

# Opportunities and challenges in low dose risk research

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Despite major research efforts during the past decades worldwide there are uncertainties remaining associated with health risks and effects due to exposures to low dose ionizing radiation. These uncertainties impair the available decision-making capabilities, whether in responding to radiological events involving large populations as well as vulnerable population groups (eg. 2011 Fukushima accident) or in areas such as the rapid increase in radiation-based medical procedures, the clean-up of radioactive contamination from legacy sites and the civilian nuclear energy production.

There is a societal need to improve the scientific understanding of radiation-induced health risks at low doses and low dose rates. Any over-, or under-, estimation of these risks could lead either to unnecessary restriction or to a lower level of health protection than intended. Compilations of specific research needs are available at international level (UNSCEAR, ICRP).

Ongoing research activities cover a wide range of topics and methodologies, including the following areas:

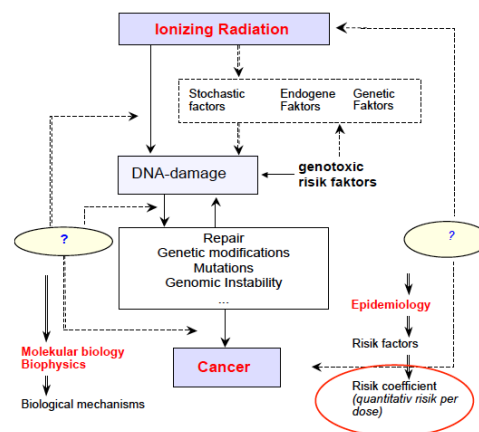
## (1) Direct effects on radiation-induced diseases

- Identification, establishment and continued follow-up of suitable cohorts of radiation exposed populations for epidemiological studies related to cancer and non-cancer effects. A re-assessment of dose (uncertainties) is highly recommended.
- Identification of the synergistic effect of combined exposure with environmental pollutants, to better match the real situation of an exposed population.
- Identification, development and validation of biomarkers for radiation exposure, effects and disease.
- Continuing development of suitable whole animal as well as human cellular models (including somatic stem cells) for radiation carcinogenesis and non-cancer diseases which bear clear relationships to human diseases.
- Examination of the impact of low dose and low dose rate radiation effects on pathways/processes contributing to human pathologies. This involves the understanding of the relationship between early and late effects, targeted and non-targeted effects as well as the role of delayed genetic instability.
- Identification of the nature and number of target cells at risk for specific radiation related diseases in humans.
- Clarification of the contribution of radiation effects in target cells as well as radiation effects and responses in the tissue environment and interaction between both target cell and tissue environment at different dose levels to the development of radiation-associated diseases.
- Examination of the impact of low dose and low dose rate radiation effects on pathways/processes contributing to non-cancer disease such as cardio- and cerebro-vascular disease, cataract and impaired cognitive function.
- Better understanding of the risks of internal emitters following internal contamination with radionuclides, paying attention to the type of decay,

particle size (if applicable), the intake pathways, chemical speciation of the radioelement (and its daughters) in the tissue or body fluids and the biodistribution. Comparison of the theoretical impact using biological effectiveness data with the experimental data.

## (2) Individual and general health and radiation protection issues

- Understanding the impact of inter-individual variation of radiation risks in relation to cancer and non-cancer diseases, and how this might impact on dose response relationships in populations.
- Examination of the impact of low dose and low dose rate radiation effects on the immune function.
- Understanding the effect of age-at-exposure on radiation risk, from unborn child to adult ageing stage.
- Examination of the effect of cell death in carcinogenesis during chronic irradiation in tissue level.
- Understanding of the dependence of radiation risk on gender.
- Analysis of the role of trans-generational effects and heritable radiation effects.



According to the MELODI statement of 2013 priority of future work should be given to the:

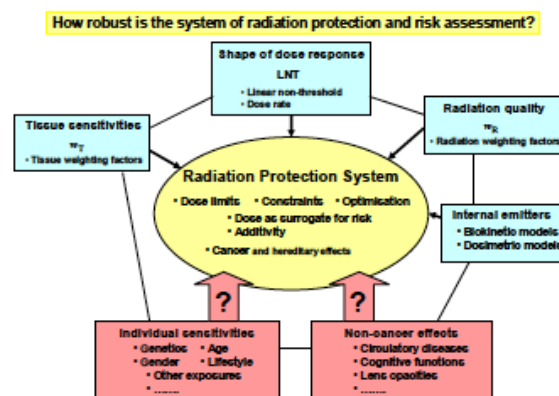
- Quantification of the role of ionising radiation in the development of non-cancer disease such as cardio- and cerebro-vascular disease, eye lens opacities and impaired cognitive function after low dose (< 500 mSv) irradiation.
- Development of suitable biomarkers for exposure, cellular and tissue effects as well as for in situ stages of diseases. The biomarkers should be usable for molecular epidemiological studies.
- Clarification of the role of effects in target cells and in the tissue environment (including stem cells and cells of the immune system) in a dose range with clear focus on low doses and low dose rates. This may include in vivo detection systems as well as suitable in vitro systems.
- Identification and analysis of suitable epidemiological cohorts if available with archived biomaterial to improve low dose radiation risk assessment by reducing uncertainties especially for the investigation of age- and gender-dependency of radiation risk. Uncertainties due to the exposure assessment should be clearly announced. Suitable data and biomaterial banks should be established with a clear focus on the possibilities to share data, material and knowledge within the scientific and wider radioprotection community.

- Development of guidelines for short, medium and long-term exposure and health risk monitoring in case of a major nuclear accident in Europe. This is to ensure the public that all possible scientific efforts are undertaken to record, document and analyse exposed populations in the scientifically best available way to generate in a comprehensive manner information about health consequences from possible accidents in the future.

The European High Level and Expert Group (HLEG) on Low Dose Risk Research addressed the key aspects of current knowledge in the low dose risk field and identified ways to improve the overall situation by answering the key policy questions by targeted research. The complex and multidisciplinary nature of these issues is such that their resolution can be achieved only through the integration of research at a European, or even international, level. The HLEG report (2009) proposes the establishment of a trans-national organisation capable of ensuring an appropriate governance of research in this field. To reach the ambitious goals, stability of R&D policies at European and national levels will be required for at least a decade.

The HLEG report is

- formulating the policy goals to be addressed by low dose risk research;
- developing a strategic research agenda (SRA) and road map for low dose risk research in Europe;
- specifying the essential elements of and next steps to establish a sustainable operational framework for low dose risk research in Europe.



According to the HLEG report, the more important issues are:

- The shape of dose-response for cancer;
- Tissue sensitivities for cancer induction;
- Individual variability in cancer risk;
- The effects of radiation quality (type);
- Risks from internal radiation exposure;
- Risks of, and dose response relationships for, non-cancer diseases;
- Hereditary effects.

The scientific and administrative challenges in implementing such a research program are to

- Enhance multi-disciplinarity;
- Include societal aspects in the scope.
- Develop a holistic research strategy;
- Secure sustainable funding.

Major EU research programs (MELODI, DoReMi, OPERRA, CONCERT) have been established to implement the ideas developed by HLEG; they provide good opportunities to integrate the available resources for research in Europe within a strategic and sustainable effort. The existing programs address a variety of scientific questions relevant to medical radiation protection, emergency preparedness and response, and radioecology.

The Multidisciplinary European Low Dose Initiative MELODI is a European Platform dedicated to low dose radiation risk research. MELODI was founded in 2010 as a registered association with 15 members (2014: 30 members).

The purpose of MELODI is to:

- Propose research and training (R&T) priorities for Europe in its field of competence;
- Contribute to the EUROPE 2020 Strategy of the European Commission;
- Seek the views of stakeholders on the priorities for research, keep them informed on progress made;
- Contribute to the dissemination of knowledge.

Key features of the MELODI working concepts are the

- Shared understanding of the overall goals and of the key questions to be addressed by research activities;
- Agreement on a long-term strategic research agenda and on a road map for the implementation of the research agenda;
- Identification of key fields of expertise (biology, biophysics, dosimetry, modelling, epidemiology), as well as of research infrastructures (research facilities, cohorts, etc.) needed for the implementation of the programs.

By integrating education and training activities the programs contribute towards sustainability in the field of low dose risk research.

One of the key objectives of MELODI is the development of a strategic research agenda (MELODI SRA) and a wide cooperation for its implementation. The MELODI SRA frames the research strategy with three key research questions:

- Dose/dose rate dependence of cancer risk?
- Threshold exposures for protection from health risks other than cancer?
- Reliable methods for identifying individual radiation sensitivity, and addressing related ethical issues?

The research approaches recommended to answer the questions are

- Radiobiology research to improve understanding of mechanisms contributing to radiation risk;
- Epidemiology Research to integrate biological indicators into radiation risk evaluation;
- Radiation protection research to better understand the specifics of internal or inhomogeneous exposures, and of different radiation qualities.

Four European Research Platforms focused on core radiation protection activities are contributing to the work:

- Low dose effects and risks: MELODI;
- Radioecology: ALLIANCE;

- Nuclear emergency preparedness: NERIS;
- Dosimetry: EURADOS.

Addition consultations with networks focussing on radiation protection in medicine are underway with the aim of integrating the existing and future research activities in this important field in the planning and implementation process.

To achieve consensus on priorities within a strategic research agenda is a complex undertaking, which requires among other things the sharing of available expertise and resources at all levels, openness, transparency and trust between the partners as well as the integration of a broad spectrum of research organizations and programs.

Four out of 15 highest ranked synergetic research priorities from the European Research Platforms SRA identified in 2014 are:

- Biological indicators of radiation exposure, effects, health risks and disease susceptibility to inform emergency management and epidemiological studies;
- Development of monitoring strategies, processes and tools;
- Spatial and temporal environmental modelling and human dose assessment after a nuclear accident;
- Development of health surveillance procedures.

Projects within these priority areas will be subject to funding by the EURATOM research program.

The purpose of the DoReMi Network of excellence (funding period: 2010 to 2015, 32 partner (2013)) is to promote the sustainable integration of low dose risk research in Europe in order to aid the effective resolution of the key policy questions identified by the High Level Expert Group (HLEG). It provides an operational tool for the development of the MELODI platform (Multidisciplinary European Low Dose Risk Research Initiative - [www.melodi-online.eu](http://www.melodi-online.eu)). The Joint Programme of Activities (JPA) include three main activities:

- Development of a Joint Programme of Research (JPR) on a rolling basis covering the issues outlined above and providing an overview of the needs for research infra-structures of pan-European interest and facilitating multilateral initiatives leading to better use and development of research infrastructures.
- Establishing a Joint Programme of Integration (JPI) to develop a coordinated European roadmap for the long term needs of the key players in Europe.
- Establishing a Joint Programme for the Spreading of Excellence (JPSE), covering knowledge management, training and mobility and its implementation.

A substantial proportion of the JPA is dedicated to the Joint Programme of Research. The programme describes a multidisciplinary approach including interfaces with the broader biological toxicological and epidemiological communities.

Within the „Open Project for the European Radiation Research Area” OPERRA, the MELODI Association takes the lead in establishing the necessary administrative and legal structures able to manage the long-term European research programmes in radiation protection, also taking advantage of the valuable experience gathered through the DoReMi network of excellence.

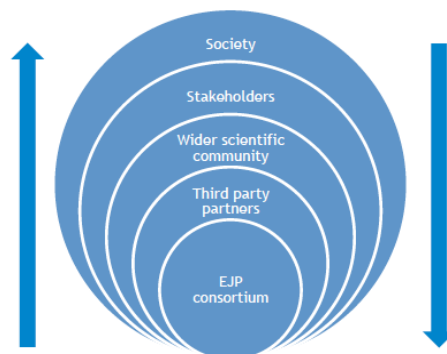
The main objectives of the, OPERRA, are to

- Build up an umbrella coordination structure that has the capacity in a legal and logistical sense to administer future calls for research in radiation protection on behalf of the European Commission as the main funding agency;
- Support the MELODI Association to take the lead to manage the long-term European research programmes together with the support of sister research structures as equal partners (e.g. Alliance, NERIS, EURADOS, EURAMET, EUTERP, etc.).

The European Strategy for Radiation Protection Research European Strategy for Radiation Protection Research, CONCERT EJP builds on the ideas described above; it has recently been established as an innovative two way street to integration. It defines an umbrella structure for radiation protection research in Europe by including activities for open research calls, integrative activities, joint programming and co-funding actions. CONCERT is open to new national Programme Managers at any time.

The EJP consortium is aiming at spreading excellence, multi-disciplinarity, and state of the art knowledge through the application of two approaches:

- Co-operation, competitive open calls processes, communication between the partners as well as
- Listening to needs, expression of priorities and innovative ideas of society through appropriate mechanisms.



The CONCERT funding scheme has a total budget of around 27 M€ over the next 5 years. 70% of the budget is covered by EURATOM, 30% by the EJP Partners; 60% of the total budget for 2016 and 2017 are allocated to two CONCERT open research calls, 30% for CONCERT integrative activities (joint programming, stakeholder engagement, access to research infrastructure, education and training (E&T), etc., and 10% for administration and management.

### **Literature**

Concert EJP: [www.melodi2014.org/files/presentations/09102014/3\\_Jung.pdf](http://www.melodi2014.org/files/presentations/09102014/3_Jung.pdf)

DoReMi: [www.doremi-noe.net](http://www.doremi-noe.net)

HLEG report: [www.hleg.de](http://www.hleg.de)

MELODI SRA: [www.melodi-online.eu/sra.html](http://www.melodi-online.eu/sra.html)

OPERRA: [www.melodi-online.eu/doc/DPP\\_OPERRA.pdf](http://www.melodi-online.eu/doc/DPP_OPERRA.pdf)