation. Radiation also induces and influences the process of programmed cell death. Consequences of these changes culminate into genomic instability. These events and their molecular mechanisms are only partly understood in case of low-LET radiation. On the other hand, the situation for high-LET radiation remains far from being clear. A proper assessment and evaluation of biological effects of low- and high-LET radiation is therefore, highly relevant. It is not only important in fundamental understanding of cellular response to effects of radiation, but also has applied potentials.

The search for an effective way of applying radiation to human cancer radiotherapy has been probably one of the main objective of radiobiologists. Its obvious importance has led to extensive radiobiological studies. One universal aim and interest in radiobiology research is to understand the interaction and mechanisms of action of ionizing radiation and its effects on biological systems. It may be of low linear energy transfer (LET) radiation i.e., sparsely ionizing radiation, such as X-rays, gamma rays, electrons, ultra soft X-rays or high-LET radiation i.e., densely ionizing like alpha particles, protons, neutrons etc. and other heavier particles produced by certain types of high energy accelerators. The knowledge of this is important in medicinal application such as radiotherapy and radiodiagnostics, and also for radiation protection on earth and in the space environment.

Ever since the elucidation of structure of deoxyribonucleic acid (DNA) molecule in the early 1950’s by Watson and Crick, studies related to understanding and manipulation of DNA has grown by leaps and bound in various branches of biological sciences. The focus has not been different in radiobiological investigations too. Because of the universal acceptance of DNA as the genetic material, it is considered to be a critical target for damage induced by radiation in cellular systems. The damages inflicted upon by radiation are known to cause the consequent biological effect. Apoptosis, transformation and
carcinogenesis via mutation and reproductive cell death are closely related to molecular damages in the DNA. The DNA damages have been studied experimentally and theoretically employing several approaches. Consequently, several models have been established in order to explain the biological observations. At molecular level, the studies involved different endpoints like cell survival, chromosomal aberration, DNA rejoining, mutation and DNA strand breaks both single strand breaks (SSB) and double strand breaks (DSB). Yet variation in results at different conditions defies working out a firm stand in explaining the mechanism. Most of the existing studies on DNA damage give quantitative insight such as, the yields of such damages and their dependence on radiation quality. The knowledge of the quality and nature of DNA damage is limited. Interaction of radiation with a matter is random. The interaction elicits changes in the target site, which may alter the normal course of cellular metabolism, their consequential repair and expression of the effects.

One general view is that it may be due to the differential repair capacity that each living cell possesses to repair damages particularly inflicted by radiation. This has an important implication since radiosensitivity of a cell is mostly defined depending on the ability of a cell to repair the wide spectrum of DNA damages. An increasing body of experimental evidences has accumulated indicating that distribution of the DNA radiation damage and the complexity and fluidity of the nuclear organization can affect repair. This has led to an indication that the structural organization of DNA or chromatin compactness determines the radiosensitivity of cells. Well within this line of observation, experimental reports also suggest that structural organization of DNA may not be the only factor influencing the radiosensitivity. Thus, because of such diverse observations, it is not surprising that a single concept has so far not emerged in defining radiosensitivity of a cell. The molecular basis of the variable inherent radiosensitivity and genomic instability, therefore, remains enigmatic. In this context, understanding the nature of the initial lesion to its DNA and its link to the eventual expression of biological damage is of utmost importance.

In the light of these information, this work envisages to study the DNA damage induced by low- and high-LET radiation with the aim of contributing in the understanding of the molecular consequences of radiation induced DNA damages. It is to be noted that, the work with high-LET radiation in both the sections is limited due to scarce beam time that was available at Nuclear Science Center, New Delhi.

The study has been separated into two main sections:
(1). **Study of DNA damage in non-cellular system:**

In this first section, a system was selected where the effect of radiation on DNA damage in non-cellular condition could be clearly observed at molecular level. For this reason, naked plasmid and bacterial genomic DNA were selected. The study attempts to understand the quality and nature of DNA damage induced by low- and high-LET radiations. The results discuss certain likely factors within the DNA molecule that may be influencing its interaction with radiation.

(2). **Study of DNA damage in cellular system:**

In this latter section, the investigation covers study on effect of radiation on DNA and other components, and their response in cellular condition. Mammalian cells *in vitro* and *ex vivo* was selected for this purpose. In a likely effort to shed light on the mechanism of interaction of radiation with DNA in its *vivo* organization, the study attempts to describe and understand the radiation induced DNA damage in relation to the biological endpoint that is measured.

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