Emerging issues with regard to organ/tissue dose

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Low-dose ionizing radiation risk research: key issues

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MELODI (Multidisciplinary European Low Dose Initiative)

- MELODI is an European Platform dedicated to low-dose ionizing radiation risk research.
- The purpose is to integrate national and European research activities
- Prior to EU research funding calls, MELODI develops a short statement indicating its view on *current research priorities*

MELODI priorities
Rank 1: high priority

- potential impact of individual susceptibility : gender, age at exposure, state of health, genetic and epigenetic make-up, lifestyle, and age attained.
- Important in emergency response and in post-accidental situations – children, pregnant women and elderly/ill persons being priority groups.
- Extremely relevant for radiation protection of patients

MELODI priorities
Rank 2

- Health effects of inhomogeneous dose distributions, including internal emitters.
  - Current radiation weighting factors: reflect only spatial dose distribution differences between radiations of differing quality
  - Need of updated fundamental dose concepts and quantities

MELODI priorities
Rank 2

- To identify, develop and validate biomarkers for exposure, early and late effects for cancer and non-cancer diseases

- Target cells for cancer and non-cancer diseases

MELODI priorities
Rank 3: low priority (because long term)

- Shape of the dose-response relationship for all radiation-induced health effects (also non-cancer diseases)

MELODI priorities
Rank 2

- Last but least!

- role of **epigenetic modifications**
  - without DNA mutation
  - linked to the induction and persistence of IR-induced genomic instability
  - Concern all effects: cancers, non-cancer diseases and hereditary/transgenerational effects.

Article 31 Working Party on Research Implications on Health and Safety Standards (WP RIHSS)

Potential topics for research, developments and assessments in support of radiological protection and implementation of Basic Safety Standards

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RIHSS main RP issues: very similar

- Non cancer radiation-induced effects (including Nervous Central System and circulatory diseases):
  - important potential impact on organ dose optimisation (EU BSS)

RIHSS main RP issues

- The *development* of quantities other than effective dose which could quantify the **risk**
  - Underlying issue is if the currently used concept of equivalent/effective dose is a right risk indicator for all types of effects (including all types of non-cancer effects).

RIHSS main RP issues

- Combined effects: interaction of ionising radiation with other toxicants (that may be present in the daily environment), such as recently illustrated in the EU CEREBRAD results (combined effects of IR and nicotine, methylmercury, the pesticide Paraquat or the flame retardant pentabromodiphenyl ether).

RIHSS main RP issues

- Chronic internal exposures:
  - data still very limited
  - topic central in any future nuclear accident
  - In particular, the role of age at exposure and of radiation-induced genomic instability should be further explored (epigenetic alterations)

RIHSS main RP issues

- Low dose irradiation in utero
  - still many uncertainties: role of genetic disorders in the pathways of DNA-repair, role of radiation-induced epigenetic effects, subtle effects or long term effects particularly after Nervous Central System irradiation, effects of chronic internal exposures.
  - The potential implications are important, particularly in emergency and post-accidental situations and in medical exposures

RIHSS main RP issues

- Transgenerational mutagenesis:
  - observable effects in the somatic cells of offspring over several generations that are not attributable to the inheritance of a simple mutation through the parental germline (**epigenetic** mechanism)
  - after irradiation of males, at least at high doses
  - up to now been observed almost only in animals (except microsatellites) but « lack of human evidence does not mean evidence of lack of effect": serious potential implications
  - Possible differences between external and (chronic) internal exposures are an important issue: the vast majority of human data are currently based on follow-up of populations after external exposures (Life Span Study, radiotherapy studies).

Transgenerational mutagenesis

- Chromosome damage
- Somatic gene mutations
- Minisatellite mutations, also in humans: evidence in groups with internal or mixed exposure from environmental contamination (Chernobyl, Kazakhstan, Techa-River)
- Induced radiosensitivity: 1 report in Chernobyl (Aghajanyan 2009)
- Cell proliferation defects: persistant gene expression changes (multigenerational)

A cross-cutting issue:
IR-induced epigenetic alterations
New paradigm?

IR-induced Epigenetic alterations (1)

- ?: DNA-methylation, Histone modifications, micro-RNAs
- DNA methylation (of cytosine) : repression of gene expression (gene silencing); mechanism that safeguard genome stability
  - cancer cells: frequently global DNA hypomethylation (genomic instability) ; with hypermethylation (silencing) of tumor suppressor genes
  - IR exposure : dose-dependent and tissue-specific global hypomethylation , linked to genomic instability
  - involvement in transgenerational effects induced from the paternal irradiation (global loss of DNAmethylation in the thymus, bone marrow, and the spleen of F1 offspring) with genomic instability

IR-induced Epigenetic alterations (2)

- Histone modifications
  - numerous transcriptional consequences
- Micro-RNAs
  - abundant small non-coding RNAs that regulate gene expression (e.g., post-transcriptional gene silencing)
  - play key roles in numerous biological contexts, including cellular differentiation, proliferation, apoptosis

Role of epigenetic in embryo risk?

- Wertelecki 2010 (University of South Alabama)
  - Ukraine oblast of Rivne: one of the populations most exposed to chronic low-dose radiation from Chernobyl
  - 200 km distant from the Chernobyl site
  - births between 2000 and 2006: overall rate of neural tube defects (including spina bifida) among the highest in Europe
  - limitations of this study: lack of data regarding levels of low-dose radiation, possible folate deficiency, prenatal alcohol exposure, consanguinity.
- Dancause 2010: diet and exposure routes in Rivne
  - Wild foods, especially mushrooms and berries, and locally produced foods, especially milk related, were major radiation exposure routes
  - Alcohol intake was low

Blastopathies and microcephaly in a Chornobyl impacted region of Ukraine, W. Wertelecki et al, 2014

- During the 2000–2009 decade, confirms and expands previous studies (with role of consanguinity seeming unlikely)
- The CM reported are blastopathies, therefore induced prior to the embryonic implantation and organogenesis
- Advances in molecular biology and embryology suggest that this increase of blastopathies reflects IR-induced transgenerational alteration of methylation processes (with genomic instability)

Epigenetic in Chernobyl children morbidity?

- Series of IRSN studies: Rats exposed to ^{137}Caesium through drinking water (comparable with a typical low intake in the contaminated territories): *various unexpected biological effects*
- Series of longitudinal studies in Ukraine in conjunction with the US University of South Carolina: for example:
  - significant reduction in red and white blood cell counts, platelet counts and haemoglobin with increasing residential soil contamination
  - spirometry: statistically significant evidence of both airway obstruction and restriction with increasing soil contamination (immune mechanism?)
  - Recently: confirmed by anthropogammametry

Way forward (1)

There is a need to explore the potential role of these epigenetic effects, particularly in non-cancer and hereditary diseases, and the relation with age at exposure (incl in utero) and environmental stress, including chronic internal exposures.

This is the area where the uncertainties are the largest and at the same time for which the potential implications for radiation protection are the most striking, particularly in post-accidental situations..

Way forward (2)

The continuation of the Chernobyl research programs, in particular a long term LSS-like follow up, is an ethical need.

Even if the situation for conducting such studies is not ideal, it is the only possibility to study a large population exposed to protracted and/or chronic exposures of IR and showing a large inhomogeneity in the dose distribution.

This issue will be central in any future nuclear accident.

An important issue is that the scope of these programs should include exploring the possible role of accumulation of epigenetic effects, particularly in children chronically exposed by ingestion of caesium 137.

Beware of some current (and malicious) statements

- « Estimated doses are so small that IR cannot be the cause »
- « OK LNT is confirmed by recent medical studies but Low Dose Rates (as post-accidental) are safe! »
- « An accident will never occur » becomes « an accident will occur but don’t worry about consequences : after an accident the main issue is psycho-social »

Under the “precautionary principle” , those who dictate or advocate policies in the absence of scientific evidence or consensus have the responsibility to demonstrate that their proposed, imposed, or advocated policies are not harmful to the public or the environment. Arguably, official assertions that Chornobyl IR is not teratogenic contradict this precautionary principle.

In any case, the repeated unsubstantiated official denials of teratogenic impacts or even the possibility of such impacts posed by Chornobyl had a chilling effect on initiatives to investigate their validity.”

(Wertelecki)