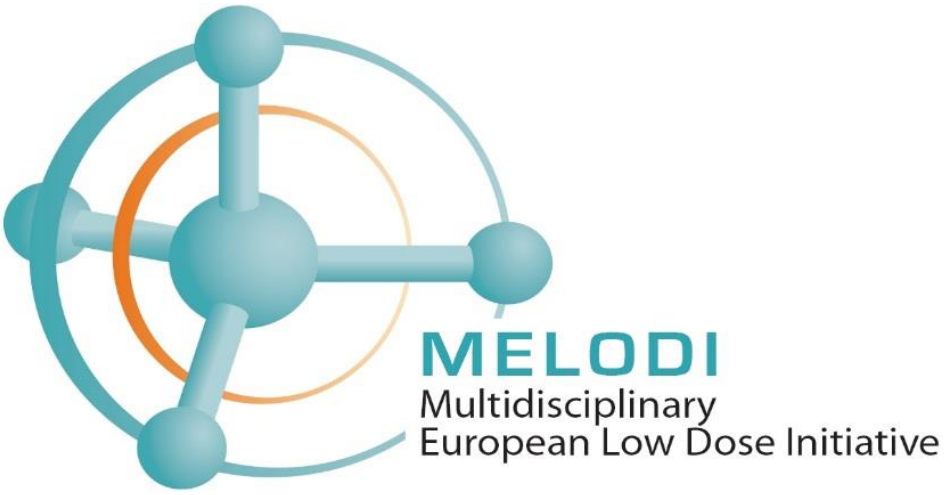

Strategic Research Agenda of the Multidisciplinary European Low Dose Initiative (MELODI) - 2015

M. Kreuzer, D. Averbeck, I. Balashazy, S. Bouffler, E. Cardis, P. Jacob, J.R. Jourdain, M. Harms-Ringdahl, K. Kojo, S. Pazzaglia, K. Prise, F. Zölzer

A. Ottolenghi, L. Sabatier

MELODI Working Group SRA

Michaela Kreuzer, BfS, Germany (chair)
Friedo Zölzer, University of South Bohemia, Czech Republic (vice-chair)
Imre Balashazy, MTA-EK, Hungary
Simon Bouffler, PHE, UK
Elisabeth Cardis, CREAL, Spain
Peter Jacob, HMGU, Germany
Jean-René Jourdain, IRSN, France
Katja Kojo, STUK, Finland
Simonetta Pazzaglia, ENEA, Italy
Mats Harms-Ringdahl, University of Stockholm, Sweden

Invited external experts

Kevin Prise, Queen's University of Belfast, UK
Dietrich Averbeck, IRSN, France

Observers from other MELODI WG's

Andrea Ottolenghi, University of Pavia, Italy
Laure Sabatier, CEA, France

Content

1. Executive Summary

MELODI (Multidisciplinary European Low Dose Initiative) is a European Platform dedicated to low dose ionizing radiation risk research. In 2010, MELODI was founded as a registered association with 15 members. As of December 2015, the association's membership increased to 43.

A major activity of MELODI is the establishment and updating of a long term (>20 years) Strategic Research Agenda (SRA) for research on low dose risk for radiation protection in Europe. The SRA is intended to guide the priorities for national and European research programmes and the preparation of competitive calls at the European level. A key priority for radiation protection research is to improve health risk estimates for exposures corresponding to the dose limits for occupational exposures and to reference levels for the exposure of the population in emergency situations. The approaches will need to be multidisciplinary and innovative. The integration of expertise outside of the conventional fields of radiation research will widen the possibilities to integrate modern technologies in health research in the assessment of health risk relevant to radiation protection.

Another activity of MELODI is to ensure the availability of key infrastructures as an essential basis for research activities, and the maintenance of competences in radiation research and health risk assessment in the long term via an integrated European approach for training and education. For these purposes, MELODI in February 2014 established three working groups, one on the MELODI SRA, one on Education and Training and a third on Infrastructures.

The SRA will be updated annually by the MELODI WG SRA, taking into account results of ongoing and completed research and key radiation protection research issues, which arise during the year. An open consultation process via website and the annual MELODI workshops are regularly conducted, the results of which are taken into account in the revised SRA report. Prior to calls, in addition to the SRA report a short MELODI statement presenting the top priorities is developed by the MELODI WG SRA and an open consultation process initiated.

An important operational tool for the establishment of MELODI and setting up the structures for sustainable integration of research on low dose risk in Europe is the DoReMi Network of Excellence (2010-2015) funded by Euratom FP7 radiation protection programme.

In the future, radiation protection research will be organized within a European Joint Programme Co-fund Action (EJP). The aim of the EJP is to bring together relevant funding agencies from the EC and the Member States to integrate European research and to administer calls for research proposals in radiation protection on behalf of the European Commission. This activity will build upon the Strategic Research Agendas from five European radiation protection research platforms and aims to establish interaction and synergies between the different areas of expertise. The five radiation protection platforms are MELODI, ALLIANCE (Radioecology), NERIS (Emergency management), EURADOS (Dosimetry issues) and a medical platform. An important operational tool for the establishment of EJP is the European project OPERRA (Open Project for European Radiation Research Area).

The current 6th MELODI SRA report for the year 2015 describes three key research questions in low dose or low dose-rate radiation risk research.

1) Dose and dose rate dependence of cancer risk

   Epidemiological studies provide evidence of dose-related increases in total cancer risk due to acute exposures with doses of about 100 mSv and above. However, there are major uncertainties concerning (i) the magnitude of total cancer risk following protracted exposures of the order of 100 mSv or less; (ii) organ specific risks following acute or protracted doses of a few hundred millisievert, particularly for inhomogeneous dose distributions; iii) the most scientifically evidence-based models to infer risk at doses and dose-rates that are lower than those for which direct epidemiological evidence is available. Knowledge of health risks from such low-dose and low-dose rate exposures is of relevance for the optimal response to emergencies, including decisions about the relocation of the population, and radiation protection of occupationally exposed persons.

2) Non-cancer effects

   It has been traditionally assumed that health effects other than cancer and hereditary diseases show a threshold at doses that are well above the levels of exposures typically encountered in the public environment, at work or from diagnostic medical uses of ionizing radiation. Recent results from epidemiological and experimental studies indicate increased risks from vascular diseases, lens opacities, cognitive/neurological effects and others at a range of doses from 5 down to 0.5 Gy and, possibly even at lower doses (<0.5 Gy). If these findings are substantiated and positive findings are seen at lower dose levels they would have important implications for radiation protection.

3) Individual radiation sensitivity

   Individual variability in radiation-related cancer risk and genetic susceptibility to cancer is a key area to address for radiation protection. Differences in radiation sensitivity between individuals, or groups, may relate to gender, age at exposure, state of health, genetic and epigenetic make-up, lifestyle, and age attained. Such differences, if significant, raise the ethical and policy question as to whether some individuals or groups are inadequately protected by the present system and regulations.

The research required to improve the evidence base in each of the three key questions is given in three research lines:

1) Research to improve understanding of the mechanisms contributing to radiation risk at low dose and dose-rate exposure
2) Epidemiological research in humans that integrates – where possible and informative – biological approaches for radiation health risk evaluation
3) Research specifically aimed to address the effects of and risks associated with internal exposures, differing radiation qualities and inhomogeneous exposures

The current and former MELODI SRA reports and MELODI statements can be downloaded from the following website: www.melodi-online.eu.

2. Importance of low dose risk research

Exposure to ionizing radiation is unavoidable. Everybody in the population is exposed to a range of natural and artificial sources. Medical and natural sources are the largest component of the dose of the general public. Exposures to artificial sources can vary between individuals depending on occupation (e.g, employment in the nuclear industry, in airlines and in medicine, particularly interventional radiologists), medical exposures (radiological procedures, radiotherapy) and in rare cases due to environmental contaminations. Not only is exposure to ionizing radiation unavoidable and variable in the population, but it is known to damage health at certain exposure levels. At very high doses (>1 Gy whole body) radiation exposure can be acutely lethal, tissue damage can occur following more localized high dose exposures. Exposures at these levels are very rare, but tissue damage is observed in some patients following life-saving radiotherapy for cancer. Evidence accumulated over many decades indicates that radiation can cause cancer in humans following acute exposure in the dose range of a few Sv down to 100 mSv, and there are concerns that these more moderate exposures may also be associated with other conditions such as circulatory disease, lens opacities and effects on future generations (hereditary effects). The risks to humans in terms of cancer are established down to 100 mSv and for circulatory diseases and lens opacities down to about 500 mSv. The risks to human health below these levels, especially following protracted or other non-homogenous exposures are less certain. Currently the system of radiation protection aims to avoid tissue injury and minimize the incidence of cancer and probability of hereditary disease. Risks of such effects below the above mentioned 100 or 500 mSv are controlled on the basis of an assumed linear non-threshold (LNT) relationship between dose and effect, however there is a large uncertainty about the exact dose response for such low-dose exposures.

There are many and varied uses of radiation in modern society. Nuclear power generation is viewed as a carbon efficient energy source, industrial radiography plays important roles in safety assessment; medical uses of radiation for diagnostics and therapy are widespread. Increased radon exposures in buildings are a major issue in many countries. Long distance air travel can lead to greater exposures. Other sources are exposures to 'NORM' (Naturally occurring radioactive materials) in the oil extraction and other industries. There are ways to modify exposures e.g. to naturally occurring background radiation and to environmental radiation, for that matter - such as Fukushima.

Thus striking the appropriate and acceptable balance between the benefits of use of/exposure to radiation on the one hand and the health risk posed on the other is important. The regulation and protection of individuals and populations comes at a cost – there are therefore disadvantages of both underprotection and overprotection. This applies in all situations – existing elevated exposure situations such as high radon areas, occupational settings such as nuclear industry and the medical sector, and accidental situations where difficult decisions on countermeasure implementation such as sheltering and evacuation are required. In all these contexts it is critical to have robust and accurate information on the magnitude of health risks posed by given radiation doses, ranging from high to low. The main uncertainties in radiation health risk evaluation are in the magnitude of cancer risk at low and protracted doses below 100 mSv, the magnitude of non-cancer effects below 500 mSv, and the variation in disease risk between individuals in the population. These are therefore the key areas requiring further exploration to provide better and more secure evidence for appropriate decision making in all areas of radiation protection. Accurate and reliable low dose risk estimation is an essential foundation for a robust and acceptable system of radiation protection.

3. MELODI

The purpose of the MELODI Association is to constitute a European Research Platform in the field of low-dose exposure to ionizing radiation and of radiation protection from such exposure, aiming for a progressive integration of related national and European activities.

As of October 2014, MELODI has 31 members from national bodies responsible for defining funding and implementing research in this domain, and universities and research institutes committed to contribute to R&D efforts. It is a research platform that contributes to the definition of priority objectives in low dose risk research, identification of research programmes and resources to be implemented in order to achieve these objectives, assessment of results obtained, and promotion of communication on these issues between the various parties involved as well as sustainability of key research activities. These functions are carried out by organizing scientific and stakeholder workshops, promoting the visibility of the research area, nominating working groups on specific topics and facilitating collaborative research.

A major activity of MELODI is the establishment and updating of a long term Strategic Research Agenda (SRA) for research on low dose risk for radiation protection in Europe (>20 years). The SRA is intended to guide the priorities for national and European research programmes and the preparation of competitive calls at the European level. Another activity of MELODI is to ensure the availability of key infrastructures as an essential basis for research activities, and the maintenance of competences in radiation research and health risk assessment in the long term via an integrated European approach for training and education.

An important operational tool for the establishment of MELODI and setting up the structures for sustainable integration of research on low dose risk in Europe was the DoReMi Network of Excellence (2010-2015) funded by Euratom FP7 radiation protection programme.

From now on, radiation protection research will be organized within a European Joint Programme Co-fund Action (EJP). The aim of EJP is to bring together relevant funding agencies from the EC and the Member States to integrate European research and to administer calls for research proposals in radiation protection on behalf of the European Commission. This activity will build upon the Strategic Research Agendas from five European radiation protection research platforms and aims to establish interaction and synergies between the different areas of expertise. The five radiation protection platforms are: MELODI, ALLIANCE (Radioecology), NERIS (Emergency management), EURADOS (Dosimetry issues) and a medical platform. An important operational tool for the establishment of EJP is the European project OPERRA (Open Project for European Radiation Research Area).

Development of the MELODI SRA

Every year, the MELODI SRA is updated, taking into account results of ongoing and completed research and key radiation protection research issues, which arise during the course of the year. The updated draft and a short MELODI statement (only in years where a call will be launched), presenting the top priorities, is posted on the public MELODI website 6-8 weeks before the annual MELODI workshop and an open consultation process is set-up via the website and the MELODI workshop to seek input from other scientists and stakeholders before the SRA´s and statement's

revision. The updated SRA and MELODI statement are then sent by the MELODI Working Group SRA to the MELODI Board of Directors (BoD) for comments and approval. Following this, both drafts are sent for final review to the independent Scientific Committee of MELODI, and the final SRA and MELODI statement are prepared.

In October 2010, the first draft of a MELODI SRA was published on the MELODI Website and opened for public consultation. The contents were based on the considerations and key priority issues formulated by the HLEG (High Level Expert Group). In February 2014, the MELODI Board of Directors (BoD) established three WG's, one on the MELODI SRA, one on Education and Training and a third on Infrastructures.

4. Strategic Research Agenda

The SRA is based on the key policy goals to be addressed defined by the High Level Expert Group on European Low Dose Risk Research (HLEG 2009) to address the robustness of the current radiation protection system (see **Figure 1**). These 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 and hereditary effects.

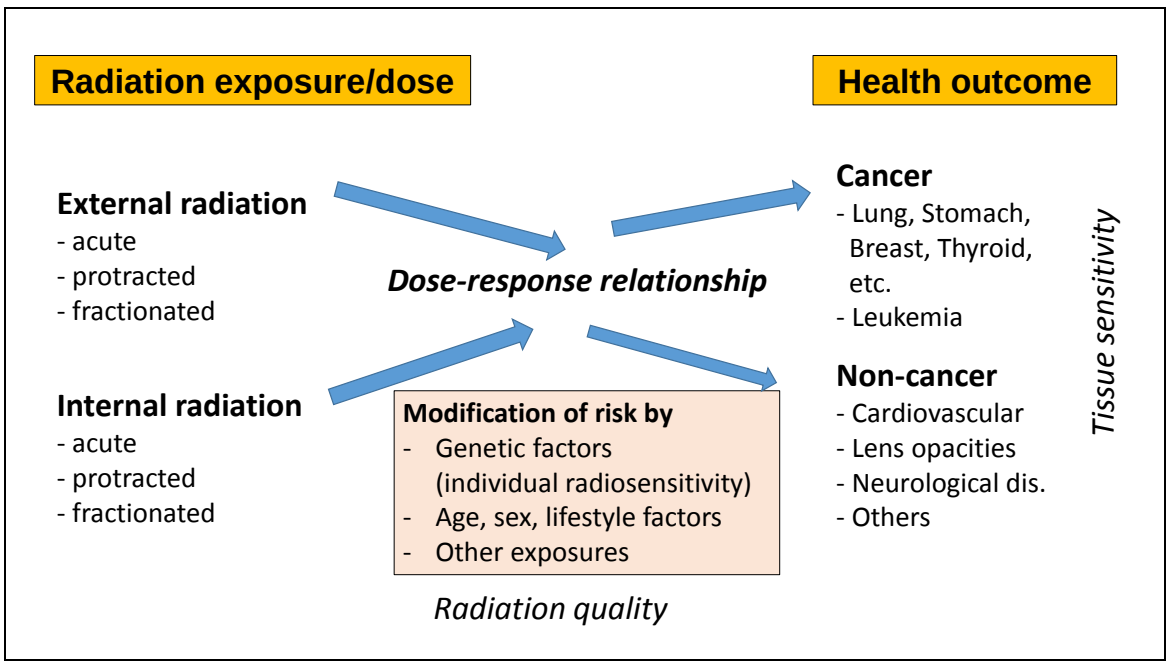

Figure 1: Key policy issues in European low dose radiation risk research defined by the High Level Expert Group

For the purpose of the MELODI SRA, these issues were restructured into three key questions:

(1) the dose and dose-rate relationship for cancer;
(2) non-cancer effects; and
(3) individual radiation sensitivity.

As discussed by the HLEG and confirmed by the DoReMi Network of Excellence and MELODI, research at low dose-rates or low doses presents significant challenges in the investigation of both radiation-related health effects and underlying biological mechanisms, because the magnitude of health risk and biological effects is expected to be low. A multidisciplinary approach is therefore essential.

For this reason, discussion of each key question is sub-divided below into three sub-sections:

- Research to improve understanding of the mechanisms contributing to radiation risk following low dose / dose-rate exposures.
- Epidemiological research in humans that integrates -where possible and informative- biological approaches for health risk evaluation.
- Research specifically aimed to address the effects of and risks associated with internal exposures, differing radiation qualities and inhomogeneous exposures.

4.1 Dose and dose rate dependence of cancer risk

Current risk estimates used in radiation protection are based upon epidemiological studies of exposed populations. Radiation protection standards aim to avoid tissue reactions (see 4.2) and minimize the incidence of the late developing stochastic effects of cancers and hereditary effects in future generations. Thus, it is of fundamental importance to radiological protection that the health risk estimates are robust and credible. Most important among the epidemiological studies are the follow-up studies of Japanese populations exposed as a consequence of the atomic bombings of Hiroshima and Nagasaki which provide clear evidence of increased cancer risk. While the Japanese studies remain the main basis for the cancer risk estimates used in radiation protection they relate to a specific population and a specific exposure scenario. The exposure was essentially an instantaneous high dose rate, total body gamma ray exposure with some neutron exposure. Information about cancer risk from the A-bomb survivor studies is to an increasing extent complemented by occupational, environmental and medical exposure studies, which allow direct investigation of effects of fractionated or more protracted exposures and effects of lower doses. There are currently no human studies on which to base hereditary risk estimates, rather these draw on studies using experimental animals, and the contribution of hereditary risk to overall risk is small by comparison with somatic cancers.

Epidemiological studies provide evidence of dose-related increases in total cancer risk after acute exposures with doses of about 100 mSv and above. Recent studies in genetically sensitive populations (ATM, BRCA1/2 mutation carriers, etc.) also suggest increased risks following diagnostic radiation exposures of the order of a few 10s of mSv. Further, recent reports indicate a possible association between natural background gamma radiation exposures and risk of childhood leukaemia and suggest an elevated risk associated with medical imaging methods.

Nevertheless, there are major uncertainties concerning (i) the magnitude of cancer risk following protracted exposures encountered in the environment and in occupational settings, particularly those of the order of 100 mSv or less; (ii) organ specific risks following acute or protracted doses of a few hundred millisievert, particularly for inhomogeneous dose distributions; iii) the risk for individual cancer sites due to possibly different tissue sensitivities, and iv) the most scientifically evidence-based models to infer risk at doses and dose-rates that are lower than those for which direct epidemiological evidence is available. In this context, there are also a number of ethical questions that need to be addressed, such as “precautionary” use of the linear non-threshold model for extrapolation to doses far below those where risk estimates are considered reasonably secure.

Classical epidemiological studies will need to be continued to refine the knowledge of risk directly in human populations, particularly in the context of low dose and protracted exposures, and internal contamination. Mechanistic and epidemiological approaches should be integrated to address cancer risks from acute whole body exposures with low-dose (< 100 mSv) or from protracted or inhomogeneous exposures with low-to moderate dose (a few hundred millisievert or less). They also need to address the impact of different radiation qualities and effects of both internal and external exposures, alone and in combination. Knowledge of health risks from such low dose-rate exposures is of key relevance for the population in emergency situations, and radiation protection of occupationally exposed persons, because the present dose limit is 20 mSv/year averaged over 5 years with no single year exceeding 50 mSv.

4.1.1 Basic mechanisms

A linear non-threshold extrapolation model is currently used to estimate risk at low doses from higher dose epidemiological data. An important aspect of the justification of using this model is that radiation carcinogenesis is assumed to be primarily driven by damage to DNA and subsequent mutation of growth regulating genes in target cells. Yet, a number of other potential mechanisms contributing to and modulating radiation carcinogenesis have been proposed and it is important to determine the roles that these might play. The extent to which these modulations and non-mutational mechanisms challenge the validity of the use of a LNT risk extrapolation model needs to be determined under relevant exposure conditions.

Therefore this area will require the use of well validated animal and human cellular / tissue models of radiation carcinogenesis (both solid cancers and leukaemias) to determine:

- The nature of the target cells for radiation carcinogenesis. These are generally taken to be stem and progenitor cell populations, which may have specific responses to radiation.
- The contribution of DNA damage / mutational processes. The DNA damage / mutational effects of radiation provide underpinning for the current risk extrapolation framework. Further information on the specific genes affected and quantitative aspects can contribute to refining novel risk extrapolation models and the identification of radiation cancer relevant biomarkers.
- The contribution of epigenetic modifications. It has become clear that gene function and cellular processes can be regulated at the epigenetic level. The extent to which radiation affects epigenetic states that relate to carcinogenesis needs to be elucidated.

- The influence of cell micro-environmental, non-targeted and systemic processes. For example, the influences of low dose radiation exposure on inflammatory reactions and effectiveness of immune surveillance against cancer cells.
- The extent to which any of the above are different at high dose / dose-rate by comparison with low dose / dose-rate.
- To elaborate further studies on the Relative Biological Effectiveness (RBE) to develop new and innovative ways to determine the RBE using up-to-date technologies and also to be able to determine/compare the effects of acute versus chronic exposure.

4.1.2 Health risk evaluation

Quantification of cancer risk at moderate dose from inhomogeneous or protracted exposure, and at low dose from acute, homogenous exposure is a key challenge. The large size of epidemiological studies required to detect small increases in cancer risk at low dose and dose-rates and the potential for bias and confounding can present practical challenges, particularly at the lowest doses. Through improvement of epidemiological studies (continued follow-up, pooling of different studies, additional collection of information on confounders and reducing misclassification of dose and health data) and, where relevant, the identification and integration of relevant biological endpoints and markers into epidemiological investigations further insights will be gained into the risks associated with such exposures.

The priorities in this area include the maintenance and improvement of key cohorts and performance of mechanistic studies based on biological material from members of the cohorts in order to improve cancer risk evaluation via molecular epidemiological studies or by mechanistic modelling. Key cohorts are characterized by large populations with exposure conditions and dose distributions that are relevant for radiation protection, good individual dosimetry, long and complete follow-up with good quality of health outcome data, particularly in relation to cancer occurrence; and the possibility of collecting information on relevant potential confounders either on the whole cohort or through targeted nested case-control studies. In addition, these studies should include – where possible and informative - the collection and appropriate storage of a large number of relevant biological samples, including tissue samples from most of the cancer cases.

Priority research areas are:

- To determine the shape of the dose and dose-rate response relationship in humans for different cancer sites at low-doses or low-dose-rates based on key informative epidemiological studies.
- To investigate cancer risks at low to moderate doses from inhomogeneous and/or protracted exposure.
- To identify and validate biomarkers of exposure and health effects related to cancer.
- To evaluate cancer risks from low-dose or low-dose-rate exposures through systems biological analyses and models of carcinogenesis based on mechanistic studies and epidemiological data, and integration of the two.
- To collect tumour tissue for the molecular characterization of tumours and the study of dose-response in relation to each tumour type.

- To investigate pre-stages of cancer in tissue or blood from members of appropriate epidemiological studies or other individuals with comparable living conditions and known exposure in order to allow modelling of carcinogenesis.
- To identify human population studies where hereditary effects could be observed if present.

4.1.3 Impact of radiation exposure characteristics

It is important but often overlooked that 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 protection makes use of radiation weighting factors to reflect spatial dose distribution differences between radiations of differing quality. The actual risk associated with all forms of dose inhomogeneity is not well understood. The extent to which these factors modify dose-response relationships for cancers is therefore important to understand.

Priority research areas are:

- Epidemiological studies of internal emitter risk, incorporating detailed dosimetric assessment and evaluation of dosimetric uncertainties and, where appropriate microdosimetric considerations. As in 4.1.2, where feasible and informative, these should include collection of appropriate biological samples and analysis of biomarkers of dose.
- Mechanisms of interaction with tissue/molecules may differ from those seen for acute exposures to low LET radiation for chronic irradiation and in the presence of strong dose inhomogeneity. These mechanisms may strongly influence health effects especially in the case of high LET radiations. Thus, experimental and numerical approaches are needed to identify and describe these phenomena at the tissue level applying accurate biokinetic and dosimetric models.
- Experimental studies in vivo or in vitro to test exposure scenarios where dose modulation plays a role, e.g. localized versus uniform exposures, acute versus protracted exposures to inform biomarker development and risk quantification.
- Epidemiological and mechanistic studies on cancer risk with exposures to different radiation qualities in order to investigate differences in dose-response relationship.

4.2 Non-cancer effects

It has been traditionally assumed that health effects other than cancer and hereditary diseases show a threshold at doses that are well above the levels of exposures typically encountered in the public environment, at work or from medical uses of ionizing radiation. Recent results from epidemiological and experimental studies indicate increased risks from vascular diseases, lens opacities, cognitive/neurological effects and others not only at doses above 5 Gy but also at a range of doses from 5 down to 0.5 Gy and, possibly even at lower doses (<0.5 Gy). Based on these findings the International Commission on Radiological Protection (ICRP) issued in 2011 a statement on tissue reactions (formerly termed non-stochastic or deterministic effects) that noted evidence that the threshold in absorbed dose for effects on the lens of the eyes is on the order of 0.5 Gy (acute and protracted exposure) rather than the previously recognized 5 Gy. Consequently a recommendation was made for a reduction in the annual absorbed dose limit for the lens of the eye to 20 mSv per year averaged over 5 years with no one year exceeding 50 mSv. In addition, ICRP

suggested that the absorbed dose threshold for circulatory diseases may be as low as 0.5 Gy. ICRP defines the threshold by a dose that causes the disease in 1 % of the exposed persons.

For all outcomes, there are uncertainties and concerns about possible effects at low doses, which would have important implications for radiation protection. Results of available epidemiological studies are not always consistent, bias and confounding cannot be excluded, and the biological mechanisms at these low doses are not known. The possibility of a stochastic nature of non-cancer effects without dose thresholds raises a wide range of questions, and needs further investigations. In contrast to cancer and hereditary effects, knowledge on the underlying biological mechanisms for other radiation-related non-cancer effects in the moderate and low dose range is very sparse and assumed to be different from high dose exposure. Therefore, research to understand the mechanisms is urgently necessary. In addition, careful epidemiological research of key cohorts, integrating – where possible and informative – biological approaches are needed to provide information on radiation related risk of non-cancer diseases following low dose, protracted or fractionated exposure, relevant for radiation protection. Individual radiation susceptibility, mixed exposures and impact of characteristics of radiation exposure also need to be considered.

4.2.1 Basic mechanisms

Deterministic effects or tissue reactions are classically thought to arise as a consequence of cell killing or functional inactivation by the (generally) high radiation doses involved. They are characterised by steep dose-response relationships at doses beyond a defined threshold. It is unlikely that cell killing/inactivation will be the basis for effects of lower radiation doses in relation to vascular disease, cataract and cognitive dysfunction. Epidemiological investigations of populations with well-characterised exposures require studies to identify the underlying mechanisms that lead to each of the non-cancer disease. Each disease may have a different mechanistic basis and it is not clear if there will be any similarity with the mechanisms that lead to radiation cancers.

The research priorities for non-cancer effects are:

- To develop *in vitro* and animal models of radiation-related non-cancer diseases. Suitable models of circulatory diseases, lens opacities, cognitive/neurological dysfunctions and other non-cancer effects will help to clarify the regulatory pathways involved. A full range of analytical methods should be applied including ‘omics technologies and consideration of the target cells and surrounding microenvironment. The mechanistic knowledge gained can be useful for the identification of radiation-relevant biomarkers, e.g. specific metabolic and pathological changes that are clearly radiation-induced.
- To determine the contribution of radiation-related changes in the immune function in the pathogenesis of non-cancer effects at low doses and dose-rates. The mechanisms of interactions between radiation damage and inflammatory processes should be investigated.
- To elaborate further studies on the Relative Biological Effectiveness (RBE) to develop new and innovative ways to determine the RBE using up-to-date technologies and also to be able to determine/compare the effects of acute versus chronic exposure (current epidemiological studies suggest they are the same but the same seems to be true for cancer where a DDREF is still recommended by ICRP).

4.2.1 Health risk evaluation

Quantification of non-cancer risk (circulatory diseases, lens opacities, others) in humans at moderate or low doses or dose-rates is a key challenge for radiation protection, because the magnitude of risk due to radiation is expected to be low and the potential for bias and confounding is high. Informative epidemiological studies in this field will be characterized by cohorts of large size with exposure scenarios and dose values of interest for radiation protection, good dosimetry, high quality of health data, long follow-up and the possibility of collecting information on relevant potential confounders either on the whole cohort or through targeted nested case-control studies. In addition, these studies should include – where possible and informative - a large number of biological samples, relevant tissue samples from most cases in a given organ, and extensive data on the health status during follow-up.

Through improvement of key epidemiological studies (e.g., increasing the statistical power by pooling studies using standardized study protocols; improvement of appropriate organ and tissue dose assessment, e.g. different parts of the heart, main arteries and veins as well as blood, brain, eyes lens,..) and, where possible and informative, the identification and integration of relevant biological endpoints and markers into epidemiological investigations further insights will be gained into the risks associated with such exposures.

Priorities in this field are:

- To determine the shape of the dose-rate and dose-response relationship in humans for circulatory diseases, lens opacities, cognitive/neurological dysfunctions and other relevant non-cancer outcomes at low or moderate doses based on key informative epidemiological studies (molecular or not, as appropriate).
- To identify, develop and validate biomarkers for exposure, early and late effects. The development of such biomarkers should allow greater precision of the actual doses received and inform the evaluation of the dose-response relationship of non-cancer effects.
- To evaluate non-cancer risk through systems biological analyses and mathematical models combining mechanistic studies and the epidemiological data, and integration of the two.
- To investigate early stages in the progression of non-cancer effects in tissue or disease-related endpoints in biological samples from members of appropriate epidemiological studies or individuals with similar living conditions and known exposure in order to understand spontaneous pathogenesis. This is a pre-requisite to understand radiation effects on pathogenesis.

4.2.3 Impact of radiation exposure characteristics

Dose fractionation and dose-rate effects have been observed for the induction of non-cancer effects (see for example, low dose-rate dependent effects (premature senescence) seen in endothelial cells of the cardiovascular system).

Priorities in this area are:

- To investigate the biological mechanisms that govern the effects observed in tissues involved in non-cancer effects after low dose exposure regarding specific exposure modalities (including internal exposures since low or high LET emitters will induce quite different types of damage)

and radiation qualities. An approach based on system biology (linked to nano- and/or microdosimetry) is highly recommended to identify clinically relevant pathways involved in low dose radiation-induced non-cancer effects.

- To conduct epidemiological studies of internal emitter risk, incorporating detailed dosimetric assessment and evaluation of dosimetric uncertainties. Where feasible and informative, these should include collection of appropriate biological samples and analysis of biomarkers of dose.

4.3 Individual radiation sensitivity

Individual variability in radiation-related cancer risk and genetic susceptibility to cancer is a key area to address for radiation protection. Differences in radiation sensitivity between individuals, or groups, may relate to gender, age at exposure, state of health, genetic and epigenetic make-up, lifestyle, and age attained. Such differences, if significant, raise the ethical and policy question as to whether some individuals or groups are inadequately protected by the present system and regulations.

At present, there is insufficient information to establish how large differences in sensitivity may exist between individuals or between groups of individuals and their consequent influence on risk estimates at low doses and dose-rates. In order to address policy questions it is necessary to obtain better scientific information on the extent of the variations in sensitivity in the population, both in the sizes of the variations and in the proportions of the population that are affected. This needs to include the impact of dose inhomogeneity, radiation quality and internal versus external exposures.

4.3.1 Basic mechanisms

Basic research is needed to establish which factors and processes predispose individuals who are at greater risk of late effects in terms of cancer or non-cancer diseases. This includes both molecular epidemiological approaches, the discovery of genetic, phenotypic and molecular markers of these pathways, and the integration of mechanistic studies in the quantitative evaluation of health risks. A major focus should be the understanding of how these different factors may modify risk keeping in mind that the radiosensitive phenotype may be multifactorial. Another important question is whether acute or late markers of radiation sensitivity (adverse healthy tissue or organ responses after radiotherapy) are related to risk of developing late effects following exposure to low and protracted doses of different LETs including internal exposures.

Priority research areas are:

- To develop a systems model of the acute (transcriptome, epigenome, proteome, metabolome, etc.) and long-term responses (senescence, oncogenesis, instability, stem cell turnover, inflammation etc.) to low doses of radiation so that differences in the response pathways can be detected and used to predict differences in outcome at both an individual (qualitative changes affecting health-relevant pathways) and population (quantitative changes in health outcomes) levels.
- To identify biomarkers of susceptibility to radiation associated disease that can be applied in molecular epidemiology.
- To investigate mechanisms by which age at exposure, attained age, sex and lifestyle and other factors, including co-exposures to other agents may affect radiation risk.

4.3.2 Health risk evaluation

The quantification of the contribution that individual sensitivity makes to overall radiation risk on both an individual and population level is the key question. Realistic estimates of how large the differences may be in extreme cases and also the spread of sensitivities in average population groups will need systems biological analyses and models of disease based on mechanistic studies and the enclosure of molecular biomarker in the epidemiological methodology.

The priorities in this area include

- To validate candidate biomarkers of individual sensitivity identified from the mechanistic studies (see above) in cohorts of exposed and non-exposed subjects that have developed cancer or non-cancer diseases.
- To improve or set-up key cohorts (see 4.1.2 for criteria for informative cohorts) and conduct molecular epidemiological studies to determine factors (host and environmental) involved in individual susceptibility to radiation-induced cancer and non-cancer effects and to quantify their effects.
- To quantify the variation in risk between different population groups and the impact of different factors (age at exposure, attained age, co-exposures and host factors). The nature of the interaction of ionizing radiation with co-exposures to other agents (e.g. tobacco smoke, heavy metals) for various cancers is important in considering risk transfer between different populations.
- To develop models of radiation-induced pathogenesis in dependence on individual risk factors.

4.3.3 Impact of radiation exposure characteristics

The impact of external versus internal emitters, dose inhomogeneities and radiation quality on individual radiosensitivity related to different dose and dose-rates has not been defined for relevant environmental, medical and occupational exposures. In case of internal contamination, individual radiosensitivity could be dependent on localized dose distributions, but there is currently no mechanistic understanding, relevant experimental models, or valid datasets for these relationships. Similarly, radiation quality is gaining importance because of the more wide-spread availability of external beam hadrontherapy, where scattered neutrons are of concern , and the increasing clinical use of radionuclides.

Individual sensitivity should be analyzed as a function of exposure and not only dose, because the same exposure can result in very different doses and dose distributions in different individuals. For internal exposure, the dose distributions can be very different in individuals because of anatomical and physiological differences (e.g. airway morphology variability, different thickness of mucus layer in the bronchi or nose contra mouth breathers). These variabilities should be taken into account and modeled for the analysis. Both accurate dosimetric models and physiologically relevant biokinetic models are required for the interpretation of the health and biological effects of internal emitters, especially for the characterization of individual sensitivities. There is also a need to characterize how internal exposure, dose inhomogeneity and radiation quality will influence the formation of candidate biomarkers identified in response to low LET external exposure. In many

situations mixed field exposures are relevant but again there is no data related to the role of individual radiosensitivity.

Priority areas are:

- To develop suitable cell, tissue and in vivo models for the quantification of the impact of dose inhomogeneities and radiation quality on individual radiosensitivity.
- To conduct epidemiological studies for the quantification of the impact of dose inhomogeneities and radiation quality on individual radiosensitivity.
- To characterize how internal exposure, dose inhomogeneity and radiation quality will influence the formation of candidate biomarkers identified in response to low LET external exposure.
- To study how dose distributions and related biological effects can vary between individuals at the same exposure conditions because of anatomical and physiological differences. Based on these differences, it is possible to identify individuals or groups of individuals who are especially sensitive to certain radiation exposures.

5. Synergistic topics of MELODI with other radiation protection platforms

Within the OPERRA project Task 2.1 synergistic topics between MELODI and the three radiation research platforms ALLIANCE (radioecology), NERIS (radiation emergency) and EURADOS (dosimetry issues) have been identified in the frame of the implementation of the second OPERRA call (published in December 2014, closed in March 2015). This is of great relevance in order to organize calls covering the whole field of radiation protection, and to encourage cross-platform cooperation. This activity aims also to provide the independent experts responsible for drafting future calls for research projects in radiation protection with the views of the radiation research platform members and the scientific community on the most important lines of research to be considered in the near future.

Currently, the following synergistic topics relevant for MELODI have been identified:

- Multiple stressors and modulation of radiation effects in living organisms.
  (MELODI, ALLIANCE, EURADOS)
- Development of health surveillance procedures.
  (MELODI, NERIS, EURADOS)
- Biological indicators of radiation exposure, effects, health risk and disease susceptibility to inform emergency management and epidemiological studies.
  (MELODI, NERIS, EURADOS)
- Improvement in the modelling of biokinetics and dosimetry of internal emitters
  (MELODI, EURADOS, ALLIANCE)
- Improved organ dosimetry in epidemiological studies
  (MELODI, EURADOS, ALLIANCE)

- Update personalized dosimetry in medical applications
  (MELODI, EURADOS)
- Investigation of the biological effectiveness of different radiation sources
  (MELODI, EURADOS, ALLIANCE)
- The roles of genetic and epigenetic changes in heritable/transgenerational and somatic effects relevant to individual and population health.
  (MELODI, ALLIANCE)
- Inter- and intra-species differences in radiosensitivity
  (MELODI, ALLIANCE)
- Biomarkers of exposure and effects in living organisms
  (MELODI, ALLIANCE)

6. Education and Training

6.1 The role of education and training in low-dose radiation research

The HLEG Report of 2009 (http://www.hleg.de/fr.pdf) identified a problem with the maintenance in Europe of the range of expertise essential to an effective programme of research into the risks to humans from low-dose radiation. The report advises that specific programmes aiming at knowledge management across generations have to be designed in order to achieve sustainable continuity and development.

A large proportion of the groundwork of research is carried out as student projects and thesis work. For this reason, the research effort relies on a continuing relationship with universities, and on a healthy stream of high-level students. It is essential that this symbiosis is recognised and taken into account in research funding structures.

A further intrinsic role of E&T within any specialized research area is in dissemination of new technologies, skills, and knowledge. To obtain maximum impact and benefit from research there should be an actively managed programme of workshops, seminars, summer schools, etc. which is integrated into the design and funding structure of all research. The programme should be aimed both at the sharing knowledge within the European low-dose research community and also at the wider radiation protection field including radioecology, emergency response, and the medical use of radiation.

6.2 Priorities for strategic support of E&T

Following the comments in the previous section, support for E&T has two priority areas: support for students and young scientists, and promotion of E&T for dissemination.

Support for students and young scientists

- Students need to be able to find places at universities and placement with research groups for project/dissertation work. This requires that the places must be available, but also that there

are sufficient incentives to attract top students. Universities are autonomous and develop new courses in response to a perceived need, taking account of staff expertise and specialization. Financial support from outside is not needed to achieve this end, although there is a role for influencing the perceived need. On the other hand, increasing the access to students Europe-wide to university courses through industry-funded scholarships could significantly help to attract students. Setting up such a post-graduate scholarship scheme for attendance at approved universities should be seen as a priority.

- In order to complement support at the post-graduate level and to help provide a career path for the most promising graduates, a scheme for provision of one or more post-doctoral fellowships should also be offered, to be taken up at approved research institutions.

Promotion of E&T for dissemination

- It should be explicitly in the wording for RTD calls that proposals will be judged favorably if up to 5% of the project budget is committed to providing workshops or training courses dedicated to the presentation of new science/technology which is being used or developed in the project.
- Parallel to the E&T supported by the RTD calls, it is seen as essential that a separately funded body (or part of a body with a ring-fenced budget) is responsible for the organization and sponsorship of targeted initiatives in order to promote the specialized skills and knowledge needed to maintain the full competence of the low-dose research community. These will be made readily available to postgraduate students and scientists. The benefit to the former will be the provision of supplements to their university courses and to give them experience of the different areas of science on offer to them in their future careers. For the latter, this will be a very effective way of providing continuing professional education, and for sharing knowledge with other research and educational institutions.

Coordination and collaboration of E&T providers

In order to get maximum benefit from E&T in the low-dose research area (both that which is already provided and the new initiatives proposed here) there should be an overall coordination of resources within the European community. Recommended priority actions are as follows:

- Continuation and extension of the MELODI Education and Training Forum in order to bring together all interested parties regularly to discuss needs and broaden the awareness of what is happening in EU member states. This should be seen as both a problem-solving and an advertising forum. There should be active participation by all other platforms involved in radiation protection (ALLIANCE, NERIS, EURADOS, EUTERP, medical groups etc.) in order to share mutual experience and resources.
- There should be an active cooperation among groups promoting and supporting E&T in the radiation protection and research area (EURAYS, ENEN, etc.) and possibly use of mailing lists or social media to advertise programmes, courses, scholarships, fellowships, etc.

7. Infrastructures

One of the roles of MELODI is to ensure the availability of and facilitate ready access to the state-of-the-art research infrastructures required to support the research efforts of radioprotection researchers. The priority is to promote the use of mature infrastructures and avoid unnecessary duplication. Furthermore, an effort should be made to harmonize practices amongst multiple facilities. Finally, the sustainability of rare but necessary facilities (such as those for internal contamination) needs to be guaranteed. This should include recommendations on the provision of the financial means to harmonize, sustain and access these facilities.

Infrastructures include so-called large infrastructures such as exposure facilities including those for animal experimentation, as well as the collection and storage of cohort data, data bases, biobanks and analytical platforms.

Within the EU-funded project DoReMi, an extensive list of relevant infrastructures was generated for low-dose research in particular irradiation facilities for internal and external exposure. In order to assess which infrastructures meet the needs of radioprotection scientists, it is necessary to develop and apply quality criteria determined by experts, specific to each type of infrastructure, for the listed large infrastructures. Financing for access to these facilities to support specific topics can then be included in future calls in which the selected facilities are partners in the future projects.

Within the EU-funded project DoReMi, a list of relevant cohorts was established. Priority should be given to cohorts and biobanks that permit studies to improve the quantification of the risk associated with low dose and low dose-rate radiation exposure, for cancer and/or non-cancer diseases and/or to identify groups of individuals with specific sensitivity. In the relative short-term, existing epidemiological cohorts can be used to support modeling and/or molecular studies for which the requirements differ. In the long-term, new prospective cohorts can also be envisaged, as well as the development of new collections of biological material that will be necessary to support radiation research in the next decades.

Within the EU-funded project STORE, an internet based platform for sharing data from epidemiological studies, as well as data and biological samples from radiation experiments, has been developed and has been further carried forward and supported by DoReMi. Going forward, it will be necessary to promote activities to maintain the STORE data base by supporting the service of a curator, to further update and continuously expand the content of the data base, and to elucidate to what extent data from other radioprotection platforms (ALLIANCE, NERIS and EURADOS) can be incorporated into STORE or whether a comparable data base would be more appropriate.

The use of STORE as a repository for data linked to all publications arising from EU-funded projects in radioprotection research should be required where appropriate in line with the recent guidelines for H2020 supported projects.

Furthermore, pointers to existing data sets from cohort studies or from radiological experiments (with animals or from the radioecology field) will need to be maintained and strengthened, and it will need to be indicated to what extent biological material is available. This should include the support of activities to identify valuable materials and archives that could be included in the database and the tissue bank, as well as to maintain relevant biobanks and rescue material from endangered biobanks. Furthermore, the use of biobanked material, where applicable, should be encouraged by including its use in future calls either indirectly for all relevant proposals or by

specific topics dedicated to its use. In addition, funding should be included to support the biobanking of samples arising from Euratom/H2020 funded projects where appropriate.

The maturation of the so-called 'omics technologies and systems biology may offer novel opportunities for European radiation protection research. As the quality of the technologies and supporting managerial and technical support varies widely, quality criteria will need to be established and applied in order to determine a limited number of facilities in each area which best meet the needs of radioprotection research. The use of these facilities should be linked to receiving funds in future calls, or at the very least a procedure will need to be put into place to assure the quality of those facilities outside of those on the list of recommended sites, such as for example, testing an agreed upon standard sample set, already tested by the listed facilities, within the scope of the funded projects.

It is obvious that in the case of a major nuclear accident or attack, that analytical platforms, such as RENEB are accessible for the rapid and reliable assessment of radiation exposure. In addition to the use of such platforms in the cases of emergency, they can also contribute to research, e.g. for molecular-epidemiological studies or long-term follow up, when large numbers of bio probes need to be analysed. Therefore, the use of RENEB for research purposes needs to be actively pursued and supported in future calls where appropriate.

Priority areas are:

- Specific call for the use of archived materials using specific retrospective approaches
- Enlargement and sustainability of RENEB

8. Research priorities

The purpose of the MELODI Association is to integrate national and European activities in the field of low dose and low dose-rate radiation research, to define priority scientific goals and to implement research. The Strategic Research Agenda of MELODI identifies these priority goals and the specific resources, infrastructures and training capabilities needed to further develop low-dose risk research.

The key priority for radiation protection research is to improve health risk estimates for exposures corresponding to the dose limits for occupational exposures and to reference levels for the exposure of the population in emergency situations. The approaches will need to be multidisciplinary and innovative. The integration of expertise outside of the conventional fields of radiation research will widen the possibilities to integrate modern technologies in health research in the assessment of health risk relevant to radiation protection.

Prior to EU calls, MELODI develops a short statement indicating its view on the highest research priorities in this field, which serve as one of the inputs to those responsible for the drafting of the call. These research priorities were identified from the MELODI SRA gradually enriched by the contributions of its members and the findings of the MELODI workshops organized annually since 2009. For the next call of the CONCERT (European Concerted Programme on Radiation Protection Research) project, a new statement has been prepared. The current and previous MELODI statements can be found on the MELODI website.

The five identified short-term priorities (see MELODI statement 2015) are summarized in the following.

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.

9. References

HLEG report 2009: http://ec.europa.eu/research/energy/pdf/hleg_report_-_january_2009.pdf

ICRP 2011, International Commission on radiological protection. Statement on tissue reactions, ICRP ref 4825-3093-1464

10. Glossary, Abbreviations, Websites

ALLIANCE (European Radioecology Alliance); http://www.er-alliance.org/

DoReMi Network of Excellence (Low Dose Research towards Multidisciplinary Integration), www.doremi-noe.net

EURADOS (The European Radiation Dosimetry Group); www.**eurados**.org/

HLEG (High Level expert group); http://www.hleg.de/

MELODI (Multidisciplinary European Low Dose Initiative) https://extranet.sckcen.be/sites/melodi/default.aspx

NERIS (European Platform on preparedness for nuclear and radiological emergency response and recovery); http://www.eu-neris.net/

OPERRA (Open project for European Radiation Research Area) http://www.melodi-online.eu/operra.html