Immediate and delayed genetic effects of ionizing radiation through irradiation and contamination

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The International Commission on Radiological Protection (ICRP) and other international committees claim that hereditary diseases after low dose exposures to ionizing radiation are virtually negligible. These organisations only take into account disorders due to dominant mutations in the first generation and they refer exclusively to the Japanese atomic bomb survivors in whom significant effects were missed. They ignore the results of a great number of scientific studies in human collectives and their progeny who show heritable diseases after occupational or diagnostic exposures and especially by Chernobyl fallout. In the introduction, I will refer on the genetic effects which are to be expected from our general knowledge about interactions of radiation in living cells and in laboratory animals. In the following chapters, early deaths, malformations, Down´s syndrome and other diseases will be reported which have been observed in humans after exposure of parents. According to current knowledge, there is no dose threshold below which hereditary damage due to exposure to ionizing radiation does not occur. Moreover, it is evident, that official risk estimates of the genetic effects of radiation are much too low.

Introduction

The most serious effects of ionizing radiation – hereditary defects in the descendants of exposed parents – had been already detected in the 1920s by Herman Joseph Muller. He exposed flies – drosophila – to x-rays and found malformations and other disorders in the following generations. He concluded from his investigations that low dose exposure, and therefore even natural background radiation, is mutagenic. Already in the thirties, the idea arose that cancer is initiated by a single cell transformation, a "somatic" mutation. Likewise, Muller concluded that there is no harmless dose range for cancer induction either (Muller 1936). His work was honoured by the Nobel prize for medicine in 1946.

After World War II Muller warned that radioactivity in the environment would cause deterioration of the human genetic pool. He was therefore excluded as a speaker at the Atomic Conference in Geneva in 1955 where the large-scale, so-called peaceful, use of nuclear energy was announced by U.S. President Eisenhower. Since then, those scientists who declared the handling of huge amounts of man-made radioactivity to be practicable and safe have been preferred and selected as experts by the authorities.

The normative body for the evaluation of radiation risks and the proposal of dose limits is the International Commission on Radiological Protection, ICRP. It replaced a committee which had been founded in 1928 by radiological societies of several countries for the purpose of developing standards for radiation protection in the medical field. For this reason, the ICRP is traditionally beholden to the interests of the users. Since 1950, over the period of the Cold

War and the development of nuclear energy consumption, the Commission became enormously important. Although it only makes recommendations these are applied by all Western and Eastern industrial nations.

The ICRP none the less developed the concept of the "stochastic" radiation effect– fully in line with Muller's understanding. If a large group is exposed to a small dose, one cannot predict which individual will suffer from radiation damage, only a probability can be inferred. Adverse health effects increase with accumulated dose, and after halving the dose there is still an increased effect. It can therefore be deduced that no "threshold" exists, i.e., a dose range without risk.

The underlying idea is that a single quantum of radiation – one alpha or beta particle or one electromagnetic wave of high energy – is able to induce or promote a cell mutation. Single hit cell mutations are manifested in chromosome aberrations and can be induced by very low doses. They are also involved in a variety of heritable diseases if induced in germ cells.

DNA as a target of ionizing radiation

Tissue cells possessing a nucleus divide by splitting their genetic material in two equal portions. When Muller started his radiation experiments it was known already that the nucleus carries genetic information in the form of chromosomes. Human cells contain 23 pairs of chromosomes, half of the material is given by the mother, the other by the father. The chromosomes can be made visible at a certain stage in cell division, called the metaphase. For the purposes of presentation, they can be arranged in pairs as a karyotype (Fig.1). The characteristic shape of the chromosome as an X with a centromere and 4 arms – the chromatids – is only present at this stage when the material has been doubled in order to be divided in two parts. The chromatids carry the genes.

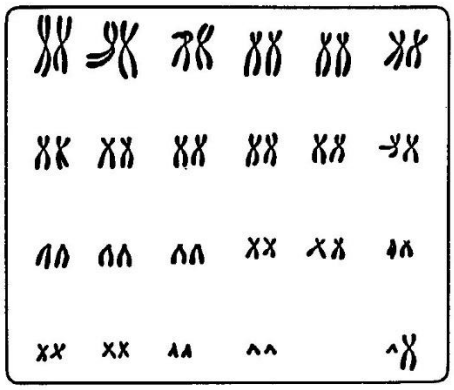


Fig. 1. Karyotype of a man, 22 pairs of autosomes, 1 pair of genosomes: xy

We learned in the meantime that the chromosomes contain deoxyribonucleic acid (DNA) which is a very long molecule consisting of two polynucleotide strands wound around each other in the form of a double helix. The sequence of bases on the DNA strand contains the genetic code.

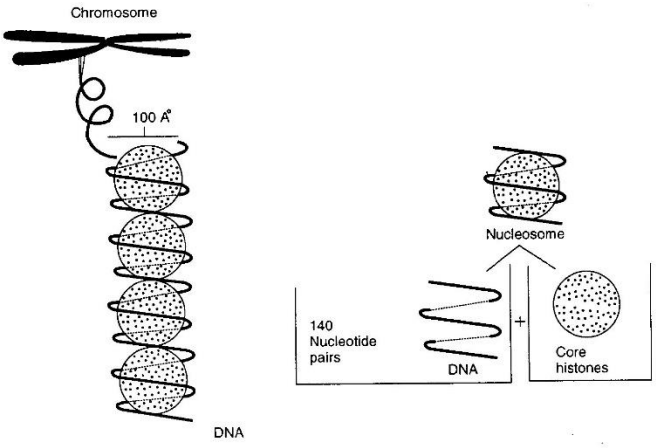


Fig. 2. Relationship between DNA molecule and chromosome (from Uma Devi 2001)
100 A° = 10 nm = 0.01 µm = 10^{-8} m

In chromosomes, the DNA molecule winds around a protein core consisting mainly of histones, which are characterized by a relatively high content of basic amino acids (Fig.2). A sequence of about 140 nucleotide pairs is wound around the histones to form a nucleosome. The nucleosomes are linked together by short stretches of DNA, giving the appearance of a string of beads.

Irradiation produces different types of lesions in the DNA molecule, which include strand breaks, base damage and crosslinks. Single strand breaks and double strand breaks are the best studied lesions. The cell has a repair system which reacts immediately to the damage. Single strand breaks are normally repaired error-free. Double strand breaks repair may be error-free or error-prone. Unrepaired or misrepaired double strand breaks can lead to cell death, mutations and cell transformations.

Base damage and strand breaks are implicated in radiation induced mitotic delay (delay of cell division) and in delay in DNA synthesis.

The evidence of low dose effects in chromosomes and genes
Radiation induces breaks in the chromosomes and chromatids. Misrepair leads to various abnormal configurations known as chromosomal aberrations. These can be numerical (change in number) as well as structural. Fig. 3 shows typical radiation-induced structural chromosome aberrations which can be regarded as radiation-specific (Hoffmann 1999).

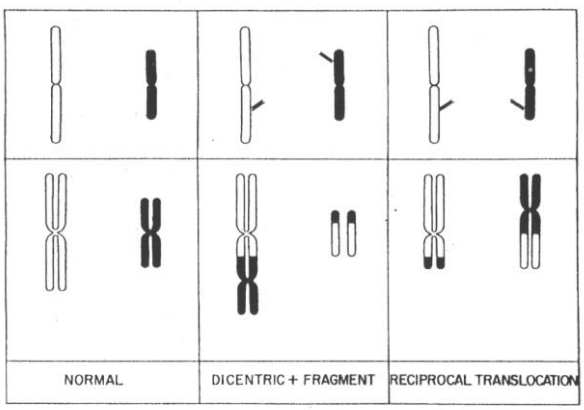


Fig. 3. Interchromosomal aberrations, radiation-induced

The formation of a dicentric chromosome requires the simultaneous induction of two "sublesions" in the DNA, certainly double strand breaks which lead to deletions in two neighbouring chromosomes which then go together at their shortened arms. Such aberrations result mainly from one ionizing track.
Counting the number of dicentric chromosomes in human lymphocytes is a very sensitive method to demonstrate radiation exposure in an individual person or in populations and is therefore a method of "biological dosimetry". Significant increases are found in populations living in regions with high background radiation (Barcinski 1975; Pohl-Rüling 1983; Wang 1990). Stephan and coworkers (2007) showed that one single CT examination of the thorax or abdomen in a child or juvenile may lead to a significant increase of dicentric chromosomes. Reciprocal translocations– made visible by a certain method of fluorescence in-situ hybridization (FISH)–are also used for purposes of retrospective dosimetry.

The pattern of chromosome aberrations in a cell after low dose exposure can deliver valuable information retrospectively about the kind of irradiation involved. In the case of x-ray or gamma radiation–so-called sparsely ionizing radiation or "low LET radiation"–we usually find only one aberration per cell, maybe a dicentric chromosome. Fig. 4 shows the metaphase of a lymphocyte after the passage of an alpha particle which causes a higher number of aberrations, in this case 3 dicentrics, along its densely ionizing track.

Fig. 4. Multiaberrant cell (metaphase of a human lymphocyte) after irradiation

Radiation-induced chromosome aberrations in somatic cells are assumed to be a direct cause of cancer induction as they can also occur in the telomeres. These are the terminal ends of the arms of chromosomes. Mutations in the telomeres are thought to play a role in the development of cancer.

Irreversible changes in genetic material as a result of radiation, i.e., mutations, may also occur in single genes. Genes are segments of DNA, the nature of which is determined by the sequence of the bases. They are arranged in linear order on the chromosomes. Each gene has a specific position or locus on the chromosome.

A mutation in any one of the genes can produce a change in morphology or physiology or both. The effects found by Muller in drosophila are gene mutations generated in the sex-linked genes. They can be dominant or recessive. Dominant genetic mutations are more easily detected as they are expressed in the F_1 generation (following the exposed parents). Dominant lethal mutations result in death of the embryo. Recessive mutations will not be expressed unless they are present at both the homologous loci, i.e. the mutation is received from both parents. An example of a recessive mutation is the cleft palate.

Mutations which affect the irradiated individual only are called somatic. Gene mutations in the somatic cells can lead to delayed effects like cancer induction. Mutation of the *p53* gene is one of the most common changes reported in human cancers.

Mutations in man are not specific to radiation and radiation-induced mutations are not distinguishable from spontaneous mutations. This poses a problem when investigating radiation effects. Studies of the children of people who were themselves affected by Chernobyl fallout have shown that gene mutations are induced by low dose exposures. Weinberg and co-workers (2001) studied DNA sequences at certain loci in parents and descendants by the method of polymerase chain reaction (PCR). They investigated a group of liquidators[1] whose families lived in regions without contamination. The children of the exposed fathers showed mutations which had newly developed. The controls were children of the same father (and mother) before exposure.

Current official risk evaluation of radiation-induced hereditary disorders

Previously, genetic effects in descendants were thought to be the most significant injuries caused by radiation. This is why the measure used in protection against x-rays in medicine was called the "genetically significant dose".

Although many genetic defects were observed after the Chernobyl accident which had not been recognized before and the evidence of known effects was confirmed, the ICRP substantially decreased their risk estimate in 2007. Their risk coefficient for heritable effects in an exposed population was lowered by a factor of 6 in comparison with the former estimate (Table 1). They refer to "new concepts" for genetic risk estimations developed by the radiation committees of the United Nations (UNSCEAR 2001) and the National Academy of Sciences of the U.S.A. (BEIR 2006).

Table 1. **ICRP Recommendations 2007**
Detriment adjusted nominal risk coefficients for radiation effects in an exposed population

	Present	ICRP 1990
Heritable effects	**0.2 % per Sv**	1.3 % per Sv
Cancer deaths	5.5 % per Sv	6.0 % per Sv

The value of 0.2 % per Sv means that, if a population is exposed to a gonadal dose of 1 Sv, a genetic disorder will occur in 0.2 % of the newborn children. 1 Sv = 1000 mSv is quite a high dose and the genetic risk is estimated to be much lower than the cancer risk – for 1 mSv additional exposure 2 hereditary disorders in 1 million persons. (Approximately 1 mSv per year is the natural background exposure, radon in houses not included.)

Their risk estimate (derived from experiments in mice) only considers heritable defects due to dominant mutations in the first generation that follows. It corresponds to a doubling dose[2] of about 2 Sv (UNSCEAR 2001).

The ICRP claims that there is no direct evidence that children of exposed parents will suffer from heritable diseases. They refer to their preferred human reference group, the Japanese sur-

[1] Men who worked at the exploded reactor for decontamination.
[2] The doubling dose is the dose which induces an effect as high as the spontaneous rate.

vivors of the atomic bomb explosions in Hiroshima and Nagasaki in 1945. An American-Japanese Institute in Hiroshima studied the health of survivors for decades after the war and did not find any mutations in descendants. A certain minimal risk is not quite excluded by ICRP refering to the evidence of such effects in animal studies.

Some scientists criticize this approach and argue that the Japanese survivors are not a suitable reference for populations exposed to chronic low dose irradiation in the workplace or by environmental contamination. And there are, indeed, many findings in exposed persons which contradict the statements of ICRP (IPPNW 2014).

Hereditary disorders expected in humans by irradiation

Hereditary disorders are classified into four categories which are described in Table 2 (below). Those diseases which have been found to be inducible by ionizing radiation are highlighted in yellow by me.

Mendelian disorders (a) are due to defective single genes and follow Mendel´s laws of inheritance. The defective gene may belong to an autosome which is a chromosome not influencing the sex of the individual, or it may be part of the X-chromosome.

The examples of autosomal dominant diseases listed here first appear in adult life and they are not known to be inducible by radiation. But congenital abnormalities of the fingers or toes occur after exposure of the parents ("congenital" means that it is a feature of the newborn baby).

The other disorders named in group (a) are not known to be induced by radiation except the deficit in female births which can be measured by the ratio of the numbers of male to female births.

(b) Certain disorders are accompanied by **chromosomal abnormalities**, i.e., they show alterations in the shape or number of chromosomes, both of which are detectable in the karyotype. The presence of abnormal numbers of chromosomes is called **aneuploidy.** A well-known example is Down´s syndrome where chromosome number 21 is present three-fold instead of two-fold as normal. This disorder is known to be induced by radiation.

Alterations in the structure of chromosomes lead to early death of the embryo or foetus which can be studied after an abortion.

(c) **Polygenic** or "multifactorial", "irregulatory inherited", "partially genetic" refer to those traits, diseases or congenital anomalies whose development has a genetic component, but whose inheritance does not follow standard Mendelian patterns, suggesting that more than one gene is involved. There may be clusters of such anomalies in families. They include severe congenital malformations ("neural tube" defects are malformations of the brain, scalp or spine with clefts as e.g. spina bifida) or severe diseases which appear in adulthood.

Cancer as a hereditary disease has been induced by irradiation of animals and must be considered also in man (see chapter "Cancer").

(d) This group includes disorders that are obviously hereditary but are not linked to gene alterations. They are also called of "epigenetic" origin.

Table 2. **Hereditary disorders (Uma Devi et al. 2000)**

(a) **Mendelian**

Autosomal dominant; examples:

Huntington´s chorea, polycystic kidney, multiple polyposis, cerebellar ataxia, myotnic dystrophy

Congenital abnormalities as syndactyly (fusion of fingers), brachydactyly (short fingers), polydactyly (more than 5 fingers or toes in each limb), taste for the chemical PTC (taste is dominant to non-taste), acondroplasia, bilateral aniridia, osteogenesis imperfecta

Autosomal recessive; examples:

Cystic fibrosis, phenylketonuria, lactose intolerance, adrenal hyperplasia

Sex-linked; examples:

X-linked dominant/Duchenne muscular dystrophy, haemophilia A, some forms of colour blindness, fragile-X associated mental retardation, X-linked retinitis pigmentosa

X-linked recessive/birth deficit of females

(b) **Chromosomal**

Aneuploidy (numerical chromosomal anomaly); examples:

Down syndrome (trisomy 21), Turner syndrome (X0), Klinefelter syndrome (XXY)

Structural anomalies; examples:

Cri du chat syndrome (deletion in chromosome 5), preimplantation loss, embryonal death, foetal abortions

(c) **Polygenic**

Cluster in families; examples:

Congenital abnormalities as neural tube defects, heart defects, pyloric stenosis, cleft lip with or without cleft palate, undescended testes

Common disorders of adult life of varying severity. Among the serious conditions are schizophrenia, multiple sclerosis, epilepsy, acute myocardial infarction, systemic lupus erythematosus. Moderately serious conditions include psychoses, Graves´disease, diabetes mellitus, gout, glaucoma, essential hypertension, asthma, peptic ulcer, rheumatoid arthritis. The least severe diseases include varicose veins of the lower extremities and allergic rhinitis.

Cancer

(d) **Non-chromosomal inheritance**

Cytoplasmic inheritance, mosaicism, imprinting etc.

Radiation-induced congenital malformations and other anomalies observed in humans

Most of the radiation-induced congenital anomalies described in the scientific literature have been observed after the Chernobyl accident, not only in the area of the exploded reactor but also in Turkey, Bulgaria, Croatia, and Germany (Busby 2009). Because men and women were both exposed continuously to radioactive fallout, the genetic effects are not clearly distinguishable from those which can be generated by exposure of embryos and foetuses in utero. The incidence of malformations over time, however, shows increases for many years after the accident.

In Belarus, a central registry for congenital anomalies was established by the Ministry of Health in 1979 for continuous follow-up. The rates of anomalies before and after the Chernobyl accident can be compared (Sevchenko 1997). Results in the 17 most contaminated regions are shown in Table 3.

Table 3. **Percentage increase in congenital malformations in 17 most contaminated regions of Belarus in the period 1987-1994 in percent** (from Lazjuk et al. 1997)

Kind of malformation	Increase
Anencephaly *(lack of brain)*	39 %
Spina bifida *(cleft vertebra)*	29 %
Cleft lip/palate	60 %
Polydaktyly *(additional fingers or toes)*	910 %*
Limb reduction	240 %*
Esophageal atresia *(clausura of gullet)*	13 %
Rectal atresia	80 %*
Multiple malformations	128 %*

* significant ($p<0,05$)

The authors think these effects are genetically induced because it is not plausible that doses in pregnant women rose in the period of decreasing environmental contamination and decreasing food contamination after the accident.

The genetic origin is confirmed in those anomalies which are combined with a recognized gene mutation that is not present in either of the parents. This can only have originated between the generations. This kind of congenital defect has also increased in Belarus (Lazjuk 1999).

Increased rates were recorded in the Belarussian registry at least up to the year 2004 (Yablokov 2009). Because the data were averaged over longer periods, it is not possible to determine how long the rates were increasing, when they reached a maximum, or if they had already decreased.

Wertelecki (2010) found increased rates of congenital malformation in the years 2000-2006 – more than 14 years after the accident – in the Ukrainian province (oblast) Rivne, about 250 km west of Chernobyl. Predominantly in the highly contaminated northern part, there are significant increases in comparison to the southern part: by 52 % for all malformations, 46 % for neural tube defects, 180 % for microcephaly, and 389 % for microphthalmos (abnormally small eyes). The author interprets the effect as induced in utero.

A region where the population has also been exposed to large amounts of radioactivity is near the former Soviet nuclear test site near the town Semipalatinsk (now in Kazakhstan). The tests above ground occurred between 1949-1963. Sviatova and coworkers (2001) studied congenital malformations in three generations of inhabitants, investigating births between 1969-1997. They found significantly increased rates of malformations as a whole, including Down´s syndrome, microcephaly and also multiple malformations in the same individual.

If a population is exposed, genetic effects will occur in the gonads of fathers as well as of mothers. In Germany, an investigation was done in women who were occupationally exposed to radiation which showed a 3.2-fold significant increase in congenital abnormalities, including malformations, in their offspring (Wiesel 2011). The authors interpret this effect as generated in utero but do not prove such a connection because it appears improbable given the short sensitive phase in pregnancy and the ban on pregnant women working in high risk environments.

Although the study was funded by the Ministry of Environment, Protection of Nature and Nuclear Safety, these alarming results have not resulted in any action. The findings confirm early results in the Department of Medical Genetics of the Montreal Children´s Hospital where the genetic effects of diagnostic X-rays were investigated (Cox 1964). The author observed the offspring of mothers who had been treated in childhood for congenital hip dysplasia since 1925 and were X-rayed for several times in the pelvis region. The ovarian dose was estimated to lie between 60–200 mSv. In 201 living births of these women occured 15 individuals with severe malformations and other congenital distortions or Down´s syndrome, who required hospitalization, and 11 cases with other abnormalities (all congenital abnormalities 12.9 per cent) while the control group showed less than half of this rate. The latter was chosen from a large group of descendants where the parents were unexposed siblings of the study group.

Studies in the descendants of occupationally exposed men where the mothers were not exposed have also been undertaken and show definite hereditary effects (Table 4).

Table 4. **Congenital anomalies, especially malformations, in descendants (1st generation) of occupationally exposed men**

No.	Cohort of fathers	Kind of defect	Dose	References
1	Radiologists U.S.A. 1951	Congenital malformations Increase 20 %		Macht 1955
2	Workers of the Hanford Nuclear facility, U.S.A.	Neural tube defects significantly increased by 100 %	In general < 100 mSv	Sever 1988
3	Radiation workers at Sellafield nuclear reprocessing plant, U.K.	Stillbirths with neural-tube defects significantly increased by 69 % per 100 mSv	Mean 30 mSv	Parker 1999
4	Radiographers in Jordan	Congenital anomalies significantly increased 10-fold		Shakhatreh 2001
5	Liquidators from Obninsk (Russia), 300 children	Congenital anomalies increased 1994-2002	Mainly 10-250 mSv	Tsyb 2004
6	Liquidators from Russia, Bryansk region	Congenital anomalies increased about 4-fold		Matveenko 2005
7	Liquidators from Russia 2379 newborns	Significantly increased by: Anencephaly 310 % Spina bifida 316 % Cleft lip/palate 170 % Limb reduction 155% Multiple malformations 19 % All malformations 120 %	5-250 mSv	Lyaginskaja 2009

There were only few studies before 1986, when the accident of Chernobyl occurred, in occupationally exposed cohorts and therefore also very few in their children. Exposures below the official dose limits were thought to be too low to produce statistically recognizable effects.

The registered doses of workers in nuclear establishments (Nos. 2 and 3 in Table 5) are very low. But the alarming findings did not lead to further studies about hereditary sequels in the American or European populations concerned.

About 800,000 mainly young men from the army and other official institutions as well as reservists were “liquidators”, sent after the Chernobyl catastrophe to stop radioactive emissions and for decontamination of the affected area. They are a great cohort for studying the health of their descendants (Nos. 5-7 in Table 5). Typically, the anomalies seen in these groups, also

indicate unexpectedly high radiation sensitivity. The doubling doses are in the region of 100 mSv and below.

Sex ratio and X-linked lethal factors

Normally, it is not possible to study how many inseminated oocytes (zygotes) will be aborted after irradiation of the gonadal cells, in humans. There is however, one way to prove such an effect. It is observed that men who were exposed before fathering will have fewer daughters than sons as normally, i.e., the male/female sex ratio increases with dose.

Gene mutations may be responsible for the death of the zygote and will also occur in the sex chromosomes where they will predominantly affect the greater X-chromosome. The X-chromosome of the male can only be transmitted to a daughter. A dominant lethal factor will then lead to the death of the female zygote. Recessive lethal factors in the X-chromosome are much more frequent than dominant ones (Vogel 1969). They also affect only female births. Studies in large exposed populations can show this effect. A very impressive result was obtained in workers of the British nuclear fuel reprocessing plant at Sellafield in West Cumbria (Table 5).

Table 5. **Sex ratio for births in Cumbria**
(Dickinson et al. 1996)

All Cumbrian children	All fathers employed*) at Sellafield	Fathers employed at Sellafield > 10 mSv**)
1.055	**1.094**	**1.396**

*) employed before conception **) dose 90 days preconceptional

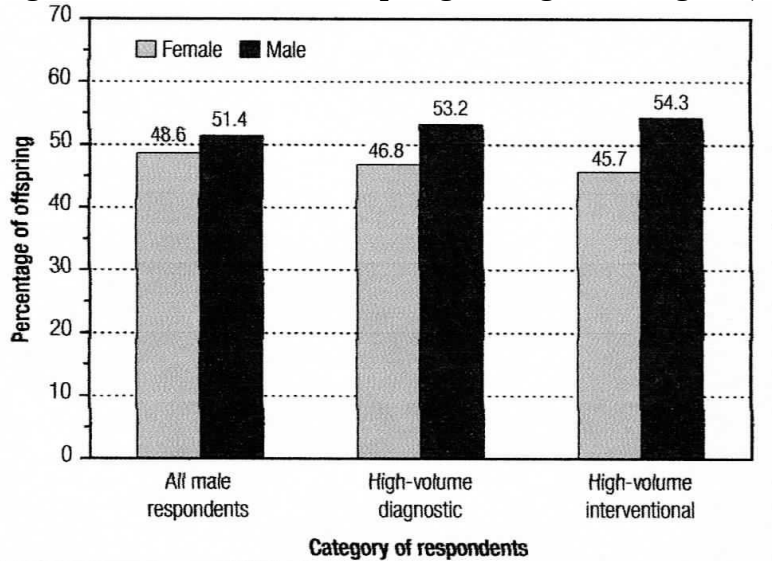
A similar effect is detected in an investigation of cardiologists, who undertook interventional angiographic procedures in patients, which involve relatively high x-ray exposures at the workplace (Fig. 5). The portion of female descendants declines significantly with higher exposures of the father[3].

German scientists Hagen Scherb, Kristina Voigt (Helmholtz Center Munich) and co-workers have shown that exposure of both parents in a population may also lead to a decline in female births. They studied different groups of inhabitants in a variety of countries after the Chernobyl accident for hereditary effects and found radiation-induced foetal deaths and early mortality, Down´s syndrome and alterations of the sex ratio in newborn children.
The sex ratio was investigated by them as a consequence of:

Nuclear tests above ground which affected U.S. inhabitants,
Chernobyl emissions in Europe,
Living near European nuclear plants.

[3] The authors wanted to study the reverse, however, if the male births will decline with dose.

Fig. 5. Percentage of male and female offspring among cardiologists (Choi et al. 2007)



They found significant decreases in the female birth rate in all these conditions. Fig. 6 shows the evolution of the male proportion of births after Chernobyl. The annual data show a sharp increase in the year 1987 after the accident in April 1986.

Fig. 6. Male proportion of birth rate before and after Chernobyl for the Czech Republic, Denmark, Finland, Germany, Hungary, Norway, Poland and Sweden combined (CDFGHNPS) and for Bavaria, the former GDR, and West Berlin combined (BGW) (Scherb et al. 2007)

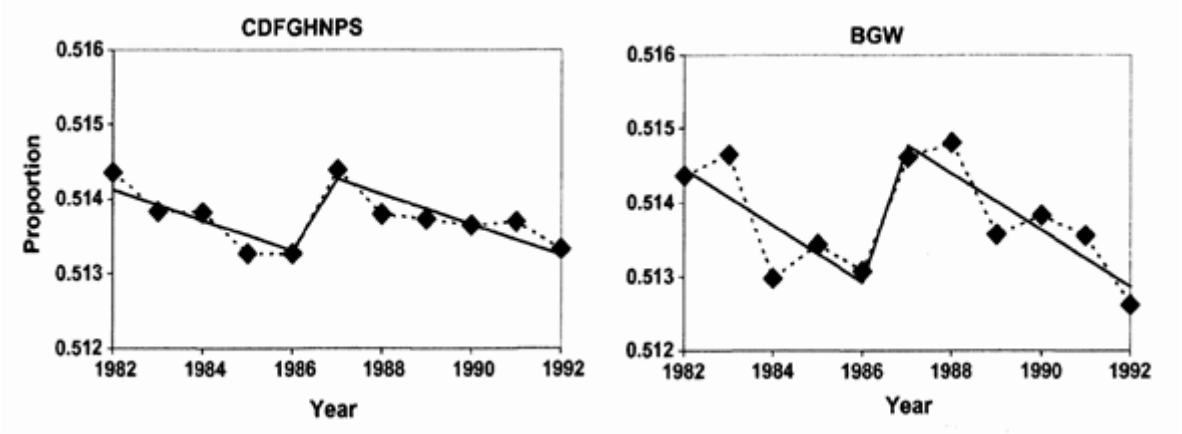


Table 6 shows their findings near nuclear plants in Germany and Switzerland. Although a fairly wide area had been chosen (radius of 35 km), because only few people live in the vicinity of nuclear power plants, a significant deficit in female births is proven there.

Sex ratio is a very relevant parameter. It shows that genetic alterations are induced in the germ cells of men by very low doses, and it proves to be a sensitive indicator for exposures of the population.

Table 6. **Sex ratio in newborn babies near nuclear facilities in Germany and Switzerland (Scherb et al. 2012)**

No. (s. Fig. 2)	NF	Type	In operation since/to	Live births < 35 km during NF operation, lagged for gestation		Sex odds ratio vs. last row of this Table	p-value (Chi^2)	hold one NF out p-value (Chi^2), compare to **
				male	female			
1	Biblis	PWR	1975 -	223,648	211,753	1.0017	0.5804	0.0007
2	Obrigheim	PWR	1969 - 2005	164,321	155,447	1.0026	0.4733	0.0010
3	Neckarwestheim	PWR	1976 -	380,463	360,212	1.0017	0.4640	0.0005
4	Philipsburg	BWR/PWR	1980 -	333,967	314,761	1.0063	0.0133	0.0019
5	Grafenreihnfeld	PWR	1981 -	95,714	90,722	1.0006	0.8957	0.0007
6	Isar I und II	BWR/PWR	1977 -	67,059	63,341	1.0041	0.4627	0.0011
7	Gundremmingen	BWR	1966 -	142,702	135,276	1.0005	0.8986	0.0006
8	Fessenheim	PWR	1977 -	99,148	93,694	1.0036	0.4290	0.0012
9	Beznau I und II	PWR	1969 -	337,335	317,880	1.0065	0.0106	0.0031
10	Goesgen	PWR	1979 -	220,979	208,604	1.0047	0.1308	0.0005
11	Leibstadt	BWR	1984 -	143,467	135,293	1.0057	0.1354	0.0008
12	Muehleberg	BWR	1971 -	218,795	207,560	0.9998	0.9387	0.0004
13	Emsland	PWR	1988 -	55,502	52,301	1.0065	0.2915	0.0011
14	Grohnde	PWR	1984 -	84,739	80,308	1.0008	0.8791	0.0009
15	Wuergassen	BWR	1972 - 1994	34,453	32,643	1.0010	0.8960	0.0010
16	BR*	PWR	1962 - 1987	5,332	5,288	0.9563	-	-
17	Doel*	PWR	1974 -	392,512	375,500	0.9914	-	-
18	Tihange*	PWR	1975 -	122,594	117,476	0.9897	-	-
19	Dodewa*	BWR	1968 - 1997	5,926	5,710	0.9843	-	-
20	Brunsbuettel	BWR	1977 -	21,085	20,003	0.9997	0.9779	0.0010
21	Brokdorf	PWR	1986 -	15,505	14,769	0.9957	0.7073	0.0009
22	Kruemmel	BWR	1984 -	35,882	33,745	1.0085	0.2662	0.0012
23	Stade	PWR	1975-2003	43,456	40,771	1.0109	0.1174	0.0021
24	Unterweser	PWR	1979 -	86,010	81,341	1.0029	0.5608	0.0010
25	Lingen	BWR	1968 - 1977	19,372	18,400	0.9985	0.8862	0.0007
26	Karlsruhe	BWR	1966 - 1991	149,269	140,584	1.0070	0.0624	0.0007
27	Ahaus	NSS	2000 -	26,427	24,866	1.0080	0.3701	0.0009
28	Juelich	NSS	2000 -	75,735	71,688	1.0020	0.7076	0.0008
29	Ellweiler	UM	1969 -	31,361	29,450	1.0100	0.2225	0.0013
30	Menzenschwand	UM	1969 -	132,037	124,574	1.0052	0.1892	0.0012
31	Gorleben	NSS	2000 -	1,753	1,573	1.0570	0.1108	0.0010
32	Hanau/Kahl	NFE	1969 -	54,772	51,343	1.0118	0.0577	0.0021
	German states and Switzerland < 35 km from NF			**2,532,471**	**2,393,556**	**1.0035**	** **0.0008**	
	German states and Switzerland > 35 km from NF			**7,948,690**	**7,538,729**	**1.0000**	**1.0000**	

*not considered

PWR Pressurized light water nuclear power plant BWR Boiling water reactor

UM former Uranium mine NSS Nuclear storage site NFE Nuclear fuel elements

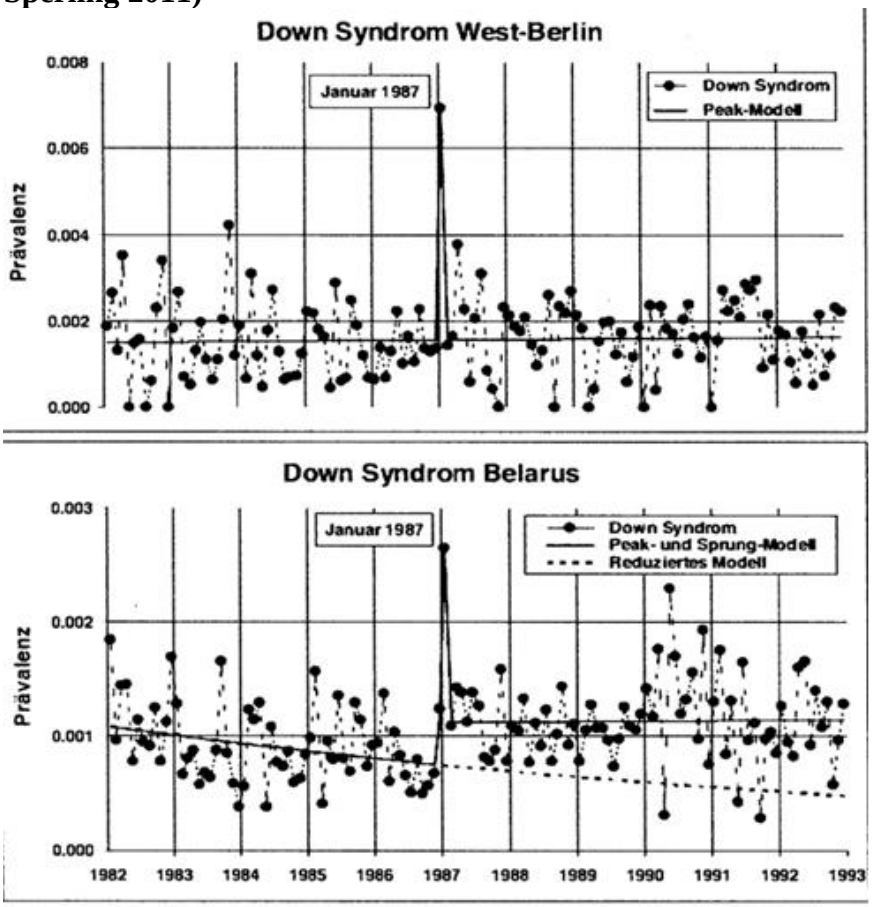
Down´s syndrome

Even before the Chernobyl accident, scientific groups had published research showing that Down's syndrome can be induced by exposure to ionizing radiation. Increased rates of this condition have also been observed in populations living in regions with high background radiation. This is the case in the Indian state of Kerala where high concentrations of natural Thorium exist in the sands (Kochupillai 1976; Padmanabhan 1994).

The effect was also shown in high altitude regions of China that have significantly increased cosmic radiation (High Background Rad. Res. Group 1980; Wei 1990). As already mentioned, the population near Semipalatinsk in Kazakhstan contaminated by the former Soviet nuclear test site also shows increased rates in the youngest generations (Sviatova 2001).

After Chernobyl, the cases of Down´s syndrome increased in several contaminated European countries (Busby 2009; Sperling 2012). Examples are shown in Figure 7. In Berlin West, which was a kind of closed island at that time, the geneticist Sperling registered a sharp and significant increase in cases exactly 9 months after the accident. A very similar situation was observed in Belarus (Zatsepin 2004). The effect of non-disjunction for chromosome 21 is assumed to occur as a result of irradiation during the first or second meiotic division of the ovum immediately before or after conception.

Fig. 7. Down´s syndrome before and after the Chernobyl accident (from Scherb and Sperling 2011)



Cancer

In 1984, an exceptionally high level of leukaemia cases in children and juveniles was reported in Seascale, a village near the British Nuclear Fuels reprocessing plant in Sellafield in Cumbria, UK. These were then explained by Martin Gardner and co-workers (1990) as a hereditary effect, because the fathers of the patients had worked in the plant. This result has been discussed in the literature for years and was confirmed or denied in several subsequent studies. The effect, however, had been described in principle already in experimental studies (Nomura 1982, 2006), and has also been found after X-ray diagnostic exposures (Table 7).

Table 7. **Cancer in children after preconceptional low-dose exposure of parents**

Exposed collective	Malign disease	Gonadal dose/mSv	Relative Risk	Doubling dose/mSv
Seascale fathers (Gardner 1990)	Leukaemia +			
all stages of spermatogenesis	lymphoma	200	7	32
6 months before conception		10	7	1.6
Sellafield workers (Dickinson 2002)			1.9	
Further occupational exposure of fathers				
Military jobs (Hicks 1984)	Cancer		2.7	
Regions of U.K. (McKinney 1991)	Leukaemia + lymphoma		3.2	
Preconceptional X-ray diagnostics in	Leukaemia			
Fathers (Graham 1966)			1.3	
Fathers (Shu 1988)			1.4-3.9	
Fathers (Shu 1994			3.8	
Mothers (Stewart 1958)			1.7	
Mothers (Graham 1966)			1.7	
Mothers (Natarajan 1973)			1.4	
Mothers (Shiono 1980)			2.6	

McKinney and co-workers found a 3.2-fold increase in leukaemia and lymphomas in children of occupationally exposed men in three British regions in a case-control study (1991). The research of Hicks and co-workers (1984) concerned exposed service men in the air force.

Statistical investigations in Belarus and the other highly contaminated neighbouring states of Chernobyl show increased cancer deaths in children who were born many years after the accident (Yablokov 2006, 2007). Higher rates of leukaemia and other cancers were also observed in children of liquidators (Tsyb 2004).

Further polygenic radiation-effects

The children of liquidators did not only show malformations and cancer but also endocrine and metabolic diseases, and furthermore mental diseases (Tsyb 2004; Pflugbeil 2006; Yablokov 2009).

The national registry of Belarus was evaluated in 1995 by a Belarussian-Israeli group of scientists (Lomat 2007). They found the following high rates of disease in children of Chernobyl-exposed parents:
Hematological diseases (6-fold),
Endocrine diseases (2-fold),
Diseases of digestive organs (1.7-fold).

Summary
Genetically induced malformations, cancers, and numerous other health effects in the children of populations who were exposed to low doses of ionizing radiation have been proved in many scientific investigations.

At present, the dose-effect dependency for these effects can only be roughly estimated. The doubling dose for malformations is in the region of a 100 mSv gonadal dose of the father or of a 100 mSv of preconceptional ovarian dose of the mother, certainly much lower than assumed by the ICRP. For cancer induction, it is even less than 100 mSv. This corresponds to the findings of Weinberg and coworkers (2001) who estimated that doses much lower than 50-200 mSv may double the generation of genomic mutations.

The question arises as to why the ICRP and UNSCEAR are denying the findings. They claim that the exposures of the population due to the Chernobyl accident were extremely low (UNSCEAR 1988). Even in the most contaminated regions of the area with more than 37 kBq/m^2 Cs-137 surface activity the mean dose in people is assumed to be no higher than 10 mSv (effective life time dose). In Turkey and the more distant countries of central Europe the mean dose is estimated at below 1.2 mSv.

Their simple conclusion is then, that such low doses are not able to produce statistically recognizable radiation effects. Many studies, however, of chromosome aberrations in the populations, equivalent to "biological dosimetry", show that the exposures are about 100-fold higher (Domracheva 2000; Schmitz-Feuerhake 2011).

The conduct of the international committees is irresponsible because much higher risks for future generations are proven than are officially considered, and the full extent of the damage cannot be estimated at present.

The possible implications of two additional effects at the cellular level, discovered only recently, must also be considered. They are called "bystander-effect" and "genomic instability" (Averbeck 2010; Baverstock 2010). Previously, the stochastic effects of ionizing radiation were thought to be the consequence of direct action of an amount of radiation on the genetic molecule. But the bystander effect shows a mutagenic effect in a cell that was not itself hit. Genomic instability means that the effect is not expressed in the immediate daughter cell of the affected one, but in a cell of a later generation of divisions.

Chromosome alterations and gene mutations found in children of liquidators and of parents exposed to Chernobyl fallout, were explained as cases of genomic instability (Pflugbeil 2006; Weinberg 2001; Yablokov 2009; Adgadzhanian 2010). Such phenomena must be taken into consideration in evaluating hereditary radiation effects, and further research on these effects must be undertaken.

References

Aghajanyan, A., Suskov, I.: Transgenerational genomic instability in children of irradiated parents as a result of the Chernobyl nuclear accident. Mutat. Res. 671 (2009) 52-57

Averbeck, D.: Non-targeted effects as a paradigm breaking evidence. Mutat. Res. 687 (2010) 7-12

Barcinski, M., Do Céu, M., Abreu, A., De Almeida, J., Naya, J., Fonseca, L., Castro, L: Cytogenetic investigation in a Brazilian population living in an area of high natural radioactivity. Am. J. Hum. Genet. 27 (1975) 802-806

Baverstock, K., Belyakov, O.V.: Some important questions connected with non-targeted effects. Mutat. Res. 687 (2010) 84-88

BEIR VII PHASE 2: Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation, Health Risks from Exposure to Low Levels of Ionizing Radiation, Nat. Academies Press, Washington D.C. 2006, www.nap.edu

Busby, C., Lengfelder, E., Pflugbeil, S., Schmitz-Feuerhake, I.: The evidence of radiation effects in embryos and fetuses exposed to Chernobyl fallout and the question of dose response. Medicine, Conflict and Survival 25 (2009) 20-40

Cox, D.W.: An investigation of possible genetic damage in the offspring of women receiving multiple diagnostic pelviv X-rays. Am. J. Human Genetics 16 (1964) 214-230

Choi, J.W., Mehrotra, P., MacDonald, L.A, Klein, L.W., Linsky, N.M., Smith, A., Riccardi, M.J.: Sex proportion of offspring and exposure to radiation in male invasive cardiologists. Proc. (Bayl. Univ. Med. Cent.) 20 (2007) 231-234

Dickinson, H.O., Parker, L., Binks, K., Wakeford, R., Smith, J.: The sex ratio of children in relation to paternal preconceptional radiation dose: a study in Cumbria, northern England. J. Epidemiol. Community Health 50 (1996) 645-652

Dickinson, H.O., Parker, L.: Leukaemia and non-Hodgkin´s lymphoma in children of male Sellafield radiation workers. Int. J. Cancer 99 (2002) 437-444

Domracheva, E.V., Aseeva, E.A. et al.: Cytogenetic features of leukaemias diagnosed in residents of areas contaminated after the Chernobyl nuclear accident. Appl. Radiat. Is. 52 (2000) 1171-1177

Feshchenko, S.P., Schröder, H.C., Müller, W.E.G., Lazjuk, G.I.: Congenital malformations among newborns and developmental abnormalities among human embryos in Belarus after Chernobyl accident. Cell. Mol. Biol. 48 (2002) 423-426

Gardner, M.J., Snee, M.P., Hall, A.J., Powell, A.J., Downes, S., Terrell , J.D.: Results of case-control study of leukaemia and lymphoma among young people near Sellafield nuclear plant in West Cumbria. Brit. Med. J. 300 (1990) 423-429

Graham, S., Levin, M.L., Lilienfeld, A.M. et al.: Preconception, intrauterine, and postnatal irradiation as related to leukemia. Natl. Cancer Inst. Monogr. 19 (1966) 347-371

Hicks, N., Zack, M., Caldwell, G.G., Fernbach, D.J., Falletta, J.M.: Childhood cancer and occupational radiation exposure in parents. Cancer 53 (1984) 1637-1643

High Background Radiation Research Group: Health survey in high background radiation areas in China. Science 209 (1980) 877-880

Hoffmann, W., Schmitz-Feuerhake, I.: How radiation-specific is the dicentric assay? J. Exp. Analysis Environ. Epidemiol. 2 (1999) 113-133

ICRP, International Commission on Radiological Protection: The 2007 Recommendations of the International Commission on Radiological Protection. ICRP-Publication 103, Ann. ICRP 37 Nos. 2-4 (2007)

IPPNW International Physicians for the Prevention of Nuclear War – Physicians for Social Responsibility: Health effects of ionising radiation: Summary of expert meeting in Ulm, Germany, October 19th, 2013 www.ippnw.de

Kochupillai, N., Verma, I.C., Grewal, M.S., Remalingaswami, Y.: Down´s syndrome and related abnormalities in an area of high background radiation in coastal Kerala. Nature 262 (1976) 60-61

Lazjuk, G.I., Nikolaev, D.L., Novikova, I.V.: Changes in registered congenital anomalies in the Republic of Belarus after the Chernobyl accident, Stem Cells 15 (1997), Suppl. 2: 255-260

Lazjuk, G., Satow, Y., Nikolaev, D., Novikova, I.: Genetic consequences of the Chernobyl accident for Belarus Republic. In: Imanaka, T. (Ed.), Recent Research Activities on the Chernobyl NPP Accident in Belarus, Ukraine and Russia, 1999, KURRI-KR-7 (Kyoto University, Kyoto), 174-177

Lomat, L., Galburt, G., Quastel, M.R., Polyakov, S., Okeanov, A., Rozin, S.: Incidence of childhood disease in Belarus associated with the Chernobyl accident. Environ. Health Persp. 105 (Suppl. 6) 1997, 1529-1532
Lyaginskaja, A.M., Tukov, A.R., Osipov, V.A., Ermalitskiy, A.P., Prohorova, O.N.: Congenital malformations at posterity of the liquidators of the consequences from Chernobyl accident. Radiazionnaya Biologiya Radioekologiya 49 (2009) 694-702 (Russ.)
Macht, S., Lawrence, P.: National Survey of congenital malformations resulting from exposure to Roentgen radiation. Am. J. Roentgenol. 73 (1955) 442-466
Matveenko, E.G., Borovykova, M.P., Davydow, G.A.: Physical characteristics and primary morbidity in liquidator´s children. In Proceed. Conference "Chernobyl 20 Years After", 2005, cited from Yablokow 2009, p. 148
McKinney, P.A., Alexander, F.E., Cartwright, R.A., Parker, L.: Parental occupations of children with leukemia in west Cumbria, north Humberside, and Gateshead. Br. Med. J. 302 (1991) 681-687
Muller, H.J.: Über die Wirkung der Röntgenstrahlung auf die Erbmasse. Strahlentherapie 55, 1936, 207-224
Natarajan, N., Bross, I.D.J.: Preconception radiation leukemia. J. Med. 4 (1973) 276-281
Nomura T 1982 Parental exposure to X-rays and chemicals induces heritable tumours and anomalies in mice *Nature* **296** 575-7
Nomura, T.: Transgenerational effects of radiation and chemicals in mice and humans. J. Radiat. Res. 47, Suppl. (2006) B83-B97
Padmanabhan, V.T., Sugunan, A.P., Brahmaputhran, C.K., Nandini, K., Pavithran, K.: Heritable anomalies among the inhabitants of regions of normal and high background radiation in Kerala: results of a cohort study, 1988-1994. Int. J. Health Serv. 34 (1994) 483-515
Parker, L., Pearce, M.S., Dickinson, H.O., Aitkin, M., Craft, A.W.: Stillbirths among offspring of male radiation workers at Sellafield nuclear reprocessing plant. Lancet 354 (1999) 1407-1414
Pflugbeil, S., Paulitz, H., Claußen, A., Schmitz-Feuerhake, I.: Gesundheitliche Folgen von Tschernobyl. 20 Jahre nach der Reaktorkatastrophe. In IPPNW, Ges. f. Strahlenschutz e.V. Berlin, April 2006, 76 p.
Pohl-Rüling, J., Fischer, P.: The dose-effect relationship of chromosome aberrations to α and γ irradiation in a population subjected to an increased burden of natural radioactivity. Radiat. Res. 80 (1979) 61-81
Scherb, H., Weigelt, E.: Zunahme der Perinatalsterblichkeit, Totgeburten und Fehlbildungen in Deutschland, Europa und in hochbelasteten deutschen und europäischen Regionen nach dem Reaktorunfall von Tschernobyl im April 1986, Berichte des Otto Hug Strahleninstituts Nr. 24 (2003) 35-75
Scherb, H., Weigelt, E.: Cleft lip and cleft palate birth rate in Bavaria before and after the Chernobyl nuclear power plant accident. Mund Kiefer Gesichtschir. 8 (2004) 106-110
Scherb, H., Voigt, K.: Trends in the human sex odds at birth in Europe and the Chernobyl Nuclear Power Plant accident. Reprod. Toxicol. 23 (2007) 593-599
Scherb, H., Voigt, K.: The human sex odds at birth after the atmospheric atomic bomb tests, after Chernobyl, and in the vicinity of nuclear facilities. Environ. Sci. Pollut. Res. 18 (2011) 697-707
Scherb, H., Sperling, K.: Heutige Lehren aus dem Reaktorunfall von Tschernobyl. Naturwiss. Rundschau 64, Heft 5 (2011) 229-239
Scherb, H., Voigt, K., Kusmierz, R.: Modelling human radiation risks around nuclear facilities in Germany and Switzerland: a case study. In Seppelt, R. et al. (Eds.) 2012 Int. Congr. Environ. Modelling and Software Managing Resources of a Limited Planet. Sixth Biennial Meeting, Leipzig, Germany http://www.iemss.org/society/index.php/iemss-2012-proceedings
Schmitz-Feuerhake, I.: How reliable are the dose estimates of UNSCEAR for populations contaminated by Chernobyl fallout? A comparison of results by physical reconstruction and biological dosimetry. ECRR Int. Conference „Criticisms and Developments in the Assessment of Radiation Risks" in Molyvos, Lesbos, Greece, May 5-6, 2009. Proceedings 2011, 70-85
Sever, L.E., Gilbert, E.S., Hessol, N.A., McIntyre, J.M.: A case-control study of congenital malformations and occupational exposure to low-level ionizing radiation. Am. J. Epidemiol. 127 (1988) 226-242
Shakhatreh, F.M.: Reproductive health of male radiographers. Saudi Med. J. 22 (2001) 150-152
Shevchenko, V.A., Platonov, E.S., Snigiryova, G.P.: Genetic consequences of disaster at Chernobyl nuclear plant on April 26, 1986. In: Int. Association for Restoration of the Environment and for Safe

Living of People “Senmurv” (Minsk-Moscow-Kiev): Chernobyl Accident. Reasons and Consequences. Ed. V.B. Nesterenko, Minsk 1997, P. 213-245
Shiono, P.H., Chung, C.S., Myrianthopoulos, N.C.: Preconception radiation, intrauterine diagnostic radiation, and childhood neoplasia. J. Natl. Cancer 65 (1980) 681-686
Shu, X.O., Gao, Y.T., Brinton, L.A., Linet, M.S., Tu, J.T., Zheng, W., Fraumeni, J.F.: A population-based case-control study of childhood leukemia in Shanghai. Cancer 62 (1988) 635-644
Shu, X.O., Reaman, G.H., Lampkin, B., Sather, H.N., Pendergrass, T.W., Robison, L.L.: Association of paternal diagnostic x-ray exposure with risk of infant leukemia. Cancer Epidemiol., Biomarkers & Prevention 3 (1994) 645-653
Sperling, K., Neitzel, H., Scherb, H.: Evidence for an increase in trisomy 21 (Down syndrome) in Europe after the Chernobyl reactor accident. Genet. Epidemiol. 36 (2012) 48-55
Stewart, A., Webb, J., Hewitt, D.: A survey of childhood malignancies. Brit. Med. J. (1958) 1495-1508
Sviatova, G.S., Abil´dinova, GZh., Berezina, G.M.: Frequency, dynamics, and structure of congenital malformations in populations under long-term exposure to ionizing radiation. Genetika 37 (2001) 1696-1704 (Russian)
Tsyb, A.F., Souchkevitch, G.N., Lyasko, L.I., Artamonova, Yu.Z., Nvolokon, V.V., Raykina, L.G.: General characterization of health in first-generation offspring born to liquidators of the Chernobyl NPP accident consequences. Int. J. Radiat. Med. Special Issue 6 (1-4) 2004 http://www.mns.gov.ua
Uma Devi, P., Nagarathnam, A., Satish Rao, B.S.: Introduction to Radiation Biology. B.I. Churchill Livingstone PVT Ltd. New Delhi 2000
UNSCEAR United Nations Scientific Committee on the Effects of Atomic Radiation: Sources, effects and risks of ionizing radiation. 1988 Report to the General Assembly, United Nations, New York 1988
UNSCEAR United Nations Scientific Committee on the Effects of Atomic Radiation: Hereditary effects of radiation. 2001 Report to the General Assembly, United Nations, New York 2001; www.unscear.org
Vogel, Friedrich et al.: Strahlengenetik der Säuger. Band 1. Fortschritte der allg. und klinischen Humangenetik. Eds. E. Becker et al., Georg Thieme Verlag Stuttgart 1969
Wang, Z., Boice, J.D., Wei, L., Beebe, G.W., Zha, Y., Kaplan, M.M., Tao, Z. et al.: Thyroid nodularity and chromosome aberrations among women in areas of high background radiation in China. J. Nat. Cancer Inst. 82 (1990) 478-485
Wei, LX., Yongru, Z., Zufan, T., Weihui, H., Deqing, C., Yongling, Y.: Epidemiological investigation of radiological effects in high background radiation areas of Yangjiang, China. J. Radiat. Res. 31 (1990) 119-136
Weinberg, H.Sh., Korol, A.B., Kirshner, V.M. et al.: Very high mutation rate in offspring of Chernobyl accident liquidators. Proc. R. Soc. Lond. B 268 (2001) 1001-1005
Wertelecki, W.: Malformations in a Chornobyl-impacted region. Pediatrics 125 (2010) 836-843
Wiesel, A., Spix, C., Mergenthaler, A., Queißer-Luft, A.: Maternal occupational exposure to ionizing radiation and birth defects. Radiat. Environ. Biophys. 50 (2011) 325-328
Yablokov, A.V.: The Chernobyl catastrophe – 20 years later. In C.C. Busby, A.V. Yablokov (Eds.), European Committeee on Radiation Risk ECRR, Chernobyl: 20 Years on. Green Audit 2006 www.euradcom.org
Yablokov, A.V., Nesterenko, V.B., Nesterenko, A.V.: Chernobyl– Consequences of the catastrophe for people and the environment. Ann. New York Academy of Sciences Vol.1181, Boston 2009
Zatsepin, I.O., Verger, P., Robert-Gnansia, E., Gagniere, B., Khmel, R.D., Lazjuk, G.I. (2004): Cluster of Down´s syndrome cases registered in january 1987 in Republic of Belarus as a possible effect of the Chernobyl accident, Int. J. Radiat. Med. Special Issue 6 (1-4), Kiev: 57-71 http://www.mns.gov.ua