

Effects of radiation exposure on offspring and next generations: Genetic and epigenetic effects

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ICRP



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Effects in offspring and next generations after preconceptional exposure of germ cells

Assessment of the effects in offspring – current situation

- Topic not updated by ICRP since UNSCEAR 2001 Report.
- Diversity of adverse effects: Mendelian diseases, chromosomal diseases, chronic diseases, congenital abnormalities
- Hereditary effects are integrated as a simple add-in risk in the radiation detriment calculation process, with no specific consideration that results being used are derived from animal experiments.
- Heritable effects on non-human biota are not considered in the RP system.
- A revised assessment of the effects of ionising radiation in offspring and next generations is needed to inform future global revisions of the system of radiological protection -> Task Group 121

Assessing genetic risk of ionizing radiation in humans – current situation

Epidemiological studies not very helpful

- Direct evidence on hereditary effects in humans is very scarce
- Difficult to study: A germline mutation may take place in any of the 20,000 genes of a human -> the type and severity of the potential harm due to the mutation vary a lot

The assessment of hereditary risk has based on

- animal experiments
- general knowledge on human genome

Effects of radiation exposure on offspring and next generations

Genetic and epigenetic effects

Preconceptional exposure of germ cells before fertilisation

Heredity, also called **inheritance** or biological inheritance, is the passing on of traits from parents to their offspring

Hereditary (heritable) effects

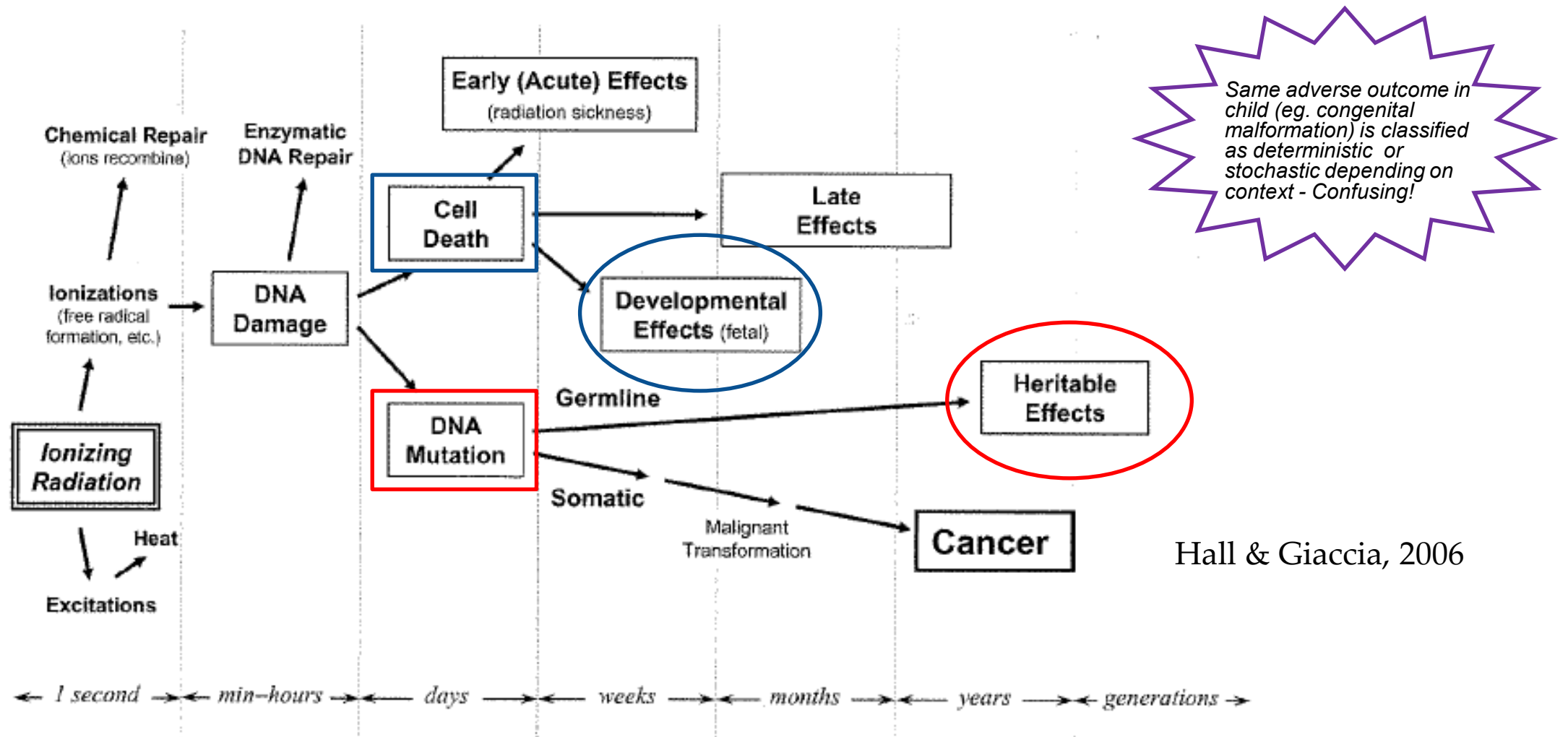
- **Genetic effects:** inheritable changes in genotype (mutations in DNA)
- **Epigenetic effects:** inheritable phenotype changes that do not involve alterations in the DNA sequence

Transgenerational inheritance is the transmission of epigenetic markers from one organism to the next that affects the traits of offspring without alteration of the primary structure of DNA

Note on terminology: For information transfer taking place

- cell-cell (-> genetic, epigenetic) - biological markers
- organism-organism (->hereditary/heritable, transgenerational) - traits

Classic Paradigm of Radiation Injury



Same adverse outcome in child (eg. congenital malformation) is classified as deterministic or stochastic depending on context - Confusing!

Hall & Giaccia, 2006

FIGURE 1.9 ● Illustration of the generally accepted sequence of events from the absorption of radiation to the expression of the various forms of biological damage. (Developed in collaboration with Dr. Noelle Metting, U.S. Department of Energy.)

WORKSHOP

Effects of Ionising Radiation Exposure in Offspring and Next Generations

31st May – 2nd June 2022
Budapest, Hungary



In parallel with the 6th
European IRPA Congress

Jointly organized by ICRP Task Group 121 under Committee 1 and
European Radiation Protection Research Platforms MELODI and ALLIANCE



Questions for group discussions

Experimental study designs?
Which species are best models for humans?
Transferability of of results from animal studies to humans?
Which endpoints / surrogate markers likely to be informative?
Dose and time dependence in progression of germ cell damage?
How many generations should be followed?
Are there stages in spermatogenesis and oogenesis that are more vulnerable?
Which organs should be studied?
New information since 2007?

Epidemiological evidence?
Which endpoints are most pertinent?
How many generations should be followed?
Genetic vs. epigenetic effects?
New information since 2007 recommendations?
Detriment?
Confounding/ modifying factors (lifestyle etc.)?
Sensitivity of germ cell stages?
Suitable age to study?

A Hereditary and epigenetic effects due to exposure of germ cell line (pre-conceptual exposure)

Mechanistic approaches?
Which are the driving mechanisms that should be explored to improve
understanding of radiation-induced effects in offspring and next generations?
What mathematical models would be useful?
Relative contribution of genetic vs. epigenetic mechanisms
in disease development?
New information since 2007?
Are there potential radiation protection actions that should be taken for
prevention of genetic or epigenetic effects after exposure has taken place?

Genetic effects: heritable changes in genotype

New knowledge on radiation effects during the last two decades:

- A reappraisal on congenital malformations and perinatal deaths among the children of atomic bomb survivors (Yamada et al. 2021)
 - Radiation is associated with increased risk of UPO, but the estimates are imprecise for direct radiation effects, and most are not statistically significant.
- Direct analysis of mutations by comparing the genetic sequence of parents and offspring (Trio studies of mother, father and child)
 - Experimental studies in mice (Adewoye et al. 2015)
 - Lack of transgenerational effects of ionizing radiation exposure in cleanup workers and evacuees of the Chernobyl accident (Yager et al. 2021)
 - Germline mutations occur much less frequently than would be expected from the results of past studies which used specific locus tests.
- Why genetic effects of radiation are observed in mice but not in humans? (Nakamura 2018, 2019)

Epigenetic effects: heritable phenotype changes

Epigenetic inheritance changes our understanding on mechanisms of heredity: not only genes but also their functional status can be inherited

New knowledge during the last two decades:

- Better understanding of epigenetic effects in general but not many studies on radiation effects
- Many factors have been shown cause epigenetic alterations: aging, nutrition, alcohol, metals, benzene, air pollutants, radiation
- A range of epigenetic markers:
 - Covalent modifications of either DNA or histone proteins (chromatin remodelling), RNA transcripts, microRNAs, mRNA, sRNAs, Prions...
- Cell-to-cell transmission of epigenetic markers are major drivers in e.g. differentiation of cells, aging, many pathologies (cancer, CVD...)
- Some evidence on transgenerational transmission of epigenetic markers
- Lack of studies on radiation-induced heritable changes in humans

Human hereditary diseases

- Mendelian diseases (one gene diseases)
 - Dominant inheritance: mutation in one allele causes symptoms, effects seen F1 generation; selection pressure against severe syndromes
 - Recessive inheritance: mutation in both alleles needed, takes several generations to see change in disease incidence
 - Each person is carrier of 5-10 recessive mutations
- Chromosomal diseases
 - Chromosomal anomalies often result in spontaneous abortion at embryonic stage
- Congenital malformations are fairly frequent among populations
 - 2-3 % of newborns have severe malformations that lead to shortening of life span or severe functional problems
 - An additional 2-3% have malformations that manifest by age 5
 - In addition, 5-13 % of people have smaller malformations
- Chronic diseases (multifactorial or polygenic inheritance)
 - predisposing genes + environment, nutrition, lifestyle (epigenetic?)

Conclusive remarks

- By the time the need of limiting stochastic effects was acknowledged by the the radiation protection community in 1960s-1970s, a major driver was the concern on genetic effects.
 - Large scale animal experiments (specific locus tests)
 - Leukemias observed among a-bomb survivors
- More recently, an increase in solid cancers, much larger in numbers, became evident
- Consequently, the relative contribution of hereditary effects in radiation detriment has come down
- Currently,
 - Whole genome analyses suggest that germline mutation rate is lower than that observed in specific locus tests
 - Epigenetic effects coming up as new class of heritable changes, caused by a number of factors.