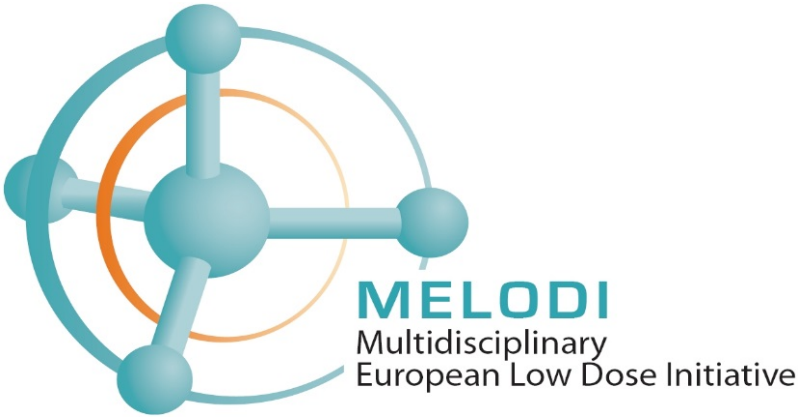

MELODI statement 2017

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 current MELODI SRA, which forms the basis for the definition of the priorities can be downloaded from http://www.melodi-online.eu/sra.html.

In the statement of 2015, MELODI has identified six ranked research topics, which have been used as input for defining priorities for the first call in CONCERT. In this statement, the highest ranked topic was “To investigate the shape of the dose response relationship for radiation-induced effects”. Assuming that this topic will be covered to a significant extent in the first CONCERT call, the MELODI statement of 2016 for the second CONCERT call included the same research topics, however, the previously highest ranked topic moved to the lowest priority for the second call.

With respect to the MELODI statement for 2017, the six previously defined research topics in 2015 and 2016 are still considered to be the current needs. Ongoing research funded within OPERRA and CONCERT involved only small pilot projects (SOPRANO, EURALOC, DIMITRA, VIBRATO, LDLensRAD) related to the originally highest ranked MELODI topic “To explore the shape of the dose-response relationship for radiation-induced health effects”. The new EU project MEDIRAD has a specific focus on cardiovascular diseases from RT in breast cancer patients and cancer following CT among children, which constitute very specific exposure situations in specific populations. For this reason, the investigation of the shape of the dose-response relationship for radiation-induced health effects is still the key research question and defined as overall priority for 2017, followed by equal ranking of the other five topics.

Criteria for prioritization

- Feasibility (research judged to be achievable in the near future)
- 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, EURAMED, European Medical Associations –ESR, ESTRO, EANM, EFRS, EFOMP)
- Timeliness
- Avoidance of overlap of topics with other calls or topics that have been recently funded and outcome from projects that have recently ended.

List of priorities (for detailed description see Annex):

Overall priority: To explore the shape of the dose-response relationship for radiation-induced health effects (cancer and non-cancer outcomes).

Other priorities:

- To understand the potential impact of individual susceptibility on radiation-induced health effects
- To identify, develop and validate biomarkers for exposure, early and late effects for cancer or/and non-cancer diseases
- To understand the health effects of inhomogeneous dose distributions, radiation quality and internal emitters
- To explore and define the role of epigenetic modifications in radiation-induced health effects
- To explore the roles of specific target cells for radiation-induced late developing health effects

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.

ANNEX: Description of MELODI 2017 priorities

Priority title	**To explore the shape of the dose-response relationship for radiation-induced health effects**
Priority description	There are major uncertainties concerning the magnitude of cancer risk following (1) Protracted exposures in the order of 100 mSv or less, and (2) organ specific risks following acute or protracted doses of a few hundred millisieviert, particularly for inhomogeneous exposures. Another major uncertainty is related to the magnitude of risk of non-cancer diseases at doses below about 500 mSv. Research is required to quantify the magnitude of cancer and non-cancer risk at low-doses and dose-rates. This can be achieved by mechanistic studies such as for example well-designed experimental animal studies and large (molecular) epidemiological studies with precise dosimetry, information on important confounders and possibly access to biological samples.
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 (**EURAMED**), 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, systemsbiology, 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 (2016): p.9-14; chapter 3.1 and 3.2 -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 -EURAMED (Nov 2015): chapter 3.2.1, 3.2.2, 3.2.3
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 robustness of present radiation protection system. 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 leading to exposures of several tens of mSv in total; and iv) regulating emergency situations (involving reference levels from a few tens to 100 mSv)..
Impact: increased quality and reliability	Experimental animal studies with well validated animal models and key informative large size cohorts, information on important confounders, and precise dosimetry will improve the quality and reliability of currently available risk estimates on the dose-response relationship.
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 and appropriate animal models for many endpoints are available..

Priority title	**To understand the potential impact of individual susceptibility on radiation-induced health effects.**
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/interventional radiology procedures). 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 exposures, where the possibility of using other medical procedures (MRI for imaging, surgery/chemotherapy/hormone therapy/immune therapy for treatment) exist (EURAMED).
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 (2016): chapter 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 -EURAMED (Nov 2015): chapter 3.2.1, 3.2.2, 3.2.3
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 quality and reliability	Understanding the potential impact of individual susceptibility will contribute to a more realistic assessment of radiation health risks.
Feasibility	Scientific / technological competences needed for this topic are available in Europe. Different approaches can be considered, including (molecular) epidemiological studies of cancer patients or cohorts of genetically predisposed individuals, system modelling, studies of biomarkers, animal models.

Priority title	**To explore and define the role of epigenetic modifications in radiation-induced health effects**
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 (2016): chapters 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 -EURAMED (Nov 2015): chapter 3.2.1, 3.2.2, 3.2.3
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 quality and reliability	The understanding gained from carrying out this research will provide supporting evidence for judgements on the model used for risk extrapolation for all health endpoints and thus increase the quality and reliability of health risk assessment.
Feasibility	The proposed research topic is feasible; many methods that can carry out high-throughput epigenetic analyses have been developed and there is a growing body of technical competence in Europe.

Priority title	**To identify, develop and validate biomarkers for exposure, early and late effects for cancer or/and non-cancer diseases**
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 have 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.. 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 diseases 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/interventional radiology procedures 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 (2016): 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 -EURAMED (Nov 2015): chapter 3.2.1, 3.2.2, 3.2.3
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.
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 quality and reliability	The understanding gained from carrying out this research will provide supporting evidence for judgements on the model used for risk extrapolation for all health endpoints and thus increase the quality and reliability of health risk assessment
Feasibility	Many methods that can carry out high-throughput "omic" analyses have been developed and the bioinformatics needed for the transfer of these results into a mechanistic understanding is at hand.

Priority title	**To explore the roles of specific target cells for low-dose/low-dose rate radiation-induced late developing health effects**
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 diseases and lens opacities.
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 exposed populations are neither under nor over protected, and this ensures effective and efficient resource usage. -MELODI (2016): chapters; 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 quality and reliability	The understanding gained from carrying out this research will provide supporting evidence for judgements on the approach used for risk extrapolation for all health endpoints and thus increase quality and reliability of health risk assessment.
Feasibility	Many methods that can identify stem cells *in vivo* and *in vitro* have been developed, 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.

Priority title	**To understand the effects of inhomogenous dose distributions, radiation quality and internal emitters on health.**
Priority description	Many of the exposures to radiation encountered in the environment, occupationally and in medical settings can be to internal contamination, often to radiations of differing quality or involve other aspects of dose inhomogeneity. The current system of radiation protection makes use of radiation weighting factors to reflect spatial dose distribution differences between radiations of differing quality. The risk associated with all forms of dose inhomogeneity, internal contamination and radiation quality is not well understood. Research is required to determine the extent to which these radiation exposure characteristics modify dose-response relationships for health effects.
European relevance	The assessment of the impact of radiation exposure characteristics on the risk of cancer and non-cancer diseases is a priority of top importance for **MELODI**. Per definition there is clear link to EURADOS with respect to updated fundamental dose concepts and quantities and improved dosimetry for epidemiological studies. 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 (**EURAMED**), 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)	A multidisciplinary approach is needed to address this topic, including epidemiologists, biologists and dosimetrists. -MELODI (2016): 4.1.3, 4.2.3 and 4.3.3) -EURADOS (May 2014): Chapter 3.1, 3.2, 3.3.3 -EURAMED (Nov 2015): chapter 3.1
Impact: decreased uncertainty	The research will improve the risk assessment in case of dose inhomogeneity and internal contamination and provide an improved assessment of radiation weighting factors.
Impact: increased radiation protection	The research will improve the scientific evidence base for judgements in radiation protection.
Impact: increased quality and reliability	A better knowledge of the influence of these exposure characteristics on the risk estimation will lead to a higher quality and reliability of health risk assessment.
Feasibility	Research is feasible, because improved biokinetic and dosimetric models are available that can be used in epidemiological studies. Experimental studies in vivo or in vitro with different exposure scenarios where dose modulation plays a role can be conducted.