Evidence of genetic effects by ionizing radiation: greater risks at the transgenerational level

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Abstract

In the past, genetic mutations occurring in children of irradiated parents have been the subject of considerable controversy. Recent research has produced persuasive evidence of such changes resulting from low level ionizing radiation. Even more striking are results from studies of trans-generational genetic changes in animals as documented in publications of in the contaminated regions of Chernobyl and Fukushima. Studies on humans reveal increased mutational rates in the genome in minisatellite regions. British scientists have hypothesized that workers employed at the Sellafield reprocessing plant have fathered increased numbers of children suffering from leukemia and non-Hodgkin's lymphoma.

Furthermore, children of Chernobyl liquidators showed significantly increased mutational rates, as compared to their siblings born before their fathers were recruited for the clean-up of that nuclear catastrophe. There is much published evidence pointing to genetic damage in offsprings caused by low level ionizing radiation.

This paper will begin with a short introduction to the different forms of ionizing radiation, the known effects of radiation and our current knowledge of its link to common diseases. We will then look in further detail at some of the existing scientific literature regarding the genetic effects of ionizing radiation on animals and humans.

Introduction

Ionizing radiation is known to enter the nucleus of any cell and can lead either to cell death or cellular damage. A damaged cell may repair itself or the cell damage may be passed on to subsequent generations if a genetic alteration has been brought about (Figs. 1 and 2).

Earlier Paradigm

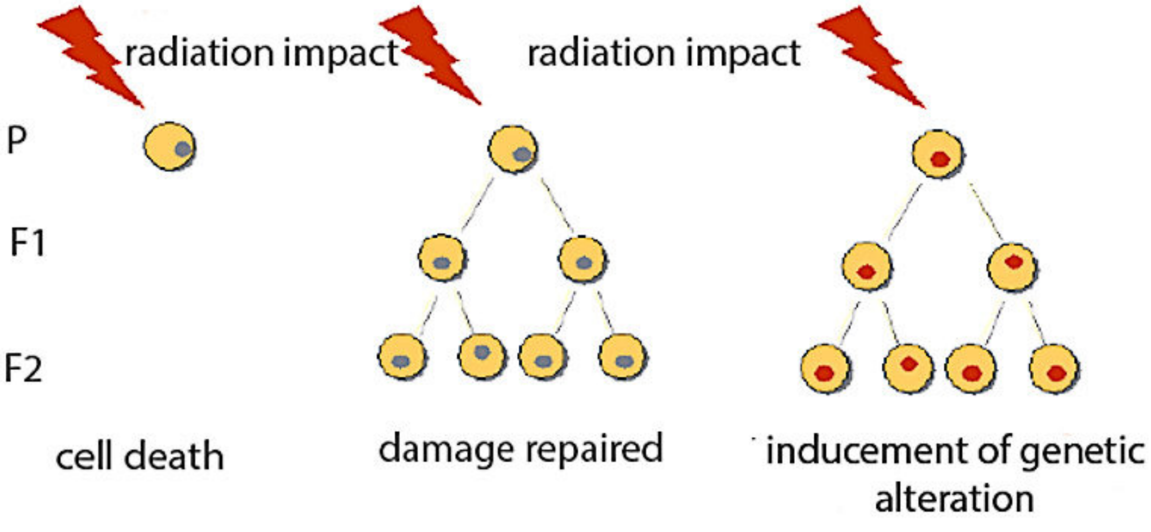


Figure 1: The clonal theory

A New Paradigm – Genomic Instability

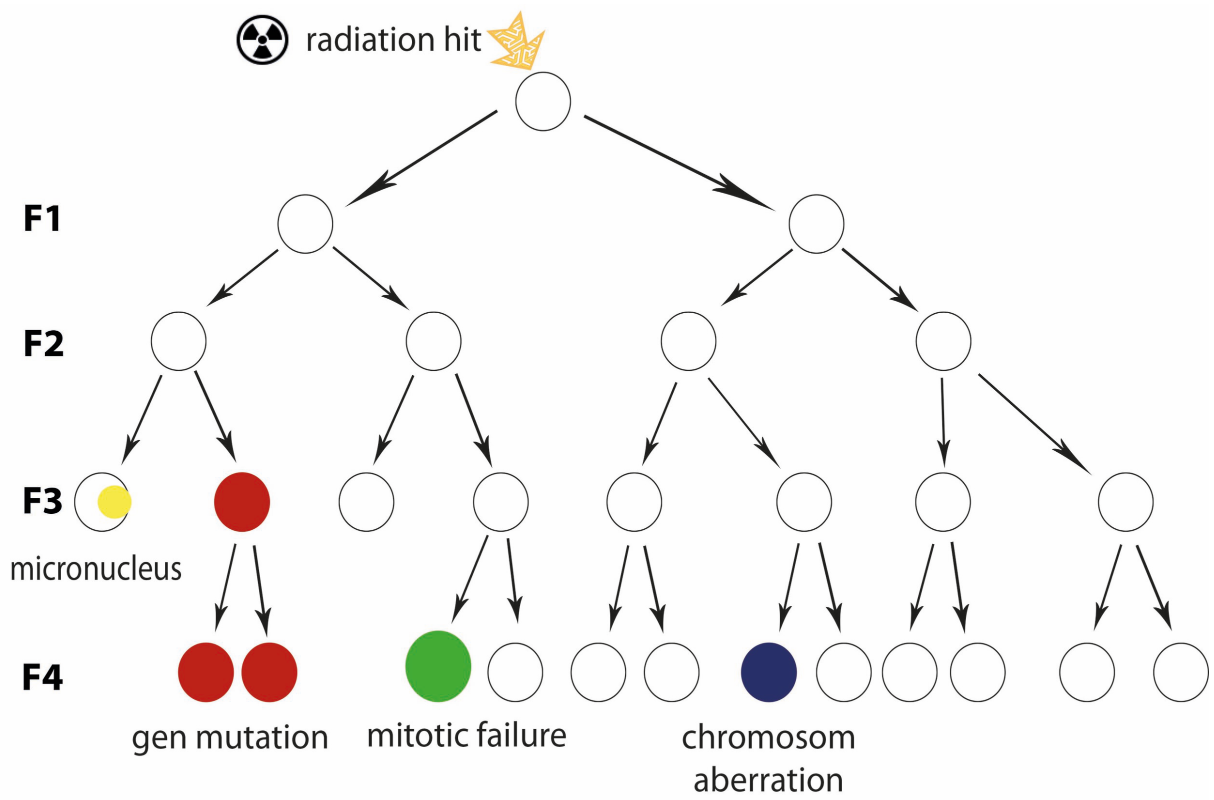


Figure 2: F1 and F2 of the irradiated cell do not show visible damage, but following generations begin to show signs of damage. White coloured cells are normal cells. The

damage is the consequence of so-called “bystander” effects on neighbouring and distant cells and indicate genomic instability which is transferred to the germline and may be passed on to following generations.

There are various forms of ionizing radiation and all have the potential to cause damage. These forms differ in their impact on organic tissue. The most potent of the three types is gamma radiation. It can penetrate walls and human bodies and travels the longest distance (several metres). X-rays (which have essentially the same characteristics as gamma-rays) are used in a controlled manner by radiologists. The X-ray tube produces X-rays in order to create radiographs (Fig. 3) or do fluoroscopy. When the tube is switched off, radiation ceases to emanate from the X-ray machine. Lead-lined walls or lead aprons protect people from direct exposure to X-ray radiation during the procedure.

Figure 3: Chest X-ray of a patient. The small dense area in the upper right lung (arrowed) shows a small bronchial carcinoma

The radioactive isotopes of iodine I-131 or cesium Cs-137 emit gamma rays which can be detected in a patient with a whole body counter. Alpha and beta particles emit radiation over a much shorter range and alpha particles may even be blocked by a sheet of paper. However, locally they have an equally strong effect on surrounding cells. This may be the case, when these radionuclides enter the body of a living human, animal or plant. This can happen indirectly by eating for example contaminated fish or meat from animals which have grazed on contaminated pastures, such as the reindeer in Sweden following the Chernobyl accident. Strontium-90 (Sr-90) is a beta emitter and behaves in the body like calcium. It “seeks out” bone where it settles and continues to radiate locally. This radiation has the potential to create bone tumours (Fig. 4) or leukemia.

Figure 4: Histological slide of bone tumour (white mass) in the lower part of a femur

One of the most dangerous substances is plutonium 239Pu which has a very long half life (the time in which it loses half of its radioactivity) of 24,000 years. A quantity as little as a few micrograms can cause lung cancer or cancer of the stomach (Fig. 5).

Figure 5: Mucosa of stomach showing cancer with central exulceration

The risks and dangers of ionizing radiation were recently studied at a meeting in Ulm in October 2013.[1] Physicians, epidemiologists and other scientists reviewed the current data on the health effects of ionizing radiation but did not focus on the genetic effects. The data showed that all forms of ionizing radiation (background radiation, radiation used in medicine and radioactivity released in the civil and military nuclear industry) can cause epidemiologically measurable health effects. The findings of these studies make more realistic risk assessments possible. Additionally, the data indicate that there is no threshold below which radiation can be considered harmless.

Even doses under 1 mSv can cause epidemiologically measurable health effects.2 Other studies indicate, that even nuclear power plants in normal operation can cause quantifiable, adverse health effects.3 If, in epidemiological studies, the concept of collective dose is used, health risks of low level radiation exposure can be reliably predicted and quantified.[4,5,6] One of the conclusions of the meeting was that the ICRP practice of using studies on Hiroshima and Nagasaki survivors as a basis for determining risk factors for low level radiation has led to an under-estimation of the risk. Therefore previous ICRP guidelines should be regarded as outdated and need to be revised.[7]

Known Effects Of Chronic Internal Low Level Ionizing Radiation

Leukemia is one of the most common types of cancer following exposure to radiation. It is usually diagnosed within 2 to 5 years following exposure and has been observed in the victims of the Hiroshima and Nagasaki atomic bombings[8] and in small children living in the vicinity of nuclear reactors.[9] Also extensively documented are carcinomas of the thyroid gland in children and thyroiditis following exposure to radiation, [10,11] in populations where, following a nuclear accident, no attempts were made by the authorities to protect the thyroid gland with iodine tablets.[12] As documented above, solid cancers may develop years after irradiation occurs. All parts of the body may be affected, the most common being stomach, bone, kidneys, lungs and pancreas.

Less well known effects of ionizing radiation in contaminated regions may also be observed. These include non-cancerous diseases such as cesium cardiomyopathy [13] and vascular diseases involving large and small vessels such as the coronary arteries and the small arteries of the retina.[14,15] There are also many reports on harmful effects of ionizing radiation on the brain, and some authors see a relation to certain mental disorders.[16,17,18]

Genetic Effects

Genetic effects in children of irradiated parents are a matter of some dispute in the radiation literature.[19,20] In the Live Span Study of the RERF only minimal effects could be identified in the children of the surviving nuclear bomb victims. [20] More recent papers, however, do indicate that genetic effects may be found following exposure to low level radiation. [2,4,5] There is also a body of papers available which show effects of low level radiation in animals and some of them will be referenced below.

Early Studies Of Genetic Damage Resulting From Ionizing Radiation

In 1927 Hermann J. Muller was the first to produce genetic effects in fruit flies by using ionizing radiation. His experiments earned him the Nobel Prize for Physiology and Medicine in 1946.[21] Muller was an outspoken scientist and even in those early years warned that ionizing radiation could have effects on the most important “asset” of human beings, namely our genetic material.

After the atomic bombing of Hiroshima and Nagasaki in 1945 initial studies did not reveal any significant radiation effects on the genome of the children of the survivors.[16] For this reason discussions of any such effects were considered controversial and rather played down at the time by science.[22,23,24]

Mutation studies are difficult to perform because phenotypical events and spontaneous mutations in fruit flies are rare in nature. By using X-rays, however, Muller was able to produce large numbers of phenotypically visible mutations which showed for the first time that X-rays could have such an effect (Fig. 6).

Figure 6: Normal fruit fly on the left. Phenotypical aberration on the right (lack of wings) [41] source of pictures (c) FREDERIC LABAUNE https://www.photomacrography.net/forum/viewtopic.php?t=25058sid=bf3a72302fb31562fd05f65b444c505e

Some Studies From The Chernobyl Region

Due to the faster reproduction cycles of many animals, genetic effects are more easily seen in animals such as barn swallows (hirundo rustica). Studies in the Chernobyl region have demonstrated a loss of physical fitness in these birds. They have also been found to exhibit partial albinism, microcephaly, morphological abnormalities in feathers and wings (Fig. 7), a reduction in reproductive capacity and premature death.[25,26] Partial albinism has additionally been observed even in mammals in the Fukushima region.

It is possible that the partial albinism of cattle has the same origin as that of the swallows.

Figure 7: Picture on left: genetic effects in barn swallows: normal bird on left, with proper plumage. Bird with genetic mutations on right displaying albinism and thinner plumage. 3rd picture shows animal with asymmetrical wings and tail.

T.A. Mousseau (c) 2006 (left two pictures) and T.A. Mousseau (c) 2005 (right picture)

Besides those phenotypical aberrations, Ellegren, Moller and other [27], by carrying out genetic studies in whole blood samples taken from the birds, have found increased mutation rates in the so-called microsatellite genome in the offspring of breeding barn swallows (Figure 8).

Swallows in Northern and Central Italy, and from uncontaminated areas in the former Soviet Union, did not show such pathologies.[27] Since 2012 this partial albinism has also been seen in the vicinity of Fukushima among swallows and cattle.

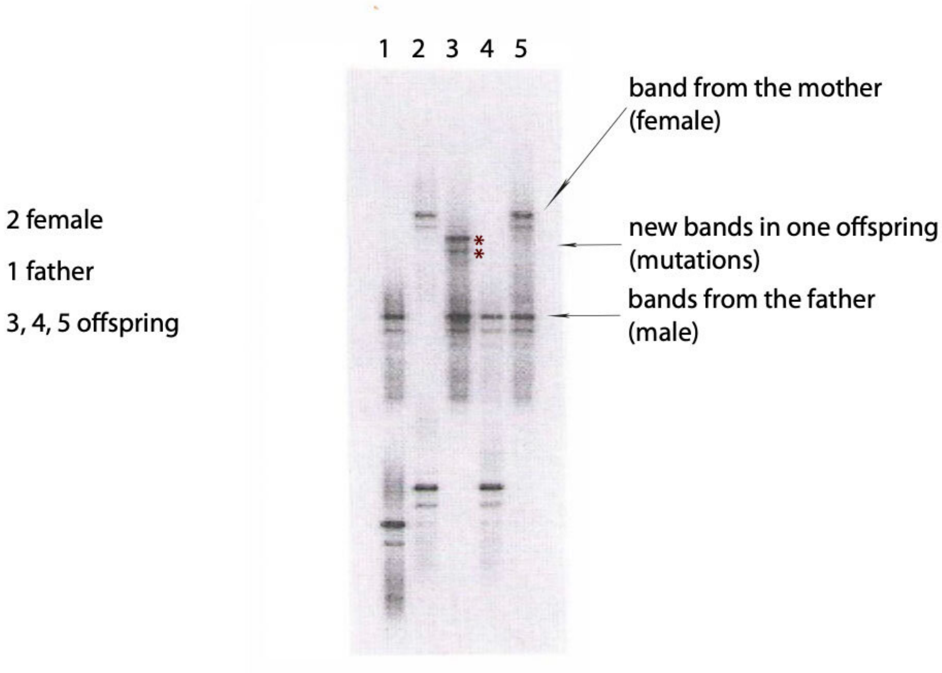


Figure 8: Examples of microsatellite germline mutations in three offspring (columns 3, 4 and 5) from barn swallows (father and mother, columns 1 and 2). The new bands (marked red) indicate a mutation in one offspring.

Studies From The Fukushima Region

Following the nuclear catastrophe on March 11, 2011 (due to an earthquake followed by a tsunami), large amounts of radioactive isotopes were released into the environment, leading to widespread contamination of the biosphere. An environment was thus created which allowed research into the effects of low level radiation on the fauna and flora. Yamato Shijimi (Zizeeria maha, pale blue grass butterfly) (Figure 9) is widely distributed in Japan and was therefore selected as an environmental indicator and model by a scientific group at the Ryukyus University in Okinawa, in the uncontaminated far south of Japan .[28,29] By May 2011 these researchers had collected 144 hatched butterflies. Their larvae had managed to survive the winter close to the ground and had received nourishment from leaves of uncontaminated oxalis corniculata (sorrel), a plant which grows widely in Japan and which does not grow higher than 10 cm. Z. maha is monophagous and this plant is the sole source of nourishment for these butterflies.

Figure 9: Zizeeria maha, bluegrass pale butterfly

The living butterflies were immediately transported to Okinawa, which had not been affected by the radioactive contamination (Figure 10). Measurements of radioactivity at the individual catchment sites were made and gamma doses between 0.09 to 3.09 µSv/h were found. In this manner, in a clean environment, eggs were harvested from the females and reared to generation F1. The butterflies were reared separately according to the location from which they had originally been collected. Later they were mated according to different criteria[28] and the generation F2 was reared. F1 and F2 follow-up generations were subsequently all examined in Okinawa.


The Japan Sea
Shiroishi
Fukushima
Dai-ichi NPP
Fukushima
Hirono
Motomiya
Iwaki
Koriyama
Takahagi
Mito
Tsukuba
Tokyo
Kobe
Ube
The Pacific Ocean
Okinawa
Shiroishi
Fukushima
Iitate
Motomiya
Koriyama
Fukushima
Dai-ichi NPP
Hirono
Iwaki
100 km

Figure 10: Study concept relating to the blue grass pale butterfly after the Fukushima disaster (from Hiyama et al. Scientific Reports 2: 570, 2012).

Although there were already minor dysplastic changes in the original butterflies taken from Fukushima, morphological damage was much more evident in generations F1 and F2. There were changes in the wing length, in the pattern of the spots, the appendages, eyes and there were tumours on the chest. Furthermore delayed hatching and reduced life expectancy were observed. A very important point was that the pathologies in the wing spot pattern were again seen in the F2 generation (Fig. 11).

Figure 11: Morphological damage in F1 and F2 butterfly generations (from Hiyama et al. Scientific Reports 2: 570, 2012)

In order to test their hypothesis that ionizing radiation and not other environmental influences were the cause of the increased trans-generational damage in F1 and F2, the researchers collected healthy butterflies from non-contaminated areas in Japan and exposed these to external radiation and to oxalis leaves from contaminated and non-contaminated regions. It was then possible to demonstrate the identical changes as compared to the butterflies collected in the originally contaminated environment of Fukushima. For the purpose of analysis, an overall abnormality rate (OAR) was calculated and statistically defined. In generation P (parents), butterflies originally collected in Fukushima, (which had been exposed through external or internal radiation due to eating contaminated leaves in their larval stage), there were 12.4% to 13.2% abnormality rates. The original collection in 2011 was done during May and September. In generations F1 and F2, the rate of abnormality increased significantly, even though the animals were fed and raised in a clean environment, indicating trans-generational damage had taken place. The results are shown Table 1. As the genome of Zizeeria maha has not been sequenced yet, no mutation analyses in the DNA of the damaged butterflies can be made, as was possible for the swallow study by Ellegren et al.

Overall abnormality rate (OAR) of adults

Adult samples	OAR (%)
Field-caught (P generation) in May (7 localities)*	12.4
Field-caught (P generation) in May (10 localities)	13.2
F_1 from the May samples (8 localities)	18.3
F_2 from the May samples (6 localities, 9 strains)	33.5
Field-caught (P generation) in September (7 localities)*	28.1
F_1 from the September samples (6 localities including Kobe)	51.9
F_1 from the September samples (5 localities excluding Kobe)	60.2
External radiation exposure	31.7
Control (no exposure)	16.7
Internal radiation exposure (excluding the Ube samples)	39.6
Internal radiation exposure (including the Ube samples)	24.5

*can be compared directly

Table 1 from Hiyama et al. Scientific Reports 2: 570, 2012

Whether or not albinism even in livestock (Fig. 12) is related to environmental nuclear contamination has not been conclusively proven, even though farmers in the Fukushima region report to never having seen such white spots in their own animals.[30]

Figure 12 Cow from a farm in the Fukushima prefecture with white spots on fur, indicating the possibility of radiation induced albinism.

Is Genetic Damage In Humans Possible And Can It Be Passed On To Following Generations?

The Sellafield Story

In Cumbria in England at the nuclear reprocessing site at Windscale (later renamed Sellafield) Yorkshire Television in 1983 broadcast the film: "Windscale: the Nuclear Laundry". This documentary highlighted, for the first time, a disturbingly high rate of childhood leukaemia among people living in Seascale, a village next to the plant.[31] In the official report by Black and his advisory committee, it was confirmed that the incidences of leukaemia and Non-Hodgkin-Lymphoma (NHL) were abnormally high in that region. Black suggested further studies be done and Gardner and colleagues found, in a case control study in 1990, that, with regard to leukaemia and NHL, the relative risk (RR) for children of fathers working at the Sellafield nuclear plant and receiving a total pre-conception ionizing radiation dose of 100 mSv or more, was 6.24 (Table 2). As one would normally expect a non-radiation value of 1.0, this may be regarded as significantly elevated.[32,33]

Gardner's hypothesis could not be confirmed in recent studies, but there is no other immediately apparent explanation for the elevated rates of leukemia and NHL in children and young adults.

LNHL (leukemia and non Hodgkin Lymphoma) 66 cases (<25 yrs old people) and preconception dose of Sellafield workers in West Cumbria UK (BMJ,Gardner et al 1990)

Dose (mSv)	**Relative risk** Area controls
1-49	1.06
50-99	1.16
100-	**6.24**

Table 2 Increased relative risk (RR) for children of fathers working at the Sellafield nuclear plant and receiving a total pre- conceptional ionizing radiation dose of 100 mSv or more (adapted from the publication of Martin Gardner in BMJ 1990)

In another separate epidemiological study at Sellafield, Dr. Louise Parker et al found a significant risk correlation of babies being stillborn and the fathers' total exposure to external ionizing radiation prior to conception, which once again, would indicate a trans- generational pathway.[34]

Mutations In The Minisatellite Genome

In 1996 Dubrova and others published a paper which showed an increased rate of mutations in the minisatellite[35] genome.[36] Children, who had been born between February and September 1994 in the Mogilev region (Fig.13), whose fathers and mothers had always lived in the villages of Bykhov, Krasnopolye and Cherikov, were examined by means of DNA fingerprinting (Fig. 14). They were compared with a control group of sex- and- age matched caucasian children from non-contaminated regions in England. By correlating the level of ground contamination with the mutation rates in the two groups the researchers discovered, on average, a twofold increase in the mutation rate of the minisatellite genome (Table 3).

Using the same method, children from survivors in Hiroshima and Nagasaki were tested. However in those children, no increased mutation rates were found. This nevertheless raises an important question.

Could a low dosage rate through long term internal contamination by consumption of contaminated food be more dangerous than the genetic effects following an acute event involving external ionizing radiation caused by a nuclear bomb or catastrophe?

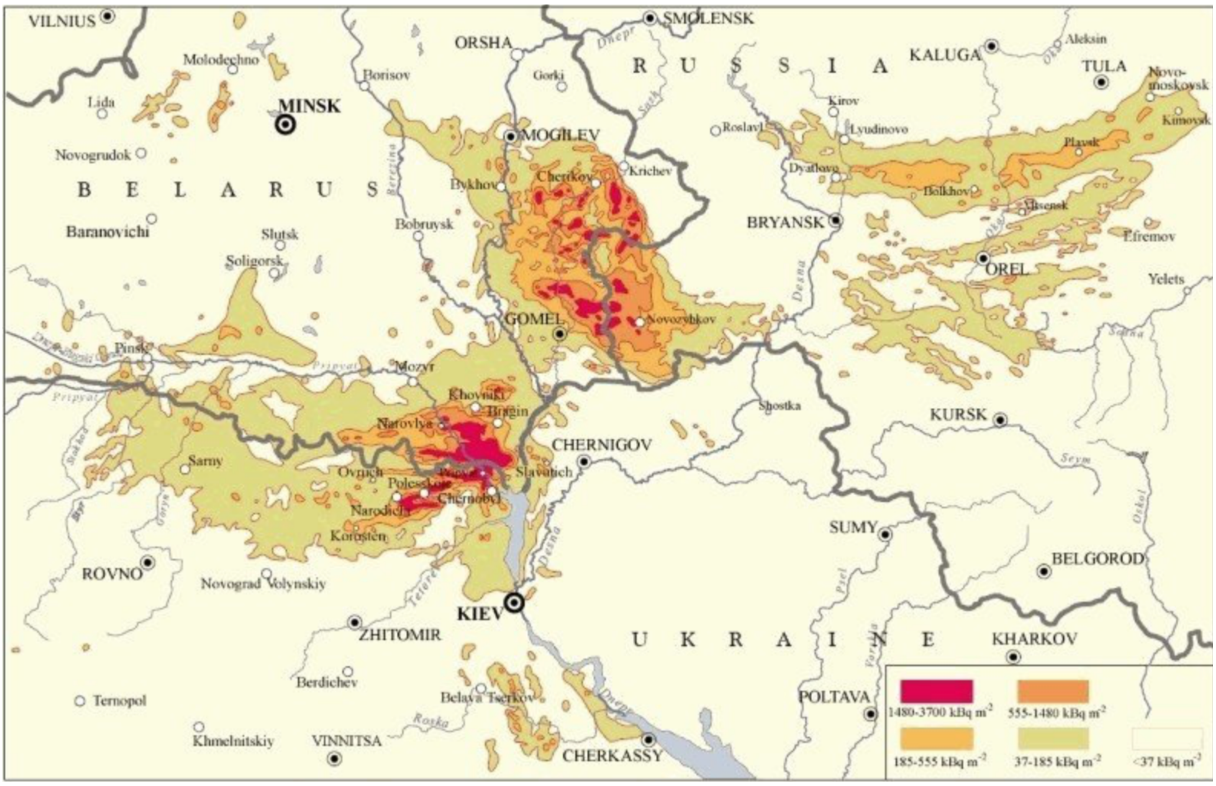


Figure 13: Contamination of the Mogilev Region (google map[37]) (map source[38])

It should be acknowledged that Dubrova's work has been criticized for the fact that the control group was from England. However, due to the widespread contamination of Belarus no other control group was available. It would have been difficult to find families living in an uncontaminated part of Belarus. According to the authors, in all examples the trans-generational effects of ionizing radiation were clearly identified.

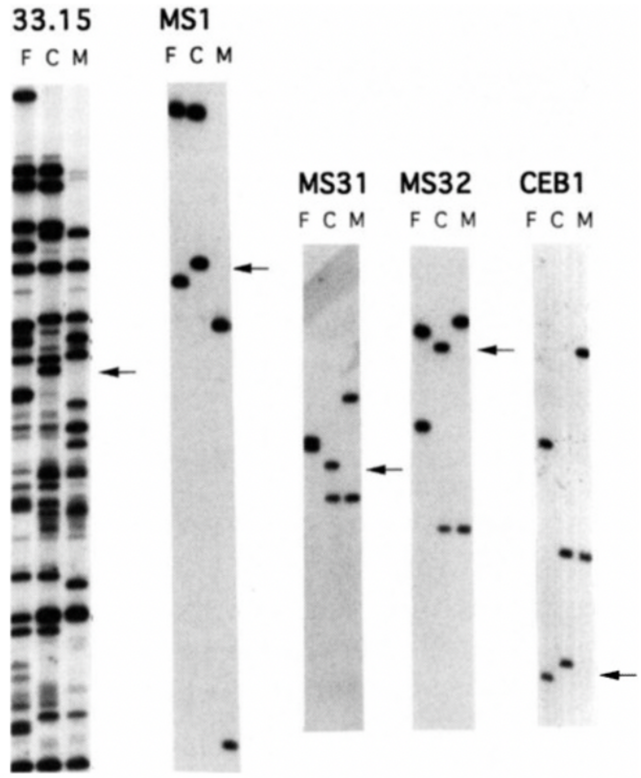
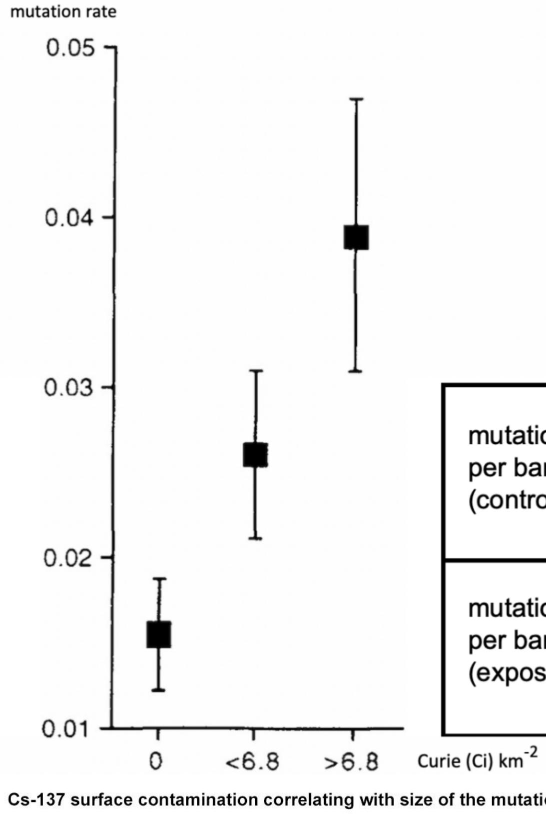


Figure 14 Examples of human minisatellite germline mutation. DNA profiles were produced for each father (F), child (C) and mother (M) using probes 33.15, MS1, MS31, MS32 and CEB1. New mutant bands are arrowed.



mutation rate per band (controls)	0.0154
mutation rate per band (exposed)	0.0303

twofold increase of the mutation rate in Mogilev children versus UK controls

Cs-137 surface contamination correlating with size of the mutation rate. Overall mutation rate in Mogilev children doubling versus UK controls

(6.8 Ci km^{-2} = 251.6 Bq m^{-2})

Table 3 Cs-137 surface contamination correlates with mutation rate

Children Of Nuclear "Liquidators"

Weinberg et al examined the children of fathers who, following the nuclear catastrophe of Chernobyl, had worked on cleaning up the contaminated site and had experienced frequent exposure to high levels of ionizing radiation. The children of those men, conceived before the accident, were compared with children conceived and born after the accident. These authors examined the minisatellite genome using a similar method to that of Dubrova. These authors found a significant increase in the mutation rate, namely a seven fold increase in new bands in the children conceived after the accident as compared to their siblings conceived before. Weinberg et al also regard a germline mutation in the fathers as the origin of these subsequent mutations. They saw that the ionizing radiation has had trans-generational consequences.[39][19]

Conclusion

There is now ample evidence produced by sophisticated newly available research methods into genetic effects of ionizing radiation. Insects were once thought to be resistant to radiation. New scientific studies on butterflies in Japan have demonstrated the contrary as has been documented in several papers.[25,26,27] Furthermore studies in the regions of Chernobyl and Fukushima have provided evidence of genetic mutations in birds and observed partial albinism both in birds and cattle in those regions where the worst nuclear power plant catastrophes have taken place.

Studies in human populations in the Mogilev region close to Chernobyl, of descendants of nuclear power plant operators in England and in liquidators of the Chernobyl fire conclusively document a clear increase in mutations in children conceived and born after the return home of those brave people, compared with children born prior to the catastrophe.

We conclude that epidemiological studies available nowadays prove, without doubt, that ionizing radiation has the potential to cause significant damage to the human germline and needs to be addressed. Compared with short term external radiation, this seems particularly to be the case in situations of long term exposure to internal radiation in humans and animals living in or near contaminated regions.

In our opinion, with regard to these risks, the precautionary principle [40] should be strictly adhered to. New legal bases need to be established globally for the protection of future generations. A new standard in human rights legislation is called for.

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Minisatellites and their shorter cousins, the microsatellites, together are classified as VNTR (variable number of tandem repeats) DNA. Confusingly, minisatellites are often referred to as VNTRs, and microsatellites are often referred to as short tandem repeats (STRs) or simple sequence repeats (SSRs)

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