

WHAT HAPPENS AT VERY LOW LEVELS OF RADIATION EXPOSURE? ARE THE LOW DOSE EXPOSURES BENEFICIAL?

D. DALCI

TAEK, Çekmece Nuclear Research and Training Center, Istanbul, Türkiye deniz.dalci@taek.gov.

ABSTRACT

Radiation is naturally present in our environment and has been since the birth of this planet. The human population is constantly exposed to low levels of natural background radiation, primarily from environmental sources, and to higher levels from occupational sources, medical therapy, and other human-mediated events. Radiation is one of the best-investigated hazardous agents. The biological effects of ionizing radiation for radiation protection considerations are grouped into two categories: The deterministic and the stochastic ones.

Deterministic radiation effects can be clinically diagnosed in the exposed individual and occur when above a certain "threshold" an appropriately high dose is absorbed in the tissues and organs to cause the death of a large number of cells and consequently to impair tissue or organ functions early after exposure. A clinically observable biological effect (Acute Radiation Syndromes, ARS) that occurs days to months after an acute radiation dose.

Stochastic radiation effects are the chronic effects of radiation result from relatively low exposure levels delivered over long periods of time. These are sort of effects that might result from occupational exposure, or to the background exposure levels. Such late effects might be the development of malignant (cancerous) disease and of the hereditary consequences. These effects may be observed many years after the radiation exposure. There is a latent period between the initial radiation exposure and the development of the biological effect. For this reason, a stochastic effect is called a Linear or Zero-Threshold Dose-Response Effect

Exposure to very low levels of radiation is a controversial issue, originating many debates throughout the scientific community. What happens at very low levels of radiation exposure?

There is a stochastic correlation between the number of cases of cancers or genetic defects developed inside a population and the dose received by the population at relatively large levels of radiation. Although there is no scientific evidence to prove, attempts have been made to extrapolate the data from these levels of dose to low levels of dose (close to the levels received from background radiation). Studies of populations living in high natural-background areas have not reported detrimental health effects attributable to radiation. The research has also demonstrated that the types and numbers of gene activated by low doses of radiation are different than those activated by high radiation doses. These changes in gene activation seem to be able to modify the response of cells to subsequent radiation exposure, termed the "adaptive response". This adaptive response seems to be the manifestation of a protective effect that may reduce risk at very low doses.

Current knowledge in molecular biology shows no evidence of a threshold effect for Stochastic Effects. Therefore, any level of radiation may be considered to cause them. Conversely, some studies show that low levels of irradiation are in fact beneficial to the health (Radiation Hormesis). However, in the absence of clear scientific evidence, the regulators adopted a conservative approach and consider all levels of radiation as being potentially damaging to the human body (LNT theory).

According to LNT theory; the effects of low doses of ionizing radiation can be estimated by linear extrapolation from effects observed by linear extrapolation from effects observed by high doses. There is not any safe dose because even very low doses of ionizing radiation produce some biological effect.

The results of many investigations do not support the LNT theory. Furthermore relationship between environmental radon concentrations and lung cancer even contradict this theory and clearly suggest a hormetic effect -radiation hormesis-. Although data are still incomplete, extensive epidemiological studies have indicated that radiation hormesis is really exist.

In this review, contradictory evidence Linear No-Threshold Theory and Radiation Hormesis Effect is discussed.

Key Words: *Low dose, adaptive response, LNT, radiation hormesis*

1. INTRODUCTION

Exposure to very low levels of radiation is a controversial issue, originating many debates throughout the scientific community. What happens at very low levels of radiation exposure? Everybody is exposed to a level of radiation called the natural radiation or background radiation. Also, was proved that the background levels vary on earth by a factor greater than 10.

The connection between effects of exposure to radiation and dose (i.e., dose-response relationship) is classified into 2 categories, non-stochastic, and stochastic. Non-stochastic effects, also referred to as deterministic are specific to each exposed individual.

The most common result of radiation damage is for the cell to die. If only a few cells are affected, it is not usually a problem as there are many cells in the body and new cells will replace the dead cells. However, as the amount of radiation absorbed (i.e the dose) increases, a point will be reached where sufficient cells are killed to affect the overall operation of the organ. The result of this is a loss of organ function which will become more serious as the number of affected cells is increased.

DETERMINISTIC EFFECTS

The different types of radiation damage resulting from the loss of organ function are known as deterministic effects. These effects are characterized by having a threshold dose (below which there is no observable effect) followed by a response where the severity of the effect increases with increasing radiation dose.

Deterministic effects are most often seen in cases of high doses of radiation delivered in a short period of time (i.e. in the case of acute exposure). Other than for controlled medical exposure, high doses are not usual in the workplace. Hence deterministic effects are only seen in accident situations and do not occur routinely in the workplace. The severity of the deterministic effects depends on the size of the dose and the period over which the dose was received^[1].

Detrimental effects have only been seen for acute exposures that large doses of radiation received in a short period of time. Acute whole body exposures in excess of 2 Gy, i.e., much higher than is normally received by radiation workers from a lifetime of radiation work, may damage a sufficient number of radiosensitive cells to produce mild symptoms of radiation sickness within a short period of time, perhaps a few days to a few weeks. The immediate somatic effects may include symptoms -Acute Radiation Syndrome such as blood changes, nausea, vomiting, hair loss, diarrhea, dizziness, nervous disorders, hemorrhage, and maybe death. Without medical care, half of the people exposed to a whole body acute exposure of 4 Gy may die within 60 days ($LD_{50/60}$). Regardless of care, persons exposed to an acute exposure exceeding 7 Gy are not likely to survive (LD_{100}). Exposed individuals who survive acute whole body exposures may also develop other delayed somatic effects such as epilation, cataracts, erythema, sterility and/or cancers.

STOCHASTIC RADIATION EFFECTS

As it is well known the biological effects of high doses exposures in humans, the effects of low doses are very confusing.

High radiation doses tend to kill cells, while low doses tend to damage or alter the genetic code (DNA) of irradiated cells. High doses can kill so many cells that tissues and organs are damaged immediately. Conversely, low doses--less than 100 mSv-- spread out over long periods of time (years to decades) don't cause an immediate problem to any body organ. The effects of low doses of radiation, if any, would occur at the level of the cell, and thus changes may not be observed for many years (usually 5-20 years) after exposure.

The delayed effects of radiation are due to low-level exposure that is called continuous or chronic exposure. In this case, the results may not be apparent for years. This type of exposure is likely to be the result of improper or inadequate protective measures.

The most common delayed effects are various forms of cancer (leukaemia, bone cancer, thyroid cancer, lung cancer) and genetic defects (malformations in children born to parents exposed to radiation). In any radiological situation involving the induction of cancer, there is a certain time period between the exposure to radiation and the onset of disease. This is known as the "latency period" and is an interval in which no symptoms of disease are present.

Genetic effects and the development of cancer are the primary health concerns attributed to radiation exposure. The likelihood of cancer occurring after radiation exposure is about five times greater than a genetic effect (e.g., increased still births, congenital abnormalities, infant mortality, childhood mortality, and decreased birth weight). Genetic effects are the result of a mutation produced in the reproductive cells of an exposed individual that are passed on to their offspring. Experimental studies on plants and animals have shown that hereditary effects can occur after exposure to large doses of radiation ^[2].

Although radiation-induced genetic effects have been observed in laboratory animals (given very high doses of radiation), no evidence of genetic effects has been observed among the children born to atomic bomb survivors from Hiroshima and Nagasaki.

A stochastic effect is one that might arise from the injury of a few cells, or even a single cell, and thus has no threshold. A cancer or genetic mutation is an all-or-none effect for the individual. Increasing the radiation dose does not increase the severity of the effect. It simply increases the frequency or incidence of the effect in a population. The probability of the biological effect occurring increases with dose, but the severity of the biological effect when it occurs is not affected by dose.

For the purposes of radiation protection, it is assumed that the probability of a stochastic effect increases linearly as the dose increases and that there is no threshold dose. If there is no threshold dose then it is considered that even small doses of radiation might cause cancer.

Stochastic effects are the only effects possible at low doses and hence, radiation protection is aimed at preventing deterministic effects and reducing the chances of stochastic effects occurring.

2. LINEAR NO-THRESHOLD THEORY

Most regulators take a conservative approach to radiation-induced cancer risk, assuming the risk from radiation is linearly related to the radiation exposure and that there is no threshold for effects.

Even so, the radiation protection community conservatively assumes that any amount of radiation may pose some risk for causing cancer and hereditary effect, and that the risk is higher for higher radiation exposures. A linear, no-threshold (LNT) dose response relationship is used to describe the relationship between radiation dose and the occurrence of cancer. This dose-response model suggests that any increase in dose, no matter how small, results in an incremental increase in risk. The LNT hypothesis is accepted as a conservative model for determining radiation dose standards recognizing that the model may over estimate radiation risk.

Since there is no evidence of a lower threshold for the appearance of Stochastic Effects, the prudent course is to ensure that all radiation exposures follow a principle known as ALARA (As Low As Reasonable Achievable).

After the atomic bomb explosions in Hiroshima and Nagasaki, studies concerning life span of atomic bomb survivors showed a linear relationship between cancer mortality and high doses of radiation ^[3]. The United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) then proposed the linear no-threshold (LNT) theory in 1958. According to LNT Theory; the effects of low doses of ionizing radiation can be estimated by linear extrapolation from effects observed by linear extrapolation from effects observed by high doses. There is not any safe dose because even very low doses of ionizing radiation produce some biological effect. In 1959 the International Commission on Radiation Protection (ICRP) adopted the LNT theory ^[4].

3. HORMESIS EFFECT

The results of many investigations do not support the LNT theory ^[5]. Conversely, some studies show that low levels of irradiation are in fact beneficial to the health-Radiation Hormesis. There is extensive evidence suggesting hormetic effects:

Cancer Prevention: Bhattacharjee in 1996 showed that when the mice preirradiated with just adapting doses of 1 cGy/day for 5 days (without a challenge dose), thymic lymphoma was induced in 16% of the animals ^[6]. Interestingly, when preirradiated mice were exposed to a 2 Gy challenge dose, thymic lymphoma was induced again in 16% of the animals. However, the challenge dose alone induced thymic lymphoma in 46% of the mice.

In 1996, Azzam and his colleagues showed that a single exposure of C3H 10T1/2 cells to doses as low as 0.1 cGy reduces the risk of neoplastic transformations. They suggested that a single low-dose at background or occupational exposure levels may reduce cancer risk ^[7].

Survival Rate: In 1996, Yonezawa and his colleagues indicated that when 21-ICR mice were exposed to an 8 Gy of X-rays, about 30% of the animals survived 30 days after the irradiation. However, when mice preirradiated with 5 cGy of X-rays, the survival rate increased to about 70% ^[8].

4. EPIDEMIOLOGICAL EVIDENCE

Although radiation hormesis data are still incomplete, extensive epidemiological studies have indicated that radiation hormesis really exists. A brief review on this irrefutable evidence is as follows:

According to UNSCEAR report (1994), among A-bomb survivors from Hiroshima and Nagasaki who received doses lower than 200 mSv, there was no increase in the number of total cancer deaths. Mortality caused by leukemia was even lower in this population at doses below 100 mSv than age-matched control cohorts ^[9,10]. Mifune (1992) and his co-workers indicated that in a spa area, with an average indoor radon level of 35 Bq/m³, the lung cancer incidence was about 50% of that in a low-level radon region. Their results also showed that in the above mentioned high background radiation area; the mortality rate caused by all types of cancer was 37% lower. Among A-bomb survivors from Nagasaki, in some age categories, the observed annual rate of death is less than what is statistically expected ^[11].

BACKGROUND STUDIES

The population living in Karunagappally taluk in Kerala, India, presents a unique opportunity for studies on the health effects of chronic exposure to low-level radiation. The environmental radiation emanates largely from the thorium deposited mostly along coastal areas. In certain locations on the coast, it is as high as 70 mGy/year and on average is 7.5 times the level seen in interior areas. A population cancer registry system has been established to obtain cancer incidence rates. There is no evidence that cancer occurrence is consistently higher because of the levels of external gamma-radiation exposure in the area ^[11].

In a large scale Chinese study, it was shown that the mortality rate due to cancer was lower in an area with a relatively high background radiation (74,000 people), while the control group (78,000 people) who lived in an area with low background radiation had a higher rate of mortality. The annual effective dose is estimated to be 6.4 mSv which is about three times the world's average of 2.4 mSv ^[11].

In a very large scale study in U.S.A, it was found that the mortality rate due to all malignancies was lower in states with higher annual radiation dose ^[11,12]. The dose rate of 100µSv/day is about 10 times the natural background rate in the United States. The total dose over a five-year period would be approximately 0.18 Sv. Although this would be considered a "high" acute dose in the context of radiation safety (as opposed to doses used for medical therapy), there is little evidence of health risk since the dose is protracted over several years.

Practically all studies have failed to reveal any significant health effects that could be attributed to living in these areas of high natural background radiation. It was observed that in areas with a high-background radiation level, the incidence of cancer and also the mortality rate due to cancer was significantly less than similar areas with a low background radiation level.

NUCLEAR POWER PLANT STUDIES

In a Canadian survey the mortality caused by cancer at nuclear power plants was 58% lower than the national average. In U.K also it was indicated that cancer frequency among nuclear power plant workers was lower than the national average.

The joint study of the occupational cohort of nuclear workers of the USA, UK and Canada revealed a statistically significant difference in the number of expected and observed leukemia only for the dose range 400 mSv and more ^[13].

Thus, the present-day epidemiological studies of the cohorts of nuclear workers in the leading countries provide no basis for saying that there are proven statistically significant risks of radiation carcinogenesis at low radiation doses (0-100 mSv).

These studies did not show any excess in cancer incidence rate above the spontaneous level. Thus, considering Hiroshima, Nagasaki, Chernobyl, the registries of nuclear workers it may be concluded that the currently available epidemiological data provide no evidence of proven radiation carcinogenesis in the region of low doses (0-100 mSv). Also, it is obvious that activities in this study area should be intensified to obtain objective data and work out optimum norms of radiation safety.

THE MECHANISM OF HORMETIC PHENOMENA

Although still we do not know the entire mechanisms of radiation hormesis, the following theories may explain this process:

DNA Repair (Molecular level): According to this theory, low doses of ionizing radiation induce the production of special proteins- cycloheximide- that are involved in DNA repair processes ^[11].

Free radical detoxification (Molecular level): Low doses of ionizing radiation cause a temporary inhibition in DNA synthesis (the maximum inhibition at 5 hours after irradiation) and this temporary inhibition of DNA synthesis would provide a longer time for irradiated cells to recover. This inhibition also may induce the production of free radical scavengers, so irradiated cells would be more resistant to any further exposures.

Stimulation of immune system (Cellular level): Despite the fact that high doses of ionizing radiation are immune suppressive, many studies have indicated that low doses radiation may stimulate the function of the immune system ^[11].

5. ADAPTIVE RESPONSE

The research has also demonstrated that the types and numbers of gene activated by low doses of radiation are different than those activated by high radiation doses.

These changes in gene activation seem to be able to modify the response of cells to subsequent radiation exposure, termed the "adaptive response". This adaptive response seems to be the manifestation of a protective effect that may reduce risk at very low doses. Cell and molecular research has also determined that cells may lose their genetic control many cell generations following radiation exposure. This is termed genomic instability and is thought to be an essential step in radiation induced cancer. There is a very active research effort being conducted to better understand the impact of all these cell and molecular effects on the risk for development of cancer ^[11].

6. CONCLUSION

Most of the accumulated research over more than 50 years has focused on the higher levels to formulate and establish exposure standards for protecting the general public and subpopulations such as affected work forces. Although most future human radiation exposures are projected to be at low levels, research has not yielded the type of information that can be readily used to make health-risk assessments related to such exposures. Newer genomic technologies promise to provide the data needed to understand the risks of low-level radiation.

In fact, radiation worker populations exposed at currently allowed standards have not shown increased cancer rates when compared to the rest of the population. The estimation of any (statistically) small increased cancer risk is complicated by the facts that there is a long, variable latent period (> 5 to 30 years) from radiation exposure to cancer manifestation, a radiation-induced cancer is indistinguishable from spontaneous cancers, the effects vary from person to person and the normal cancer incidence is relatively high.

Our radiation protection policy is based on linear extrapolation from the dose-response data of high doses of ionizing radiation. According to the results of many worldwide studies, this assumption is not compatible with observed health effects of low levels of radiation. Obviously LNT and current radiation protection regulations exaggerate the risk of low level ionizing radiation and cause radio phobia.

It is concluded that according to new findings, the existence of radiation hormesis and adaptive response are not deniable and abandoning the LNT theory in low dose risk estimations will be a real necessity in the near future.

In light of these recent advances in genetics and molecular biology, the available data and information must be intensively and thoroughly reviewed and analyzed. This will allow an authoritative assessment of the

current status of research that can contribute to a better understanding of the health effects of low dose and low dose-rate radiation.

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