MELODI statement 2018
Gap analysis

MELODI (Multidisciplinary European Low Dose Initiative) is a European Platform dedicated to low dose ionizing radiation risk research. The purpose of the MELODI Association is to integrate national and European activities in low dose and low dose rate radiation research, to define priority scientific goals and to facilitate effective implementation of research. The MELODI Strategic Research Agenda (SRA) and Feasibility and Impact Analysis (Roadmap) identify these priority goals and the specific resources, infrastructures and training capabilities needed to further develop low-dose risk research. The current draft of the MELODI SRA is available here: http://www.melodi-online.eu/doc/MELODI_SRA_2017_06102017.pdf

Prior to EU research funding calls, MELODI develops a short statement indicating its view on current research needs, which serves as an input to those responsible for defining call topics. In October 2017 the European Commission indicated its intention to open a EURATOM call that includes radiation protection. The proposed work programme includes topics NFRP-2018-8 for research and NFRP-2018-9 for review of previous activities. NFRP-2018-8 specifically indicates that a 'Gap analysis' will be required for each proposal and NFRP-2018-9 could be usefully informed by such an analysis. The SRA Working Group of MELODI consequently has undertaken a review of relevant EURATOM research undertaken (or underway) in Framework programmes 6 and 7 (FP6, FP7) and Horizon 2020 (H2020) identifying their relevance to the six key areas of research identified in the MELODI SRA and roadmap. This informed the identification of gaps that are considered as potential areas for research under NFRP-2018-8 call. A mature reflection and identification of knowledge gaps would require results of all projects to be available; this has not been possible in all cases as some projects have yet to come to completion. We also note that the NFRP-2018-8 call text indicates that the gap analysis included in proposals will be subject to evaluation. The MELODI SRA Working Group anticipates that its gap analysis will be of benefit to those applying to the call.

The areas defined by the MELODI SRA and roadmap that require further research are:

- To explore the shape of the dose-response relationship for radiation-induced health effects (Abbreviation: Shape)
- To understand the potential impact of individual susceptibility on radiation-induced health effects (Abbreviation: Susceptibility)
- To identify, develop and validate biomarkers for exposure, early and late effects for cancer or/and non-cancer diseases (Abbreviation: Biomarkers)
- To explore and define the role of epigenetic modifications in radiation-induced health effects (Abbreviation: Epigenetics)
- To explore the roles of specific target cells for radiation-induced late developing health effects (Abbreviation: Target cells)
- To understand the health effects of inhomogeneous dose distributions, radiation quality and internal emitters (Abbreviation: Inhomogeneity)

Review of FP6, FP7 & H2020 funded projects relevant to low dose risk research

(i)   FP6 projects

Project acronym	Title	Primary disease endpoint	MELODI area addressed	Comments
RISC-RAD	**DNA damage responses, Genomic instability and Radiation-Induced Cancer: The problem of risk at low and protracted doses (RISC-RAD)**	Cancer	Shape, Susceptibility, (epigenetics)	This project undertook a wide range of experimental, epidemiological and modelling work addressing cancer dose-response and susceptibility
GENE-RAD RISK	**Radiation exposures at an early age: impact of genotype on breast cancer risk**	Cancer	Susceptibility, Biomarkers	Molecular epidemiological project on DNA repair gene variants and breast cancer risk
RACE	**Radiotherapy for breast cancer and subsequent risk of cardiovascular events**	Circulatory diseases	Shape	Clinical epidemiological follow up of radiotherapy patients for circulatory disease risk
GENEPI-LOWRT	**Genetic Pathways for the Prediction of the Effects of Ionising Radiation: Low Dose**	Cancer, tissue reactions	Susceptibility, Biomarkers, (Shape)	Search for biomarkers of response to low dose exposure in normal and

Project acronym	Title			
	Radiosensitivity and Risk to Normal Tissue after Radiotherapy			severe radiotherapy reactors
GENEPI-ENTB2	**GENEtic pathways for the Prediction of the effect of Irradiation-European normal an tumour tissue bank and data base**	Cancer, tissue reactions, circulatory disease	Susceptibility, Biomarkers	Tissue banking from radiotherapy patients. Infrastructural project
ALPHA-RISK	**Quantification of cancer and non-cancer risks associated with multiple chronic radiation exposures: epidemiological studies, organ dose calculation and risk assessment**	Cancer (circulatory diseases)	Shape, Inhomogeneity, Susceptibility	Epidemiological analysis of radon, uranium and plutonium risks
SOUL	**Southern urals radiation risk research**	Cancer, circulatory diseases	Shape, Inhomogeneity, (Biomarkers)	Epidemiological analysis of disease risk in Mayak plant workers and Techa river residents
GEN RISK-T	**Genetic component of the low dose risk of thyroid cancer**	Cancer	Susceptibility, Biomarkers, (Shape)	Experimental study to develop thyroid cancer model
NOTE	**Non-targeted effects of ionising radiation**	Cancer, circulatory diseases	Shape, Epigenetics	Experimental studies to investigate non-DNA targeted actions of radiation

(ii)   FP7 projects

Project acronym	Title	Primary disease endpoint	MELODI area addressed	Comments
ALLEGRO	**Early and late health risks to normal/healthy tissues from the use of existing and emerging techniques for radiation therapy**	Cancer	Shape, Inhomogeneity	Out-of-field doses to normal tissues delivered by a range of radiotherapy techniques

ANDANTE	**Multidisciplinary evaluation of the cancer risk from neutrons relative to photons using stem cells and the induction of second malignant neoplasms following paediatric radiation therapy**	Cancer	Inhomogeneity, Shape, Target cells	Study of risks from neutrons in radiotherapy
CARDIO-RISK	**The mechanisms of cardiovascular risks after low radiation doses**	Circulatory diseases	Shape, Target cells, (Epigenetics)	Experimental study of circulatory disease mechanisms
CEREBRAD	**Cognitive and Cerebrovascular Effects Induced by Low Dose Ionising Radiation**	Tissue reactions (cognitive effects), Circulatory diseases	Shape, Target cells, Inhomogeneity, (Epigenetics), (Biomarkers)	Epidemiological and experimental studies of cognitive and cerebrovascular effects of radiation, including in utero
CHILD MED RAD	**Prospective cohort studies of children with substantial medical diagnostic exposure**	Cancer	Shape, Susceptibility	Feasibility study for CT scan risk study in children
DARK-RISK	**Studies on a cohort of Serbian children exposed to x-irradiation to determine the contribution of the non-coding genome to susceptibility at low doses**	Cancer	Epigenetics, Susceptibility, Biomarkers	Epidemiological and experimental studies in *Tinea capitus* cohort; experimental work on Long non-coding RNAs seeking biomarkers of exposure
DoReMi	**Low Dose Research towards Multidisciplinary Integration**	Cancer, Circulatory diseases, lens opacities, tissue reactions	Shape, Susceptibility, (Target cells), Biomarkers, Epigenetics, Inhomogeneity	Large scale project that undertook feasibility studies covering all areas of interest to MELODI
EPI-CT	**Epidemiological study to quantify risks for paediatric computerized**	Cancer	Shape, Susceptibility, (Biomarkers)	Epidemiological investigation of cancer risk in children

	tomography and to optimise doses			undergoing CT scans, includes biomarker considerations, dosimetric aspects as well as clinical guidelines
EpiRadBio	**Combining epidemiology and radiobiology to assess cancer risks in the breast, lung, thyroid and digestive tract after exposures to ionizing radiation with total doses in the order of 100 mSv or below**	Cancer	Shape, Target cells, Biomarkers, (Epigenetics), (Inhomogeneity)	Project aimed to integrate radiobiological data with epidemiological data to improve risk assessment for cancer in specific organs
OPERRA-SOPRANO		Cancer, Circulatory diseases	Shape, Biomarkers, Epigenetics,	Systems biological analysis to define the early cellular low dose response and its variation
OPERRA-EURALOC		Cataract (lens opacity)	Shape	Epidemiological investigation of lens opacity amongst medical practitioners
OPERRA-DIMITRA		Cancer	Shape, Biomarkers, target cells	Experimental investigations to determine Cone-beam CT effects of stem cells and to identify salivary biomarkers in children
OPERRA-VIBRATO		Cancer, immune system effects	Biomarkers, Epigenetics, Target cells	Experimental study of immune system gene expression after low dose irradiation
PROCARDIO	**Cardiovascular Risk from Exposure to Low-dose and Low-dose-rate Ionizing Radiation**	Circulatory diseases	Shape, Biomarkers, Target cells, (Epigenetics)	Epidemiological and experimental investigations on cardiovascular

				disease risk and mechanisms
RENEB	**Realizing the European Network in Biodosimetry**	Cancer	Biomarkers, Shape	Development of a European network for biodosimetry with main focus on emergency preparedness but of relevance as resource for low dose risk research and molecular epidemiology
RISK-IR	**Risk, Stem Cells and Tissue Kinetics – Ionising Radiation**	Cancer	Target cells, Shape, Epigenetics	Studies of stem cell responses to radiation at low doses and dose rates
SOLO	**Epidemiological Studies of Exposed Southern Urals Populations**	Cancer, Circulatory diseases	Shape, Inhomogeneity, (Biomarkers)	Epidemiological studies of Mayak plant workers for Pu cancer and circulatory disease risk
STORE	**Sustaining access to Tissues and data from Radiobiological Experiments**	All (potentially)	All (potentially)	Provision of database and archive for materials from radiobiological and epidemiological studies

(iii)   H2020 projects

Project acronym	Title	Primary disease endpoint	MELODI area addressed	Comments
CONCERT-LDLENSRAD	**Towards a full mechanistic understanding of low dose radiation induced cataracts**	Cataract	Shape, Susceptibility, Biomarkers	Ongoing study into quantitative and mechanistic aspects of low does radiation cataract formation
CONCERT-LEUTRACK		Cancer	Epigenetics, Shape, Biomarkers	Project just starting on role of microvesicles in radiation leukaemogenesis

CONCERT-SEPARATE	**Systemic Effects of Partial-body Exposure to Low Radiation Doses**	Biomarkers of partial body exposure	Omics, Shape, Inhomogeneity	Project just starting on effects of partial body exposure and role of microvesicles
MEDIRAD	**Implications of medical low dose radiation exposure**	Cancer, Circulatory diseases	Shape, Biomarkers, Epigenetics	Large multi-partner project recently started including epidemiological studies of CT risk and circulatory disease risk plus biomarker discovery work

Clearly there have been many projects supported under FP6, FP7 and H2020 that address issues highlighted by MELODI as key areas requiring research to improve low dose and low dose rate radiation health risk assessment. All funded projects align with one or more of MELODI's key areas as identified in the SRA and roadmap. All have contributed to advancement of the field and building the scientific evidence base for low dose/dose rate risk assessment. All diseases/health effects of actual and potential relevance to low dose risk – cancer, circulatory disease, cognitive effects and cataract are considered and a shift in emphasis amongst funded projects towards the non-cancer diseases can be seen. While all projects have made progress in building the evidence base as noted, there remain areas where additional work could be beneficial; these are considered in the gaps described below.

Gap Analysis

Following consideration of the projects listed above it is clear that there are evidence gaps that remain and areas of research that have not been fully considered in the past. On this basis gaps are identified below under each of the key areas identified by MELODI in its SRA and roadmap.

1. *To explore the shape of the dose-response relationship for radiation-induced health effects*
   - Health risk studies amongst populations exposed to background and environmental sources of radiation, and experimental model studies using relevant exposure parameters
   - Studies of second cancers arising in populations treated by radiotherapy, and relevant experimental model studies
   - Health risk and experimental model studies considering co-exposures to radiation and other agents
   - Studies that improve organ-specific cancer risk estimates
   - Studies that will reduce exposure assessment measurement errors in epidemiological analyses
2. *To understand the potential impact of individual susceptibility on radiation-induced health*
   - Studies that lead to the identification and validation of biomarkers of disease risk and/or susceptibility
   - Studies that identify and validate cohorts suitable for molecular/biomarker epidemiological studies
   - Studies of tissue level effects and the role of individual differences in tissue architecture that impact on susceptibility to radiogenic diseases

- Studies that potentially lead to the identification of biomarkers of resistance to radiation health effects
3. *To identify, develop and validate biomarkers for exposure, early and late effects for cancer or/and non-cancer diseases*
    - Studies that lead to the identification and validation of sensitive, rapid and reliable biomarkers of exposure
    - Studies that lead to the identification and validation of biomarkers of health risk/health risk susceptibility/resistance
4. *To explore and define the role of epigenetic modifications in radiation-induced health effects*
    - Studies that provide clear evidence for or against a role for epigenetic processes operating in radiation carcinogenesis, and dose/dose-rate/radiation quality information
    - Studies that provide clear evidence for or against a role for epigenetic processes operating in circulatory diseases/cataract/cognitive dysfunction, and dose/dose-rate/radiation quality information
    - Studies that provide clear evidence for or against the operation of ageing/senescence processes in radiogenic disease
5. *To explore the roles of specific target cells for radiation-induced late developing health effects*
    - Studies that identify and quantify the stem/progenitor cell populations at risk for all radiogenic cancer types and non-cancer diseases
    - Studies that provide quantitative information on the processes contributing to radiogenic diseases in relevant stem/progenitor cell populations
    - Studies employing heterotypic 3D cell/tissue/organ culture and animal models to examine radiation effects and sensitivity in stem cells
6. *To understand the health effects of inhomogeneous dose distributions, radiation quality and internal emitters*
    - Studies that consider organ dose in relation to intra-organ dose distribution in relation to health effects
    - Further investigation of sub-cellular dose distribution to elucidate potential targets for radiation action related to health effects other than DNA
7. *Infrastructures gap: Optimizing the quality of results, data integration and management via infrastructures networking*

    - Network of infrastructures for radiation protection – exposure platforms, databases, cohorts, sample banks, analytical platforms, models and tools
    - Improving the reproducibility and robustness of results
    - Harmonization of SOPs , shared standards and inter-comparisons, mobilization of European researchers when needed (eg RENEB)
    - Open access data, repositories and publication
    - Open access and review of research papers providing view on dosimetry, experimental design and statistical issues (eg FREDERICA)

MELODI also encourages education and training in disciplines to maintain, develop and improve skills amongst the low dose health risk research community. In this regard it is important to encourage training by those in relevant more fundamental sciences. The skills amongst the MELODI community in data management, data mining and bioinformatics are judged to be suitable for further development.

In terms of infrastructures for research, MELODI encourages, where appropriate, (1) the use of archived biological materials from prior research, particularly where EU funded, (2) the integration of experienced laboratory networks (eg RENEB) improving the robustness of results via intercomparisons, (3) the integration of expertise from outside the conventional fields of radiation research, where appropriate, (4) use of the wider EU scientific infrastructures for, amongst other things genomics, microscopy, structural biology, computing where relevant, (5)

where new infrastructures are proposed/developed, the provision of access to the wider community of researchers.