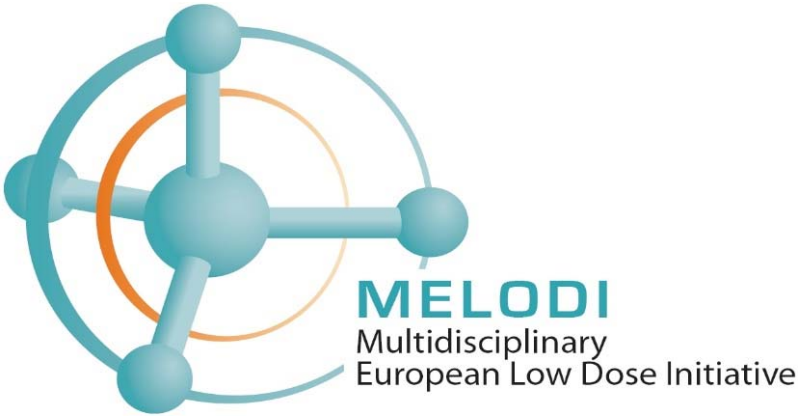

MELODI statement 2015

Approved by the MELODI Bureau: 10 Aug 2015

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 Strategic Research Agenda (SRA) of MELODI identifies these priority goals and the specific resources, infrastructures and training capabilities needed to further develop low-dose risk research.

Prior to EU research funding calls, MELODI develops a short statement indicating its view on current research priorities, which serves as an input to those responsible for defining call topics. The research priorities were identified from the MELODI SRA, which is gradually enriched by the contributions of its members, ongoing and completed research projects and the findings of the MELODI workshops organized annually since 2009. The 6th draft of the MELODI SRA for 2015 has been opened for consultation and can be downloaded from http://www.melodi-online.eu/sra.html. It forms the basis for the definition of the priorities.

The system of radiation protection has developed and evolved on the basis of an understanding of the magnitude of the health risks associated with radiation exposure and knowledge of the mechanisms of radiogenic disease pathogenesis to inform risk extrapolation. Accurate health risk assessment is fundamental to striking an appropriate and acceptable balance between the benefits of use/exposure to radiation and the associated health risks. Today the main uncertainties in radiation health risk assessment are in the magnitude of cancer risk at low and protracted doses, the magnitude of circulatory disease, cataract and other tissue injury below 500 mSv, and the variation in disease risk between individuals in the population. More information on these and associated issues is required to ensure adequate protection is afforded to populations and individuals in all situations – occupational, medical, emergency and in the course of normal life.

Criteria for prioritization

- Feasibility (research to be done within the next coming years)
- Importance in terms of improved radiation protection system
- Relevance for operational radiation protection (BSS implementation)
- Multidisciplinarity (biology, epidemiology, dosimetry)
- Synergy with other radiation research platforms (ALLIANCE, EURADOS, NERIS, medical field)
- Timeliness
- Avoidance of overlap of topics with other calls or topics that have been recently funded and outcome from projects that have recently ended.

Ranked list of priorities (for detailed description see Annex):

1. To explore the shape of the dose-response relationship for radiation induced health effects at low doses/dose-rates based on key informative epidemiological studies (including where appropriate, molecular or other biomarkers) for internal and/or external emitters, incorporating detailed dosimetric assessment.

2. To explore and define the role of epigenetic modifications in radiation-induced health effects following exposure to low doses/low dose rates.

3. To identify, develop and validate biomarkers for exposure, early and late effects for cancer or/and non-cancer diseases in relation to low doses/low-dose rates and to integrate them in molecular epidemiological studies.

4. To explore the roles of specific target cells for low dose/dose-rate radiation-induced late developing health effects such as cancers, circulatory diseases and cataract.

5. To understand the potential impact of individual susceptibility on radiation risk using cohorts and/or systems models with variations in sensitivity to low doses of radiation, so that differences in the response pathways can be detected and biomarkers validated.

MELODI encourages, where appropriate, (1) the use of archived biological materials from prior EU funded research, (2) the integration of experienced laboratory networks (such as e.g. RENEB), (3) the integration of expertise from outside the conventional fields of radiation research, in particular expertise from the medical research field where appropriate.

ANNEX: Description of MELODI 2015 priorities

Priority title	**To explore the shape of the dose-response relationship for radiation induced health effects at low doses/dose-rates based on key informative epidemiological studies (including where appropriate, molecular or other biomarkers) for internal and/or external emitters, incorporating detailed dosimetric assessment**
Priority description	Risk of all solid cancer combined due to whole body exposure with ionizing radiation is fairly well understood for doses of about 100 mSv. In this dose range there is, however, an urgent need for an understanding of health effects of internal exposures or inhomogeneous external exposures and of risks of site-specific cancer. Another major uncertainty is related to the magnitude of risk of non-cancer diseases at doses below about 500 mSv. Research: Large (molecular-) epidemiological studies with precise dosimetry and information on important confounders shall be further developed or established. Omics and system biology approaches to biological samples from study members should aim at exploring markers for radiation-induced disease and understanding the disease processes. Health risks shall be derived taking into account a multitude of models based on biological and epidemiological data.
European relevance	Per definition, the priority is of top importance for **MELODI**. By the need of improved dosimetry for key epidemiological cohorts the priority is linked to **EURADOS**. The implications of improved risk estimates for emergency management link the priority to **NERIS**. The enhanced risk characterizations may link the priority to **ALLIANCE**. Improved knowledge of health risk will also be of importance for the optimization of ionizing radiation applications in **medical** diagnostics and therapy, and for the **BSS** implementation in the future, as evidence can be expected to be taken in to account in ICRP recommendations.
Multidisciplinarity; Reference to the strategic research agendas (SRA)	This priority needs intensive collaboration of epidemiology, dosimetry, radiation biology, systems biology, experts of pathogenesis, mathematical modelling, statistics, radiation protection and emergency measurement. Expertise outside of the traditional fields of radiation research needs to be integrated. -MELODI (Aug 2015): p.9-14; chapter 4.1 and 4.2 -ALLIANCE (Sept 2013): p.6; Challenge 3; topic 3 -NERIS (April 2014): p.20, Topic 5.8 Health surveillance -EURADOS (May 2014): p.11-19; 3.2; p.35; 3.5.1
Impact: decreased uncertainty	The research will decrease uncertainty with respect to the shape of the dose-response-relationship for cancer and non-cancer diseases in the low dose range.
Impact: increased radiation protection	Improved health risk estimates together with an improved assessment of uncertainties will strengthen the solidity of present radiation protection. This will especially be the case for i) regulating occupational exposures; ii) optimizing radiation therapy for patients with good prognosis (long time risks of diseases in relatively low exposed tissues); iii) deciding about appropriate diagnostic applications of radiation in medicine (especially for procedures causing in total several tens of mSv; and iv) regulating emergency situations (involving reference levels from a few tens to 100 mSv); and v) better understanding of epidemiological findings and health effects of internal emitters.
Impact: increased acceptability	Presently, radiation protection is based on uncertain risk estimates, for which the full size of uncertainty has not even been addressed. This priority focusses on a more realistic assessment of the shape of the dose-response relationship for cancer and non-cancer diseases. The resulting robustness of the risk estimates will improve the public reliance on an important basis of radiation protection.
Feasibility	The priority is feasible in terms of scientific and technological competences available in Europe. Key informative cohorts with the potential for access to biological samples have been identified in DOREMI. The priority will need a large scale integrative action. A thorough study is estimated to require 4 ys duration and a budget of **5-7M €**

Priority title	**To explore and define the role of epigenetic modifications in radiation-induced health effects following exposure to low doses/low dose rates**
Priority description	In recent years, biological research has identified a range of processes that can modify cellular, tissue and whole organism phenotypes that do not require DNA mutation. Collectively these are termed epigenetic effects and these include modified DNA methylation, microRNA expression and histone acetylation. While there are indications in the literature that radiation can affect epigenetic endpoints, there remains a lack of understanding of dose- and dose-rate responses, and the relationship of the changes to radiogenic disease, although epigenetic phenomena have been linked to cancers and transgenerational effects. Research is required to define radiation dose-/dose-rate responses for individual epigenetic endpoints, determine radiation quality dependence and the relationship of such changes to radiogenic cancers, non-cancer diseases and hereditary/transgenerational effects
European relevance	The proposed research is relevant to (i) **MELODI** in that it requires consideration of low dose/dose-rate response and relevance for radiogenic disease and may identify biomarkers of exposure or effect (ii) **ALLIANCE** in that it will explore the relevance to transgenerational effects and population health (iii) **EURADOS** in that it will require a high standard of radiation dosimetry for cell culture systems, model organisms and a range of radiation qualities (iv) **NERIS** in that it may identify biomarkers of exposure or effect (v) **medical** applications in that biomarkers may be identified and through mechanistic understanding of effects, novel radio-protectors may be identified (vi) **BSS** implementation in the future, as evidence taken in to account in ICRP recommendations.
Multidisciplinarity; Reference to the strategic research agendas (SRA)	The research topic is of European and wider relevance in that it will help to determine the appropriate risk-benefit assessment for radiation use in all sectors, in this way, by informing the system of protection the research will ensure that the population and non-human biota are neither under nor over protected; and this ensures effective and efficient resource usage -MELODI (Aug 2015): p.10 (and others); 4.1.1, 4.1.2, 4.1.3, 4.3.1 -ALLIANCE (Sept 2013): p.6; Challenge2, topics 1 & 4 -NERIS (April 2014): p.20; Topic 5.8, Health surveillance -EURADOS (May 2014): p.17; 3.2.2 and p.21; 3.3.1
Impact: decreased uncertainty	The research will improve the scientific evidence base for judgements in radiation protection. It will address the question, whether endpoints in addition to DNA mutation need to be considered in selection of risk extrapolation models for cancer, and if epigenetic effects are important for judgements on risk extrapolation for non-cancer diseases. Detailed dose-/dose-rate response information will be generated.
Impact: increased radiation protection	The proposed research will provide evidence to inform judgements on one of the most fundamental aspects of the system of protection, namely, which is the best model for risk extrapolation for cancer and non-cancer diseases. The research thus informs judgements on dose limits and emergency reference levels.
Impact: increased acceptability	The understanding gained from carrying out this research will contribute to increasing acceptability of the radiation protection system as it will provide supporting evidence for judgements on the model used for risk extrapolation for all health endpoints. The research may provide evidence either to support or contradict the currently adopted approaches.
Feasibility	The proposed research topic is feasible; many methods have been developed that can carry out high-throughput epigenetic analyses and there is a growing body of technical competence in Europe. It may be necessary to consider funding projects that focus on one or a limited range of epigenetic endpoints. A thorough study is estimated to require 4 years duration (especially to address transgenerational issues) and a budget of **1-2 M Euro**

	To identify, develop and validate biomarkers for exposure, early and late effects for cancer or/and non-cancer diseases in relation to low doses/low-dose rates and to integrate them in molecular epidemiological studies
Priority description	In recent years, the rapid development of technologies for "omics" research has opened up for a detailed biochemical analysis of cellular responses at each regulatory level in the cell machinery. Understanding interactions at the molecular levels and the use of new software's for pathway analysis has provided new insights in the mechanisms that regulate the cellular responses to different stressors. Identifying biomarkers for radiation induced stress responses, as well as for early and late stages of diseases induced by radiation will provide a platform for a mechanistic understanding of the cellular responses to ionizing radiation, from the primary target through the repair/defence processes and the outcome of these. If persistent biomarkers for exposure and radiation-induced diseases can be identified, the integration of them in epidemiological studies will have significant implications for risk estimates of low dose/dose rate exposures. Research is required to define radiation dose/dose-rate responses for biomarkers of exposure, to determine their radiation quality dependence and the relationship of such changes to radiogenic cancers and non-cancer diseases.
European relevance	The proposed research is relevant to (i) **MELODI** in that it requires consideration of low dose/dose-rate response and relevance for radiogenic disease and may identify biomarkers of exposure or effect (ii) **ALLIANCE** in that biomarkers of exposure from the human model systems may be of relevance for the studies of other types of species and help to explore the relevance to transgenerational effects and population health (iii) **EURADOS** in that it will require a high standard of radiation dosimetry for cell culture systems, model organisms and a range of radiation qualities (iv) **NERIS** in that it may identify biomarkers of exposure or effect (v) **medical** applications in that biomarkers may be identified that can be used for diagnosis of individual sensitivity to radiotherapy and early detection of cancer and non-cancer diseases (vi) **BSS** implementation in the future, as evidence taken in to account in ICRP recommendations.
Multidisciplinarity; Reference to the strategic research agendas (SRA)	The research topic is of European and wider relevance in that it will help to determine the appropriate risk-benefit assessment for radiation use in all sectors, in this way, by informing the system of protection the research will ensure that the population and non-human biota are neither under nor over protected; and this ensures effective and efficient resource usage -MELODI (Aug 2015): Chapters 4.1, 4.2 and 4.3. -ALLIANCE (Sept 2013): p.6; Challenge2, topics 1 & 4 -NERIS (April 2014): p.20; Topic 5.8, Health surveillance -EURADOS (May 2014): p.17; 3.2.2 and 21; 3.3.1
Impact: decreased uncertainty	The research is expected to be of significance for the development of better risk estimates for other types of genotoxic stressors that are challenging the health of humans and other species. Biomarkers of exposure and diseases applied in epidemiology will significantly reduce the uncertainties of the present risk estimates in the low dose/dose rate range as detailed dose-/dose-rate response information will be generated. Precise dosimetry of internal emitters may also significantly decrease uncertainty.
Impact: increased radiation protection	The proposed research will provide evidence to inform judgements on one of the most fundamental aspects of the system of protection, namely, which is the best model for risk extrapolation for cancer and non-cancer diseases. The research thus informs judgements on dose limits and emergency reference levels.
Impact: increased acceptability	The understanding gained from carrying out this research will contribute to increasing acceptability of the RP system as it will provide supporting evidence for judgements on the model used for risk extrapolation for all health endpoints.
Feasibility	The proposed research topic is feasible; many methods have been developed that can carry out high-throughput "omic" analyses and the bioinformatics needed for the transfer of this results into a mechanistic understanding is at hand. A thorough study is estimated to require 4 ys duration and a budget of **2-4 M €**

Priority title	**To explore the roles of specific target cells for low dose/low dose rate radiation-induced late developing health effects such as cancers, circulatory diseases and cataract**
Priority description	Currently, radiation risk extrapolation does not specifically include mechanistic considerations, but is more a statistical curve-fitting approach. To improve mechanistic understanding of radiogenic disease processes that can inform mechanistic approaches to cancer risk extrapolation several key pieces of information will be required. Most fundamentally, it is important to identify the cells at risk of conversion into the disease state, and enumerate these. For the case of cancer it is generally assumed that stem and early progenitor cell populations are relevant, but these are not generally well characterised, understood in their responses to low dose/dose-rate radiation or enumerated. Research is required to clarify these aspects, and similarly to identify, enumerate and define radiation responses of target cell populations for other late-developing diseases such as circulatory disease and cataract.
European relevance	The proposed research is relevant to (i) **MELODI** in that it requires consideration of target cells relevant for radiogenic diseases and low dose/dose-rate response, providing important input for mechanistic models for risk extrapolation (ii) **EURADOS** in that it will require a high standard of radiation dosimetry for cell culture systems, model organisms and a range of radiation qualities (iii) **NERIS** in that in the longer term it will strengthen and improve risk estimation and thus exposure threshold for emergency action (iv) **BSS** implementation in the future, as evidence can be expected to be taken in to account in ICRP recommendations.
Multidisciplinarity; Reference to the strategic research agendas (SRA)	The research topic is of European and wider relevance in that it will help to determine the best approaches to risk extrapolation for all late developing diseases, in this way , by informing the system of protection, the research will ensure that the population are neither under nor over protected; and this ensures effective and efficient resource usage -MELODI (Aug 2015): p.10 (and others); 4.1.1, 4.2.1, 4.3.3 -ALLIANCE (Sept 2013): p.26; Challenge 2, 3.2.2.1 -NERIS (April 2014): p.18; Topic 5.1 -EURADOS (May 2014): p.17, 3.2.2
Impact: decreased uncertainty	The research will improve the scientific evidence base for judgements in radiation protection. It will address the issue of the improvement of risk extrapolation and strengthening the scientific evidence base for risk extrapolation.
Impact: increased radiation protection	The proposed research will provide evidence to inform judgements on a fundamental aspect of the system of protection, namely, which is the best approach for risk extrapolation for cancer and non-cancer diseases. The research thus in the long term informs judgements on dose limits and emergency reference levels.
Impact: increased acceptability	The understanding gained from carrying out this research will contribute to increasing acceptability of the radiation protection system as it will provide supporting evidence for judgements on the approach used for risk extrapolation for all health endpoints. The research may provide evidence either to support or contradict the currently adopted approaches.
Feasibility	The proposed research topic is feasible; many methods have been developed that can identify stem cells *in vivo* and *in vitro,* fundamental research in stem cell biology has developed an impressive range of methods for cell manipulation and imaging that can be utilised and there is a growing body of technical competence in Europe It may be necessary to consider funding projects that focus on a specific disease/target cell population. A potentially useful study is estimated to require 4 years duration and a budget of **2-3M Euro**

Priority title	**To understand the potential impact of individual susceptibility on radiation risk using cohorts and/or systems models with variations in sensitivity to low doses of radiation, so that differences in the response pathways can be detected and biomarkers validated.**
Priority description	Studies of carriers of BRCA1/2 mutations and studies of cancer patients have shown that single nucleotide polymorphisms (SNPs) in a number of genes can modify the radiation responses – either in the long term (risk of cancer) or in the short to medium term (adverse reaction to radiotherapy). Differences in sensitivity have also been observed in relation to gender, age at exposure, state of health, genetic and epigenetic make-up, lifestyle, and age attained. At present, there is insufficient information on the influence of individual radiation sensitivity on health risk estimates at low doses/dose-rates. Research is required on the extent of variation of individual sensitivity in the population, on the factors contributing to this variation, as well as integration of mechanistic studies in the quantitative evaluation of health risk.
European relevance	Individual sensitivity is one of the three key policy questions in the **MELODI** SRA and one of the main research priorities in the HLEG. It is also important for **NERIS** in emergency response and surveillance after accidents – children, pregnant women and elderly/ill persons being priority groups for radiation protection in the case of an accident - ; for **ALLIANCE** in protection of non-human biota. Studies of radiation sensitivity obviously need adequate dosimetry, including biological dosimetry, and hence there is an important role for **EURADOS**. -Individual sensitivity is extremely relevant for radiation protection of **patients** undergoing both diagnostic and therapeutic irradiations, where the possibility of using other medical procedures (MRI for imaging, surgery/chemotherapy/ hormone therapy/immune therapy for treatment) exist.
Multidisciplinarity; Reference to the strategic research agendas (SRA)	A multidisciplinary approach is needed to address this topic, including epidemiologists, biologists, clinicians, dosimetrists and modellers, as well as –for aspects related to response to radiation accidents – social scientists, ethicists and psychologists. -MELODI (Aug 2015): p.15-17; 4.3 (Individual Radiation Sensitivity) -ALLIANCE (Sept 2013): p.26; Challenge 2, topics 1 & 2 -NERIS (April 2014): p.20; Topic 5.8, Health surveillance -EURADOS (May 2014): p.17; 3.2.2 and p.21; 3.3.1
Impact: decreased uncertainty	Individual differences in sensitivity raises ethical and policy question as to whether some individuals or groups are inadequately protected by the present system and regulations. Answers to this question are therefore urgently needed.
Impact: increased radiation protection	Identification of sensitive persons in the population can lead to better RP –in medicine (where approaches not involving IR can be used), in occupational settings as well as in the general population after, for example, accidents
Impact: increased acceptability	Understanding the potential impact of individual susceptibility will contribute to a more realistic assessment of radiation health risks increasing the acceptability of the radiation protection system.
Feasibility	Scientific / technological competences needed for this topic are available in Europe. Different approaches can be considered, including (molecular) epidemiological studies of cancer patients (e.g. WECARE study) or cohorts of genetically predisposed individuals (carriers of specific mutations, AT heterozygotes,...), system modelling, studies of biomarkers, animal models. A thorough study is estimated to require 4 years duration (especially to address transgenerational issues) and a budget of **2-4M Euro**