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D2.1 MELODI SRA topics relevant to medical radiation protection research

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Abbreviations

AOP Adverse Outcome Pathways

CT Computed Tomography

E&T Education and Training

JRM Joint Road Map

RT Radiotherapy

SRA Strategic Research Agenda

Disclaimer

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1. Objectives and methodology

The general aim of WP2 “Analysis of existing approaches of SRAs and related documents in the field of medical radiation protection and medical use of radionuclides” is to elaborate the ideas of the European radiation protection research platforms which are not primarily dealing with the medical radiation protection field (MELODI, EURADOS, SHARE, ALLIANCE, NERIS), in the context of medical applications of ionising radiation and the corresponding radiation protection.

WP2 is divided into 6 tasks and the topics identified in each task are expected to describe the research priorities in development and radiation protection of medical applications of ionising radiation as perceived by the abovementioned platforms and increase interdisciplinary interaction between these platforms and EURAMED. WP2 is meant to provide these priorities in order to enable EURAMED to update its SRA and establish a roadmap in WP6.

The objective of **Task 2.1** is to identify and prioritise research needs relating to MELODI SRA topics relevant to medical radiation protection research and to provide EURAMED with a concise statement on these priorities to be considered for inclusion in their SRA.

The Task 2.1 panel members consists of 14 members:

Task 2.1 Panel members:
Laurence Roy / Sophie Jacob, *IRSN, France*
John Damilakis / Eleftherios Tzani, *UoC, Greece*
Hugo de las Heras Gala / Erik Mille / Simone Mörtl, *BfS, Germany*
Nathalie Impens / Sarah Baatout / Rafi Benotmane, *SCK CEN, Belgium*
Jean-Michel Dolo / Delphine Lazaro, *CEA, France*
Géza Sáfrány, *NNK, Hungary*
Boris Brkljacic, *RBI, Croatia (EURAMED rocc-n-roll Advisory Board member)*

To ensure broad MELODI community involvement and to facilitate consensus, an ad hoc group has been created involving the following members:

25 Members in the EURAMED rocc-n-roll MELODI ad-hoc group
Eva Forssell-Aronsson, *University of Gothenburg Sweden (Member of SAC)*
Horst Zitselsberger, *KVSF Germany*
Ivica Prlic; *IMROH Croatia*
Anna Genesca Garrigosa, *UAB, Spain*
Silva Mitro, *IOV, Italy*
Andrea Ottolenghi, *UNIPV, Italy*
Sotiris Economides, *EEAE, Greece*
Simonetta Pazzaglia, *ENEA, Italy*
Géza Sáfrány, *NNK, Hungary*
Pedro Vaz, *IST Portugal*
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Balazs Madas, *MTA EK, Hungary*
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Sisko Salomaa, *UEF and STUK, Finland*
Antonella Rosi, *ISS, Italy*
Joan Francesc Barquinero Estruch, *UAB, Spain*
Laure Sabatier / Jean-Michel Dolo, *CEA, France*
Prof Stephanie Combs, *head of the HMGU institute of Radiation Medicine, Germany*
Christoph Badie, *PHE, UK*

With its established panel, Task 2.1 aims to analyse the **MELODI SRA**, the **MELODI Annual Statement** and the **Joint Roadmap for Radiation Protection Research** to identify radiation biology related research topics such as tools to evaluate effects of ionising radiation, risk estimates for medical applications, radiosusceptibility and radiosensitivity and research on confounders. This document includes synergies with topics of the EURAMED SRA, and may elucidate missing topics for medical applications of ionising radiation and medical radiation protection, and reveal topics that are of specific interest to MELODI.

A first MELODI ad hoc working group meeting took place on October 30th, 2020 to discuss the working strategy including a questionnaire. To catch the MELODI medical priorities a survey has been conducted. The survey was based on a questionnaire with two main questions:

(1) In which medical applications is low dose effects research most needed?

(2) Within these contexts, which low dose effects research would deserve the highest priority?

The working group was asked to answer these questions, taking into account the priority topics from the existing MELODI SRA, the MELODI Annual Statement and the Joint Roadmap for Radiation Protection Research. The questionnaire and working strategy were discussed with the EURAMED rocc-n-roll Task 2.1 panel on December 9th, 2020. The developed questionnaire combined priorities of MELODI SRA and MELODI Annual Statement 2020 crossed with the priorities of the EURAMED SRA (Joint Roadmap for Radiation Protection Research) (see Appendix).

The aim of the questionnaire was to identify overlapping priorities between MELODI and EURAMED which were, to the respondent's opinion, the most important research subjects for the next 10 years in the field of low dose research, linked to medical applications of ionizing radiation.

The answers from the ad hoc working group on the questionnaire were collected. A second meeting of the ad hoc working group took place January 26th, 2021 to discuss the analysis of the questionnaire and to distil the most important research priorities of MELODI in the medical context. A presentation was then prepared to consult the EURAMED rocc-n-roll T2.1 panel about the outcome in April 2021. The present document reflects the resulting synthesis of the MELODI priorities obtained through this consultation process.

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2. MELODI priorities related to medical application of ionising radiation

2.1. Scope

A consensus of the MELODI ad hoc group has defined the scope of MELODI relevant for medical applications of ionizing radiation. Ionizing radiation exposure from diagnostic and therapeutic applications covers a very large range of doses from low, moderate to high doses. This might result in both stochastic and tissue reaction effects (previously called deterministic effects)[1]. Therefore, the research scope of MELODI related to the field of medical exposures should include both effects, considering late-developing effects.

In relation with medical applications of ionizing radiation, MELODI is interested to support and perform mechanistic and epidemiological studies. To perform such research in a context of medical application of radiation, access to cohorts and biobanks of exposed patients is needed for longitudinal studies, with samples and data from before and after the diagnoses and treatments. The research outcome will inform risk assessment studies which in their turn are needed for updated risk management and radiological protection of patients and medical workers.

2.2. Patient exposures

The MELODI ad hoc group considers as priority to focus on therapeutic and diagnostic medical exposures resulting in the highest collective doses for patients, in combination with elevated morbidity and/or mortality. Special emphasis should be given to the most sensitive populations and to populations with long life expectancies that are more likely to develop late health effects, being primarily children and the unborn child. From an epidemiological point of view, dose-response relationship is the cornerstone of radiation protection requiring to investigate cohort of individuals with various dose ranges.

In diagnostic imaging, of concern for radiological protection is the increasing use of computed tomography (CT) scans and other diagnostic imaging procedures (isotope-based imaging approaches including CT, positron emission tomography, and single photon emission computed tomography). The most important medical exposures are considered to be repeated CT scans on children, and more specifically multiple CTs exposing the more sensitive organs.

Interventional radiology procedures, in particular interventional cardiology and neuroradiology, are increasing in numbers and types as new procedures have emerged in recent years. These procedures involve both exposure of medical staff and patients. For patients, these procedures involve fluoroscopic effective doses in the range of low doses but may result in higher doses to healthy tissues (NB: local, skin exposure of patient might be as high as 2 Gy). For sensitive individuals as children, radiation-induced health outcomes induced by such exposure remains to be further investigated.

Radiation therapy is an important component of cancer treatment with approximately 50% of all cancer patients receiving radiation therapy during their course of illness. Such treatment involves exposure of healthy tissues in different dose ranges justifying investigation of health

[1] Tissue reaction effects (previously called deterministic effects) are characterised by a threshold dose for a given effect which can be defined as a dose below which the effect does not occur. This dose is often difficult to determine. One way in which epidemiological evidence for a threshold can be assessed is by examination of the lowest dose at which a significant positive dose–response relationship can be detected. The 'threshold dose' is defined as the estimated dose for 1% incidence, denoting the amount of radiation that is required to cause a specific, observable effect in only 1% of individuals exposed to radiation. This is not a 'true' threshold in the sense of the effect not occurring at all, it is used in a practical sense for protection purposes

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outcomes in this population, in particular paediatric patients and adult patients with long life expectancy.

Nuclear medicine treatments, including targeted molecular radiotherapies, are important given the increasing popularity. The huge variety of such therapies, each of which can lead to different long-term effects, is a very broad field.

2.3. Medical workers exposure

In addition, it is also relevant for MELODI ad hoc group's viewpoint to consider medical occupational exposures resulting in elevated individual or collective doses and that may lead to increased morbidity and mortality as a priority.

The highest medical occupational exposures of interest are found in interventional radiology. Even if occupational exposures cannot exceed the yearly dose limits, cumulative doses might be interesting as they might be high. Interventional procedures guided by fluoroscopy are the highest doses registered among medical staff using X-rays and interventionalists represent the most important group of medical specialists involved in such practices. Scatter radiation levels in the vicinity of the patient may be quite high and may potentially lead to increased morbidity and mortality.

3. Elaboration of priorities for the EURAMED rocc-n-roll SRA

3.1. Topic 1: Dose and dose rate dependence of cancer risk

3.1.1. Introduction

Extrapolation of cancer risk estimates based on observations at moderate to high doses is the primary basis for estimation of radiation-related risk at low doses and dose rates[2] [1]. These cancer risk estimates used in radiation protection are largely based on studies on Japanese atomic bomb survivors who were exposed to ionizing radiation at high dose rate. According to the ICRP, the linear non-threshold (LNT) model for extrapolation remains a prudent basis for radiation protection at low doses and low dose rates. The risk coefficients obtained from these studies can be reduced by the dose and dose-rate effectiveness factor (DDREF) to account for the assumed lower effectiveness of low-dose and low-dose-rate exposures. But these hypotheses remain controversial and research on the dose and dose-rate dependence of cancer risk is still important. However, there is now growing evidence from epidemiologic studies of dose-risk relationships at low dose levels, for all cancers and for specific cancer sites. Although risk models are available for many cancer sites that incorporate modifying factors such as sex, age at exposure and time since exposure, there are still large uncertainties related to radiation-induced risks at low doses.

These uncertainties are concerning the magnitude of total and specific cancer risks following specific exposure situations such as fractionated or protracted exposure encountered, in particular, in medical settings, and when the dose is heterogeneously distributed, more particularly after internal contamination (further developed in Topic 4 of the document); the risk for healthy tissues surrounding cancer sites and systemic effects for individual cancer sites due to possibly different tissue sensitivities; and the shape of the dose-risks relationships at dose and dose-rates that are lower than those for which direct epidemiological evidence is available.

[2] Total doses lower or equal to 0.1 Gy are classified as low doses of radiation, while dose rates below 0.1 mGy/min are defined as low dose rates of radiation (UNSCEAR 2012), and examples of carcinogenicity of such exposures are rare.

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3.1.2. Medical context requiring specific attention

Of concern for radiological protection is the increasing use of computed tomography (CT) scans and isotope-based diagnostic imaging. Patients receiving repeated CT scans, especially children, are of particular interest. Premature babies monitored for pulmonary development with repeated X-rays could also be investigated. Among adults, cancer related to population (>45y) screening for lung cancer using low dose CT (link with EURADOS) may also be an issue.

The widespread use of interventional radiological procedures in the heart, lungs, abdomen, and many vascular beds, with extended fluoroscopic exposure times of patients and operators, emphasizes the need for recording of dose and later follow-up studies of potential radiation effects among these populations. Studies of infants who experience diagnostic exposures related to cardiac catheterization is of particular interest.

Studies on second primary malignancies in young patients with thyroid cancer treated with radioiodine (iodine-131) are scarce and should be further investigated

For cancer treatment, patients treated with radiotherapy may develop treatment-related secondary cancer, unrelated to the primary cancer. The topic of second cancer post RT is also important. Effects of emerging techniques of radiotherapy would also deserve further research, in particular FLASH radiotherapy using ultra-high dose-rate exposures.

3.1.3. Proposed priorities for EURAMED rocc-n-roll SRA

The MELODI SRA and JRM priorities related to cancer risks are presented in Annex.

In the context of medical application of ionising radiation, the MELODI ad hoc panel group considers that there is a priority to:

- develop or improve long-term large molecular epidemiological studies in order to enhance knowledge on determining the shape of the dose and dose-rate relationships for all cancers and for specific cancer sites
- Identify and validate radiation exposure and cancer biomarkers and the nature and role of various target cells related to cancer, from early exposure through intermediate steps to disease

NB: the specific topic dealing with individual variation in risk is detailed in Topic 3.

3.1.4. Tools / methodologies / research projects - approaches of interest in the medical field

In order to provide new insight on the issue of dose and dose-rate dependence of cancer and to help in consolidating the assessment of cancer risks associated with low doses, further large epidemiological studies are needed with extended follow-up, improved characterization of modifying factors of the dose-risk relationship, individual dose estimation to the site of interest, evaluation of the uncertainty in dose estimation and collection of biological samples of normal and diseased tissues in order to better understand the radiation impact on the disease process. Epidemiological studies with long follow up of patients receiving repeated CT scans, especially children, are particularly useful to investigate cancer risk, in particular for leukaemia, lung, brain or breast cancer. Studies of infants who experience diagnostic exposures related to cardiac catheterization is of particular interest.

In order to investigate mechanisms involved, there is a need to identify biomarkers from patients' cohorts and experimental studies which have the potential to link changes at tissue,

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cellular and sub-cellular levels to observed health effect, and to understand the role of specific target cells. This covers in particular,

- Studies on radiosensitivity of different target cells and interaction of low dose and low dose rate on stem cell/progenitor cells possibly leading to cancer.
- Studies on DNA damage according to radiation quality, based on genetic and epigenetic processes
- Studies on effects of immune system alteration and inflammatory reactions. Use of Omic approaches, organoids.

Epidemiological data and mechanistic studies should be integrated for biologically-based modelling and the AOP approach.

3.2. Topic 2: Non-cancer effects

3.2.1. Introduction

There is increasing accumulation of evidence from epidemiological studies that some non-cancer effects (tissue reactions) take decades to manifest and present clinically. Recent results from epidemiological and experimental investigations indicate possible increased risk of circulatory diseases, lens opacities, cognitive/neurological effects, and perturbation on the immune system, not only at high doses, but also at doses down to 500 mGy, and possibly even lower. But there are still uncertainties related to the risks of late-developing non-cancer diseases end effects of radiation exposure.

Besides the results of the survey of the MELODI Ad Hoc working group, the proposed priorities are also based on a MELODI workshop entitled ‘Non-cancer effects of ionizing radiation’ that was held in Sitges, Spain 10–12 April 2019, resulting in a special issue published in Environment International (Volume 89 issue X (2021). A synthesis and a MELODI view on the research needs for the future is presented in the editorial by M. Kreuzer and S. Bouffler. “Non-cancer effects of ionizing radiation – clinical implications, epidemiological and mechanistic evidence and research gaps” [2].

In this issue, four papers were published specifically dedicated to eye lens opacities/cataracts, circulatory and metabolic diseases, cognitive effects, and effects on the immune system. These papers [3] [4] [5] [6] , as well as the issue of potential hereditary effects of radiation on offspring and next generations which is a recurrent major concern as stated in the article by Laurier et al. [1], are presented in Annex and were considered by the MELODI ad hoc panel group to identify priorities for medical application context

3.2.2. Medical context requiring specific attention

Radiotherapy is known to cause a variety of tissue injuries, depending on the cancer site. A number of advanced radiotherapy technologies such as magnetic resonance-guided radiotherapy or proton beam radiotherapy have emerged, allowing to reduce healthy tissue exposure, but with little evidence that their use reduces these tissue injuries. Thoracic radiotherapy is known to cause a variety of cardiovascular damage that should be further investigated in paediatric (Hodking Lymphoma) and adult cohorts (breast, lung cancer). Orbito-ocular/central nervous system/head and neck radiotherapy and repeated diagnostic imaging examinations (brain CT scans) are particularly likely to induce cognitive impairment that should be further investigated in paediatric cohorts. In addition to lens opacities, retinopathies were poorly studied whereas some studies suggested that they may be relevant as a radiation-induced tissue reaction effect.

Radiopharmaceuticals for cancer treatment: include therapeutical or theranostic molecules. Each molecule / therapy may have different organs at risk (glands, kidney, liver, bones, …). Some tissue reactions may also be expected.

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The use of interventional radiology procedures, in particular interventional cardiology and neuroradiology is increasing. These procedures involve both exposure of medical staff and patients. The population of interventional radiologists is of great interest to evaluate the risk of lens opacities that should be further investigated. For patients, these procedures involve fluoroscopic doses. In particular, sensitive individuals such as children, such exposures to specific organs at risk (heart and brain) could lead to non-cancer effects.

Patients receiving repeated imaging procedures (CT and PET) are also a population of interest to investigate non cancer effects. Repeated paediatric brain CT should be further investigated for cognitive effects. Among adults, the cardiac risk induced by lung cancer screening using low dose CT should be followed up in the population older than 45 y (link with EURADOS).

3.2.3. Proposed priorities for EURAMED rocc-n-roll SRA

The MELODI SRA and JRM priorities related to non-cancer risks are presented in Annex.

In the context of medical application of ionising radiation, circulatory diseases and cognitive impairment and neuropathies are identified by the MELODI ad hoc panel group as priorities for long term non-cancer effects. For these non-cancer effects, there is a priority to:

- Determine the shape of the dose-response relationship by development or improvement of long-term epidemiological studies (molecular or otherwise).
- Identify biomarkers in biological samples from epidemiological studies for exposure, individual sensitivity, and for early and late non-cancer effects
- Identify the underlying mechanisms that lead to each of the non-cancer diseases, integrating potential dysregulation of the immune system.
- Evaluate non-cancer risk through systems biology and mathematical models

3.2.4. Tools / methodologies / research projects - approaches of interest in medical field

There is a need to provide new insight on the issue of non-cancer risk in medical application context and to help in consolidating the assessment of non-cancer risks associated with low doses in such medical context. The medical context for this research is described in the previous section.

In order to determine the shape of the dose-response relationships, epidemiological cohort studies require good dosimetry, explicit definition of the disease outcome, long follow-up, information on the lifestyle risk factor, medical history, and the collection of biological samples.

In the medical context, some specific population cohorts of patients treated with radiation therapy or young patients receiving repeated imaging procedures, further detailed in previous part on “Medical context requiring specific attention” are of particular interest and could reach these quality criteria. Artificial Intelligence is a promising tool to support these studies by exploring dosimetry and the characterisation of the outcomes.

In order to investigate mechanisms/pathways involved, there is a need (1) to identify biomarkers for early and late non-cancer effects on biosamples from patients cohorts; (2) to develop animal and in vitro models of radiation-related non-cancer diseases, including organoids derived from human pluripotent stem cells in order to clarify the pathways involved and conduct appropriately powered induction studies; and (3) to investigate radiobiological molecular mechanism in the different organs employing multiomic approaches.

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In vivo experiments will help evaluating dose-response relationships for non-cancer effects for different organs.

The role of systemic effects should also be addressed, specifically the immune system, epigenetics, and the bystander effect.

Epidemiological data and mechanistic studies should be integrated for risk-predictive biologically-based modelling and the AOP approach.

3.3. Topic 3: Individual variation in risk

3.3.1. Introduction

Besides the results of the survey of the MELODI Ad Hoc working group, the proposed priorities are also based on a MELODI workshop entitled 'Individual Radiosensitivity and Radiosusceptibility which took place in 2019, resulting in a special issue published in the International Journal of Radiation Biology (Volume 96 issue 3 2020). A synthesis and a MELODI view on the research needs for the future is presented in the editorial by Salomaa S, Jung T. "Roadmap for research on individual radiosensitivity and radiosusceptibility – the MELODI view on research needs" [7]

In this special issue the term radiation sensitivity / radiosensitivity is used for individuals who are at higher risk for early or late reactions in normal tissue after radiation and the term radiation susceptibility / radiosusceptibility is used for individuals who exhibit higher cancer risk after radiation than the general population. The related papers [8] [9] [10] [11], are presented in Annex and were considered by the MELODI ad hoc panel group to identify priorities for medical application context.

3.3.2. Medical context requiring specific attention

The medical contexts regarding individual variation in risk requiring specific attention are:

- Radiation-induced cancer and non-cancer diseases in patients undergoing imaging procedures (CT, PET), radiotherapy and therapeutic nuclear medicine applications;
- Certain medical imaging procedures.

3.3.3. Proposed priorities for EURAMED rocc-n-roll SRA

The MELODI SRA and JRM priorities related to individual variation in risks are presented in Annex.

In the context of medical application of ionising radiation, the MELODI ad hoc panel group considers that there is a priority

- To develop an understanding of the cellular, organ and systemic responses determining individual susceptibility to radiation-induced health effects including, for example inflammatory processes and immunological states and other cofactors, so that differences between individuals in the response pathways can be considered, and biomarkers be identified for both sensitivity and susceptible reactions.

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3.3.4. Tools / methodologies / research projects - approaches of interest in medical field

Collaborative prospective studies addressing normal tissue responses with a combination of assays after moderate doses thus appears to be the most feasible approach.

Prospective molecular epidemiology study to assess radiosensitivity following radiotherapy as the most tractable group of patients suffering enhanced radiosensitivity; use data from well-defined cohorts with good exposure assessment and biological material already collected; focus on study quality with standardized data collection and reporting; improve statistical analysis; cooperation between radiobiology and epidemiology; and take consequences of radiosensitivity and radiosusceptibility (including DNA damage and other initiating events) into account.

3.4. Topic 4: Health risk related to various doses inhomogeneities and dose rates

3.4.1. Introduction

This topic is prepared based on the work of the MELODI Ad Hoc Working group, a virtual MELODI workshop on the Effects of Spatial and Temporal Variation in Dose Delivery organised in November 2020, and the Finnish CORES workshop on “Radiation Safety of radiation in medical use” held in October 2020.

Relevant information of MELODI and CORES workshops organised in 2020.

The relevant topics of the MELODI workshop were related to research of the temporal variation and dose rate effects including spatial variation including radiation quality, internal exposures from radionuclide therapy, and partial body exposures. The general conclusion of the workshop is that there is a need to better understand underlying mechanisms for better risk predictions on the patient population or even on patient level. However, there is a lack of data of exposed humans at mid-dose rates and very low dose rates in cellular models: Patient data and biobanks are needed to perform mechanistic low dose research. The ultimate goal of this research is to optimise diagnosis and treatments with limited adverse acute and long-term side effects. Next to cancer, epigenetic (non-cancer) effects in terms of dose-rate need to be considered. Dose rate effects for different radiation qualities need to be understood for a range of patient groups (disease history, age, sex, background, pregnancy). Five papers to be submitted to *Radiation and Environmental Biophysics* will provide more accurate information on the research needed.

In the CORES workshop it is shown that 0.5-1% of patients receiving CT get cumulative doses above 100 mSv within a year. Dose estimations from CT are difficult using the current phantoms as imaging is usually for whole body or trunk. Doses to healthy organs are also of high interest and adverse effects on healthy tissues at risk in certain treatments should be considered.

3.4.2. Medical context requiring specific attention

In medicine, partial body exposures are applied via external radiation but internal exposure via targeted radionuclide therapy (TRT) is gaining interest. Radiation treatments are often applied in combination with or after (a series of) other therapies.

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More and more different radiation qualities are used in therapy. Therapies with different dose rates (remaining in the range of high dose-rates for external and internal RT; in a small proportion of brachytherapy, low and moderate doses are applied), fractionation schemes or dose-volume histograms are being used.

Flash radiotherapy and hypofractionated radiation therapy use higher doses in fewer sessions. Some of these therapies are applied sequentially or in combination with chemotherapy or immunotherapy.

3.4.3. Proposed priorities for EURAMED rocc-n-roll SRA

The MELODI SRA and JRM priorities related to health risk related to various doses inhomogeneities and dose rates are presented in Annex.

In the context of medical application of ionising radiation, the MELODI ad hoc group considers that there is a priority to study mechanisms elicited by inhomogeneous dose deposition, integrating “dynamic” dose assessment and identification of relevant pathways (both for cancer and non-cancer diseases) in a systems biology approach, in order to characterize the response of the complex system as a whole.

3.4.4. Tools / methodologies / research projects - approaches of interest in medical field

Suitable tissue and in vivo models for the quantification of the impact of dose inhomogeneity and radiation quality need to be further developed

Partial body exposures occur in external radiotherapy and brachytherapy, nuclear medicine but also in the workplace (medical staff); the identification of mechanisms of out-of-field pathological pathways and the identification of organs at risk are needed.

The dose-effect studies should be focused on well-defined patient groups where heterogeneous doses are applied and on highly exposed nuclear medicine staff in terms of cumulative dose. This input will feed mechanistic studies with the aim of better understanding the adverse effects of diagnoses and treatments. It is important to take into account patient history and health status. Hence, individualised patient risk / benefit estimations with reduced uncertainties may be achieved.

As Targeted Radiotherapy (TRT) is gaining interest, biokinetic and dosimetry models are needed for the radiopharmaceuticals and respective building blocks (vector molecules and radionuclides), and the long-term effects should be investigated. Combined toxicity of TRT and previous medical treatments needs to be considered in a holistic way.

It should be highlighted that the dosimetry research and patient dose registration are sine qua non for the proposed dose-effect studies.

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4. Summary of Topic 1 to 4

4.1. Highlights and priorities for the EURAMED rocc-n-roll SRA

In general, it can be concluded from the topics 1-4 that a mix of epidemiological studies and mechanistic studies is needed to improve the understanding of adverse effects of medical applications and ultimately improve radiation protection in the different medical applications of ionising radiation for patients and medical workers receiving high occupational cumulative doses in the long term.

Mechanistic studies should be based on good molecular epidemiology and in vitro research. This combination of research could lead to the setup of adverse outcome pathways related to various medical applications for various adverse outcomes. The combination of knowledge gathered by mechanistic and epidemiological studies may contribute to the selection of the best therapies in the future at an individual patient-base.

The highest research priority should be dedicated to frequently used medical procedures resulting in high individual doses on patients (1) with a long life expectancy or (2) with increased risk of decreased quality of life by the treatment.

Whatever the topic, it appears that we need biobanks, more samples, and a better organization to have access to patient data and biobanks. Big data management and the use of artificial intelligence on the interpretation of the data will be needed.

4.2. Challenges and perspectives for the EURAMED rocc-n-roll SRA

In the future, new European projects to study the effects of ionising radiation from medical exposure and develop knowledge for better individualized application of medical exposure should allow access to radiation databases and biobanks. The setup of such infrastructures exhibits legal (privacy), organisational and IT challenges on national and even European level. It should be noted that MELODI experts (especially epidemiologists) should be involved in the setup to ensure the usefulness of the infrastructure for effects studies.

5. Education and training

5.1. Introduction

Education and training (E&T) are mandatory for the development and maintenance of the expertise and competence of the community of research scientists working in the area of radiation protection research. An Education and Training Working Group is supporting the goal of MELODI to coordinate and build long term competence following its statutes and Strategic Research Agenda (SRA).

One of the roles of MELODI is the promotion and support of E&T in the scientific areas that underpin research into the risks to human health from low dose and low dose-rate ionising radiation. Covering in particular the field dedicated to medical applications of ionizing radiation.

5.2. Priorities from the MELODI perspective

There are many ways in which MELODI E&T can provide support to the low dose research community, in particular in the field of medical application:

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1. Providing entry points for attracting new students into one of the relevant disciplines. Students need to be able to find places at universities, placement with research groups for project/dissertation work and build their own research network. These require that the places and, sufficient incentives to attract top students and economical support for networking through for example joining congresses, scientific visits etc must be available.

2. Supporting students with career development to help them continue in the area. In order to encourage the career development of new scientists entering the radiation research field by promoting the interest of and the development of these students and young scientists, initiatives such as the European Radiation Research Association for Young Scientists (EURAYS, http://www.eurays.eu/) should be encouraged, in particular in the field of medical applications of ionizing radiations.

3. Economically supporting students who need to be able to find places at universities, placement with research groups for project/dissertation work and build their own research network. These require sufficient incentives to attract top students and economical support for networking through for example joining congresses, scientific visits etc. must be available. In 2020, within MELODI Education and Training Working Group the MELODI Mobility Programme have been established, offering a total of €5,000 per year for travel awards to early career scientists, PhD and MSc students. The intention is to financially support participation in a conference, a course, a visit, an internship or enable a student exchange to carry out scientific research, all in order to increase the applicant's involvement and knowledge/skills in European research in radiation protection.

4. Integration of university teaching departments with institutions engaged in cutting edge research programmes for the benefit of both.

5. Contributing to continuing education for professional researchers in order to provide access to new and emerging developments and infrastructures, and to stimulate interdisciplinarity. In particular, providing radiobiology course for medical doctors dedicated to the effect of IR should be encouraged.

6. To provide a conduit for new research results to a wider scientific and operational radiation protection audience in order to raise the profile of the topic of fundamental radiation risk research.

For more dedicated Education and training needs in the field of medical applications of ionizing radiation we refer to WP 7.

6. Infrastructures

6.1. Introduction

One of the roles of MELODI is to promote and facilitate access to the state of-the-art research infrastructures to support the research efforts in the radiation protection field. In order to identify, characterize and quantify health risks accurately, the quality of raw data and final results produced from research projects is essential. So, the harmonization practices amongst multiple facilities are becoming an increasingly important indicator of reliability and finally, of the sustainability of the virtual network of infrastructures as well as a guarantee of the dynamism and high quality of the research area.

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6.2. Priorities from the MELODI perspective

Infrastructures used for research about medical applications of ionizing radiation (including radiation protection aspects) and mainly facilities with various irradiation systems as well as databases (including cohorts) and biobanks especially developed for the domain.

STORE, an Internet-based platform for storage and sharing data about the radiation protection field has been developed and continues to grow. Going forward, it will be necessary to promote activities to maintain and develop this database and continuously expand it as STORE also includes systemically all new data and results issued from Euratom/Horizon Europe supported projects. The use of this repository for data linked to all publications arising from funded projects in radioprotection research could be easily included various connected aspects of medical applications of ionizing radiation and it should be required, where appropriate and possible (ethics requirements and informed consent in epidemiological studies) keeping and assuming the FAIR principles and rules edited for Horizon Europe. Particular attention has to be dedicated to aspect related to sensitive data management. The implantation in 2018 of the GDPR (679/16) requires efforts and dedicated budget to streamline the compliance with GDPR rules.

Harmonisation of quality standards, practices and protocols, and co-operation between the European radiation protection research platforms in relation to the provision and use of infrastructures will continue to be extremely important to guarantee the quality of produced results. Efforts could be done to sample/data acquisition and sample/data storage with the aims to re-use of archived materials (particularly medical biobanks). There is a need for transnational agreement on a strategic work plan for maintenance, updating, mutual use of suitable infrastructures.

Simultaneously, education and training actions should be developed to promote the use of existing powerful European research infrastructures rather than local and inadequate ones. The advantages of using these relevant infrastructures through common rules for a transnational access should be obvious and incentive.

MELODI's recommendations about infrastructures, which are summarized below, seem largely applicable also for the field dedicated to medical applications of ionizing radiation:

- Develop easy access and improve the common organization of the existing network of infrastructures, using feedback from approaches applied for infrastructures networks issued from past initiatives within Europe,
- Develop intercomparisons and harmonization activities to guarantee the quality of data and results issued from funded projects,
- Develop protocols and guidance documents, approaching a common compliance with GDPR rules, with data management (storage and sharing) applying FAIR principles, favour open access within STORE and promote the re-use of archived materials and existing epidemiological data retrospective approaches. This includes access to medical data and biosamples which need particular attention due to anonymization and authorization rules. A panel of experts at an European level could define a protocol to harmonize in-house guidance from institutions or at national levels to give common addresses for the future scientific scenario,
- Improve the awareness of existing relevant infrastructures through E&T courses, and promote their use implementing on site practical courses

For more dedicated infrastructure needs in the field of medical applications of ionizing radiation we refer to WP 4.

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7. References

1. Laurier, D., et al., *Areas of research to support the system of radiological protection.* Radiat Environ Biophys, 2021. **60**(4): p. 519-530.
2. Kreuzer, M. and S. Bouffler, *Guest editorial: Non-cancer effects of ionizing radiation - clinical implications, epidemiological and mechanistic evidence and research gaps.* Environ Int, 2021. **149**: p. 106286.
3. Ainsbury, E.A., et al., *Radiation-induced lens opacities: Epidemiological, clinical and experimental evidence, methodological issues, research gaps and strategy.* Environ Int, 2021. **146**: p. 106213.
4. Tapio, S., et al., *Ionizing radiation-induced circulatory and metabolic diseases.* Environ Int, 2021. **146**: p. 106235.
5. Pasqual, E., et al., *Cognitive effects of low dose of ionizing radiation - Lessons learned and research gaps from epidemiological and biological studies.* Environ Int, 2021. **147**: p. 106295.
6. Lumniczky, K., et al., *Low dose ionizing radiation effects on the immune system.* Environ Int, 2021. **149**: p. 106212.
7. Salomaa, S. and T. Jung, *Roadmap for research on individual radiosensitivity and radiosusceptibility - the MELODI view on research needs.* Int J Radiat Biol, 2020. **96**(3): p. 277-279.
8. Seibold, P., et al., *Clinical and epidemiological observations on individual radiation sensitivity and susceptibility.* Int J Radiat Biol, 2020. **96**(3): p. 324-339.
9. Gomolka, M., et al., *Potential screening assays for individual radiation sensitivity and susceptibility and their current validation state.* Int J Radiat Biol, 2020. **96**(3): p. 280-296.
10. Averbeck, D., et al., *Establishing mechanisms affecting the individual response to ionizing radiation.* Int J Radiat Biol, 2020. **96**(3): p. 297-323.
11. Kalman, C. and D. Oughton, *Ethical considerations related to radiosensitivity and radiosusceptibility.* Int J Radiat Biol, 2020. **96**(3): p. 340-343.

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8. Appendix

8.1. Questionnaire for the survey

Two tables in excel were sent to the Ad hoc members with the priorities of the EURAMED SRA and priorities of MELODI SRA in Table 1 and Statement 2020 in table 2. In addition, a third table with open questions was send.

The following information was given: Please select in the two matrices the overlapping priorities between MELODI and EURAMED which are, to your opinion, the most important research subjects for the next 10 years in the field of low dose research, linked to medical applications of ionizing radiation. For these subjects, please include (a) which field of medical application would benefit from this research (b) what type of research would be needed (c) what is the expected outcome (d) what would be the relevance in terms of increased radiation protection for medical applications within 10 years (e) same as (d) but only achievable after 10 years". The number of most important research subjects is not limited, you may for example only fill one priority field or you may wish to select multiple fields in the two matrices, according to your professional opinion.

Table 1

	EURAMED SRA priorities linked to low dose research ↓			
	Normal tissue reactions, radiation-induced morbidity and long-term health problems			
MELODI SRA topics linked to medical applications ↓	I. Exposure-associated cancer risk: dose, dose distribution and dose-rate dependence	II. Non-cancer effects in various tissues and radiobiology-based effect models for individual morbidity endpoints	III. Individual patient-related radiation sensitivity and early biomarkers of response and morbidity	IV. Radiobiological mechanism of radiation-induced side effects and protective strategies
Dose and dose-rate dependence of cancer risk				
Non-cancer effects				
Individual variation in risk				
Effects of spatial and temporal variation in dose delivery				

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Table 2:

	EURAMED SRA priorities linked to low dose research ↓			
	Normal tissue reactions, radiation-induced morbidity and long-term health problems			
MELODI Statement 2020: priorities 2020 - 2025 ↓	I. Exposure-associated cancer risk: dose, dose distribution and dose-rate dependence	II. Non-cancer effects in various tissues and radiobiology-based effect models for individual morbidity endpoints	III. Individual patient-related radiation sensitivity and early biomarkers of response and morbidity	IV. Radiobiological mechanism of radiation-induced side effects and protective strategies
• To evaluate the risks of, and dose-response relationships for, non-cancer diseases at low and intermediate dose levels (100 - 500 mGy and below): in particular cardiovascular, cognitive, neurological and immunological effects.				
• To define the processes contributing to cancer development in relevant target stem/progenitor cell populations after low dose/low dose-rate exposures; including for example the role of epigenetics, metabolic status, ageing, and immuno-senescence amongst others, in single and multiple stressor exposure situations.				

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• To identify, develop, validate and implement the use of biomarkers of exposure, and for early and late effects for cancer or/and non-cancer diseases and individual susceptibility. The relationship between these radiation biomarkers and those emerging biomarkers of healthy/unhealthy ageing needs to be considered and explored				
• To understand the health effects of inhomogeneous dose distributions, radiation quality and internal emitters in particular addressing the difference between risks from acute and chronic exposures through the integration of experimental and epidemiological data applying biologically-based risk models. Also to improve the understanding of the effects of intra-organ dose distribution through observations in patients exposed to inhomogeneous				

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fields and experiments with organotypic tissue models.				
• To continue to refine risk estimates for cancers after low dose and low dose-rate exposures in occupational, medical and other cohorts. Such quantitative risk estimations are required to inform judgements on risks from acute, chronic and inhomogeneous exposures, and will provide important input to the development of quantitative mechanistic risk models and adverse outcome pathways (AOPs), see below				
• To identify, explore and define AOPs for radiation-induced health effects, and determine if those operating at low doses and dose-rates are the same as those operating at higher levels of exposure, and when the triggering of an AOP is sufficient to disrupt normal homeostasis and lead to pathologies.				

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Table 3

OPEN QUESTIONS	ANSWERS
(a) which low dose research do you perform actually related to medical applications?	
(b) which medical application will benefit from your research outcome?	
(c) which research would be needed in the future to improve?	
(d) which area of medical applications deserves the highest attention with regard to low dose research? Please indicate max 3 areas.	

All the responses received have been collected and are presented below for each MELODI SRA priority.

8.2. Topic 1 – Information sources for identification of priorities for EURAMED rocc-n-roll SRA

8.2.1. Answers to the questionnaire

Which field of medical application would benefit from this research:

- Imaging procedures (CT and PET), especially in children
- Interventional radiology procedures, especially in children
- Nuclear medicine applications
- Radiotherapy (external RT : proton / hadron therapy, other modern external RT; internal radiotherapy: radiopharmaceutical therapy in cancer)

What type of research would be needed:

- Long term epidemiological studies
- large studies to link biomarkers with epidemiological data; for dose limit + dose-rate effects biomarkers for individual sensitivity; response and morbidity
- biomarkers of healthy tissues late effects for screening and follow-up
- biomarkers of exposure
- robustness of biomarkers for low LET / homogeneous exposure versus high LET and inhomogeneous exposures
- in vitro systematic studies to determine biological effects; radiosensitivity of different target cells, for low LET, hadron and neutron,
- in vitro studies on relevant human cells and tissues and in vivo in patient samples
- basic cytogenetic research on populations (both occupational and patients) relating doses and cancer risks

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- effects of immune system alteration, inflammatory reactions, confounding factors, multi-exposure; role of non-clonogenic and bystander reactions in the development of radiation-induced late sequel; genetic and epigenetic processes
- interaction between DNA damage and immune system
- interaction of Low Dose and LDR on neural stem cell/progenitor cells possibly leading to cancer
- explore role of specific target cells for rad induced late health effects (incl age @ exposure
- individual sensitivity: assessment of genetic and epigenetic processes
- radiosensitivity linked to anatomic heterogeneity within and between critical organs
- immune surveillance against cancer cells
- increase effectiveness of imaging (better extraction of biomarker features + artificial intelligence techniques)

What is the expected outcome?

In general:

- optimisation of diagnosis and treatment protocols, enabling/increasing personalised medicine
- optimisation of medical exposures, limitation of the use of ionising radiation in sensitive patients
- decrease in the long term adverse effects of medical diagnosis and treatments,
- scientific knowledge,
- guidelines and recommendations
- identification of mechanisms caused by radiation towards cancer development: although such pathways may overlap with those of other stressors, it is important to define the mechanisms from societal point of view.

In particular:

- Models to relate dose and dose rate for cancer risk in patients (based on systematic studies' datasets, for different radiation energies and qualities)
- mechanistic understanding and identification of cellular pathways of cancer development including role of immune system, genetic and epigenetic effects, non-clonogenic radiation effects, bystander effects
- genetic and epigenetic (and other?) biomarkers for individual radiosensitivity for individualised therapy, for early "health" effects, for screening and follow-up

What would be the relevance in terms of increased radiation protection for medical applications within 10 years

In general the research will lead to optimised medical exposures in terms of radiation protection and safety, and to optimised medical procedures with a better trade-off between exposure and diagnostic or therapeutic treatment.

In particular:

- identification of patients at risk; minimise CT for sensitive patients and search alternatives
- better RP of patients, improve quality of life, improved outcome, less side effects, improve survival
- use of biomarkers, including immune biomarkers to identify sensitive patients or to predict individual doses, or to determine adverse outcomes or treatment outcomes.

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- Use of radiation mitigators to protect healthy tissue
- optimised procedures (trade-off between radiation versus treatment and diagnosis); optimised cardiology procedures
- selection of techniques resulting in lower doses (molecular therapies or theranostics)
-

What would be the relevance in terms of increased RP for medical applications after 10 years

- more emphasis on real personalised medicine, and development of regulations is expected

8.2.1. MELODI SRA and JRM priorities

8.2.2.1. Text from SRA

Research line Health Risk evaluation

- To determine the shape of the dose and dose-rate response relationships in humans for total cancer, and where possible specific cancer sites, based on key informative epidemiological studies, including medical and occupational cohorts as well as those accidentally exposed.
- To determine the risk for different cancer sites based on key cohorts (see above) in order to investigate differences in tissue sensitivity.
- To evaluate the dose-response for tumour types, ideally defined by molecular characterisation
- To investigate pre-stages of cancer in any available biological samples, e.g. tissue or saliva/blood and by imaging methods in study populations with well-characterised exposure to allow modelling of carcinogenesis, including adverse outcome pathway approaches.
- To identify and validate biomarkers of exposure and health effects related to cancer, both working from early exposure biomarkers through intermediate steps to disease, and from epidemiological studies to disease markers and back to exposure –the 'meet in the middle' approach.
- To determine the value of evaluating cancer risks through systems biological analyses and models of carcinogenesis based on mechanistic studies and epidemiological data, and integration of the two.

Research line Basic Mechanisms

- To determine the nature, roles and radiosensitivity of the various target cells for radiation carcinogenesis. The most important of these are generally taken to be stem and progenitor cell populations, which may have specific responses to radiation.
- To determine the contribution of DNA damage / mutational processes at low doses and dose-rates and with differing radiation quality. Further information on the specific genes affected at low doses in the development of specific cancers and quantitative aspects can contribute to refining risk extrapolation models and the identification of radiation exposure and cancer biomarkers.
- To determine the contribution of epigenetic modifications. 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, and also how epigenetic factors affect response to radiation.
- To determine the influence of cell micro-environment, non-targeted and systemic processes that may promote or restrict the growth of pre-malignant cells in tissue, and

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how radiation exposure affects the tissue environment to facilitate or retard the growth of (pre)-malignant cells. For example, the influences of low dose radiation exposure on inflammatory reactions and effects of radiation on of immune surveillance against cancer cells.

- To examine the extent to which any of the above are different at high dose / dose-rate by comparison with low dose / dose-rate
-

8.2.2.2. Text from JRM

Game Changers	Potential impact on the radiation protection system and/or practice
A2. Integration of epidemiological estimates of cancer risk with a more complete understanding of radiological disease pathogenesis to improve cancer risk assessment Priority with highest potential to advance understanding in the short term: defining processes contributing to cancer development after exposure; e.g. role of epigenetics, metabolic status, in single and multiple stressor at low doses and dose-rates Long term research topics: definition of target cell populations and cell interactions/microenvironmental effects	If a dose and dose-rate effectiveness factor is no longer needed, or requires alteration, this could lead to reconsideration of dose limits. Should a signature that unambiguously identifies radiation-induced cancers be identified, this would have impacts for compensation scheme criteria and programmes. Developing an understanding of all contributory mechanisms for radiation carcinogenesis at low dose/low dose rate, and the associated dose-response relationships, is essential for the development of risk projection models and predictive biologically based models Knowledge of the nature and size of target cell populations for radiation carcinogenesis is critical for further development of biologically based predictive modelling

8.3. Topic 2 – Information sources for identification of priorities for EURAMED rocc-n-roll SRA

8.2.1. Answers to the questionnaire

MELODI Ad hoc priority and comments

which field of medical application would benefit from this research?

- Radiobiology, medical radiation therapy,
  Radiobiology, medical therapy,
  Diagnostic and treatment regimen
- Radiotherapy and cardiology (effects on patients healthy tissues in general) -
-)+ cohorts of medical staff (incl cardiologists)
- Radiation-induced non-cancer effects in patients undergoing imaging procedures (CT, PET), nuclear medicine applications and radiotherapy
- CT scan especially in children
- Radiotherapy for pregnant women

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- This research is of great importance for addressing risks related to diagnostic and interventional radiology
- Radiation-induced non-cancer diseases in patients undergoing imaging procedures (CT, PET), radiotherapy and nuclear medicine applications (internal radiotherapy of new radio-pharamaceuticals, modern external radiotherapy (hadrontherapy, radiotherapy using nanosensitizers, IRM linac, Flash radiotherpy...)
- beta and alpha emitters for internal RT,
- Radiation-induced early and late sequel in patients and in experimental animal systems

what type of research would be needed?

b) epidemiology and mechanistic studies,
b) long term epidemiological studies and animal experiments
b) targeted exposure, sparing of healthy tissue, particle therapy effect on short and long term,
b) cardiovasculare and neurological effects c-
b) dose effect relationship for organ at risk (salivary gland, red marrow, heart, kidney)
b) biomarkers (genetic and epigenetic) for individual sensitivity
b) identification of biomarkers of individual sensitivity, response and morbidity
b)prospective data collection required for some oucomes such as QoL or anlayses of biomakers (relevant in long term 10 years or more -example cataract -relevant within 10 years)
b) biomarkers for cancer/non-cancer diseases detection, early exposure and long term follow up,
b) focus on the role of non-clonogenic radiation effects and potential bystander reactions
b) improve multiscale models based on track structure characterisation, new dose concepts and quantities
b) Healthy tissue effect, early and long term effect on cardiovascular, central nervous and immunological systems,
b) in vivo experiments to help evaluating the dose-response relationship for non-cancer effects and difference between different organs, as well as molecular investigations on radiobiological molecular mechanisms in the different organs employing multiomic approaches
b) Investigate mechanisms of prenatal radiation effects on brain development (microcephaly) and long-term cognitive function using new experimental models (e.g. brain organoids, transgenic mice) and methods (e.g. single-cell transcriptomics, epigenomics; localized irradiation in animal models; proton/hadron irradiation);
b) Uncertainities related to risk evaluation at low doses

(c) what are the expected outcomes?

(c) better control of side effects while maintaining treatment efficiency
c) Use of radiation mitigators to protect healthy tissue
c) relationship among dose and dose-rate and non-cancer effect risks in medical patients
c) the role of non-clonogenic effects and bystander reactions in the development of radiation-induced late sequel
c) less frequent usage of ionizing radiation related diagnostic procedures in sensitive patients

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c) functional and mechanistic studies on patients samples, animal models, cell line and/or organoids
c) to improve the use of ionizing radiation in medicine;
c) More reliable evaluation of risks related to low doses d&e) Optimised medical exposures in terms of radiation protection and safety.
c) Early and long term effects, adverse outcome pathways,
c) adverse outcome pathways, Individual dose assessment

(d) what would be the relevance in terms of increased radiation protection for medical applications within 10 years

d) improve quality of life of cancer survivors
d) to limit repeated CT scan on a sensitive population and to promote the use of alternative techniques
d) better radiation protection of patients
d)individualized treatment
d) A good feasibility; e) A good impact, intended as the possibility of the new scientific information to inform judgements in the radiation protection system in this time period. . Better information on mechanisms (can lead to protective strategies: countermeasures) and alternative irradiation strategies (e.g. proton). Might lead to improved RT treatment of pregnant women. There is no reason to believe that while 50% of cancer patients benefit from RT this would not be the case for pregnant women;
d) protection of patient, improve quality of life

(e) what would be the relevance in terms of increased radiation protection for medical applications after 10 years

e) application of biomarkers in RP
e) identification of biomarkers, better radioprotection

8.3.1. MELODI SRA and JRM priorities

8.3.2.1. Text from SRA

Research line Health Risk evaluation

- To determine the shape of the dose-rate and dose-response relationship, notably the presence or absence of threshold doses, in humans for non-cancer outcomes at low or moderate doses based on key informative epidemiological studies (molecular or otherwise, as appropriate). While increasing numbers of studies concern circulatory diseases, little work is available on cognitive impairment and neuropathies, and there is little current work on hereditary and transgenerational effects. Any such studies require careful and explicit definition of the disease outcomes being assessed.
- To identify, develop and validate biomarkers for exposure (especially for low doses and protracted/inhomogeneous exposures), early and late non-cancer effects. Relevant tissue banks are currently available. The development of such biomarkers should allow better estimation of the actual doses received and inform the evaluation of the dose-response relationship of non-cancer effects.

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- 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.
- To evaluate non-cancer risk through systems biological analyses and mathematical models combining and integrating mechanistic studies and the epidemiological data.

Research line Basic Mechanisms

- To develop animal and in vitro models of radiation-related non-cancer diseases (circulatory diseases, cataract, cognitive/neurological dysfunctions, hereditary/transgenerational effects and other non-cancer effects), including organoids (e.g. cerebral, retinal, and others) derived from human pluripotent stem cells in order to clarify the pathways involved and conduct appropriately powered induction studies. In particular early stages of disease should be explored to define adverse outcome pathways for radiation-induced non-cancer effects.
- To apply a full range of analytical methods including 'omics' technologies and consideration of the target cells and surrounding microenvironment. In this context emerging technological innovations including single cell 'omics' may help to identify differences in radiation sensitivity between relevant cells and tissues. The mechanistic knowledge gained is likely to be useful for the identification of relevant biomarkers, e.g. specific metabolic and pathological changes that are clearly radiation-induced, and the development of mechanistic models of disease development.
- To determine the contribution of radiation-related changes in the immune function and inflammatory processes in the pathogenesis of non-cancer effects at low doses and dose-rates.
- To determine if other pre-existing conditions, such as neuropathies, inflammatory conditions or metabolic and mitochondrial diseases for example, affect the incidence of radiation induced non-cancer outcomes.
-

8.3.2.2. Text from JRM

Game Changers	Potential impact on the radiation protection system and/or practice
A1. Define the risks of non-cancer diseases at low and intermediate dose levels (100 - 500 mGy and below). Priority with highest potential to advance understanding in the short term (5Y): circulatory effects at near-field / out-of-field therapeutic doses and dose-rates and following interventional radiology; Long-term research topics: cerebrovascular / neurocognitive, metabolic and immune diseases, at progressively lower doses	If present, these risks could lead to re-consideration of calculations of radiation detriment, dose limits and reference levels; there would also be a need to re-consider tissue weighting factors and potentially additional protection measures.

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8.3.3. MELODI workshop on the topic

A MELODI workshop entitled 'Non-cancer effects of ionizing radiation' was held in Sitges, Spain 10–12 April 2019, resulting in a special issue published in Environment International (Volume 89 issue X (2021). A synthesis and a MELODI view on the research needs for the future is presented in the editorial by M. Kreuzer and S. Bouffler. "Non-cancer effects of ionizing radiation – clinical implications, epidemiological and mechanistic evidence and research gaps" [2].

In this issue, four papers were published specifically dedicated to eye lens opacities/cataracts, circulatory and metabolic diseases, cognitive effects, and effects on the immune system.

The first paper, by Ainsbury et al. [3], focussing on lens opacities, highlights as a priority research to better understand the impact of dose and dose-rate and radiation quality, genetic background and sex, on radiation-induced lens opacities. Recommendations for future studies include in particular improvement of the quality of estimation and reconstruction of lens dose and of lens opacities assessment and to implement statistical methods dealing with dose-uncertainty in risk estimation. Integration of epidemiology and biology is indispensable for cataracts (similarly to cancer and circulatory diseases), allowing risk-predictive biomathematical modelling and the AOP approach.

The second paper, by Tapio et al. [4], focusses on the interrelation between circulatory and metabolic diseases, with metabolic disease as a major risk factor for circulatory diseases. Recommendations for future research include the continuation of the follow-up of large cohort studies (adults and paediatric cohorts) and identification of cohorts with good dosimetry and information on the lifestyle risk factor. Where possible more biological samples should be collected in order to better understand the radiation impact on the disease process. Studies to gain new insights on potential mechanisms and effects of modulating factors are needed for a better understanding and for the development of an AOP of circulatory diseases.

The third paper by Pasqual et al. [5], focusses on cognitive function and neurodevelopmental and neurodegenerative effects. Recommendations for future research include better characterization of the cognitive deficit across the human life span, because cognitive function changes with age, understanding of the effect modification by age-at-exposure, and identification of factors influencing individual susceptibility. For cognitive development, Pasqual et al. consider that cohorts of paediatric patients who undergo long-term follow up, in particular childhood cancer survivors, are an ideal population for study. The collection of biological samples in epidemiological studies evaluating cognitive defects could help to advance the understanding of the mechanisms behind such effects and to identify susceptible populations. However, before investigating biologically-based models, experimental studies are needed for a better understanding of the mechanisms.

The fourth paper by Lumniczky et al. [6], focusses on the immune system which changes could impact on multiple pathologies. The main recommendations by the authors are (1) that epidemiological cohort studies should link identified immune changes to changes in the incidence of specific chronic diseases and (2) that future studies should collect pre-exposure blood samples to distinguish the mechanisms of age-related degenerative disorders and cancer. Other research needs concern (3) a better understanding of the mechanisms underlying different immune response patterns with low/moderate and high doses and different radiation quality, and (4) the conduct of long-term follow-up animal studies taking into account the state-of-the-art in non-radiation fields of research.

The issue of potential hereditary effects of radiation on offspring and next generations is a recurrent major concern as stated in the article by Laurier et al. [1]). There is little evidence from epidemiological studies to suggest the evidence of heritable deleterious effects resulting

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from radiation exposure in humans. There is still a lack of knowledge about the fundamental mechanisms of potential radiation-induced genetic and multifactorial diseases that largely manifest later in life, and about the role of epigenetic process. Further research is needed in genetics, epigenetics, radiobiology, toxicology, and epidemiology, to better characterise and quantify potential heritable effects among humans. A workshop on this thematic is foreseen in spring 2022 and will be organized by ICRP in collaboration with MELODI and other platforms.

8.4. Topic 3 – Information sources for identification of priorities for EURAMED rocc-n-roll SRA

8.4.1. Answers to the questionnaire

Responses from the Ad Hoc Working group:

Which field of medical application would benefit from this research:
Radiotherapy, diagnostic and interventional radiology, imaging procedures (CT and PET), theranostic procedures

What type of research would be needed

- Molecular epidemiological research to identify prospective biomarkers such as biomolecules like RNA, proteins and metabolites.
- Functional essays such as cognitive tests, medical imaging to support the molecular epidemiological research
- Biomarker types: of exposure, individual sensitivity, response, morbidity;
- Large studies to correlate clinical and biological parameters with toxicity grades
- Extraction of biomarker features from imaging – including artificial intelligence techniques
- Mechanistic studies and verification of robustness of biomarkers for low LET in case of inhomogeneous / different radiation quality.

What is the expected outcome?

- Better knowledge of individual radiosensitivity / susceptibility through better mechanistic understanding and epidemiology
- Optimised use of ionising radiation in medical applications allowing individualised medicine, minimising radiation applications for radiosensitive / susceptible individuals

What would be the relevance in terms of increased radiation protection for medical applications within 10 years

- Individual variation in risk is an important crosscutting issue for cancer and non-cancer late effects and for early effects.
- Identification of high-risk patients
- Improved risk models
- Better trade-off between benefits of treatment and drawbacks
- Optimised protection of patients
- Application of biomarkers in radiation protection

What would be the relevance in terms of increased RP for medical applications after 10 years

- Towards truly personalised medicine
- Optimised medical exposures in terms of RP and safety

(a) which field of medical application would benefit from this research?
a) Radiation-induced cancer in patients undergoing imaging procedures (CT, PET) and nuclear medicine applications
a) secondary effects of radiotherapy (external and internal)

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a) Radiation-induced non-cancer effects in patients undergoing imaging procedures (CT, PET), nuclear medicine applications and radiotherapy
a) Radiobiology, medical therapy,
a)Radiobiology, dosimetry, medical radiotherapy
a) Radiotherapy (side effects to healthy tissue
a) Radiation therapy for cancer treatment,
a) This research is of great importance for addressing risks related to diagnostic and interventional radiology
a)Mammography (further improve identification of sensitive patients in the context of screening for personalised care) - relevant within 10 years
a) Radiation-induced non-cancer diseases in patients undergoing imaging procedures (CT, PET), radiotherapy and nuclear medicine applications
a) Medical Imaging with external or internal radiation; radiation therapy
a). Radiation therapy for cancer treatment/ space exploration
a) Radiation-induced early and late sequel in patients and in experimental animal systems
a) all fields where medical radiation techniques are performed
a) Diagnostic and Theranostic Medical Imaging
a) Radiation Therapy & Nuclear Medicine;

a)Radiobiology, medical radiation therapy, biomarkers for cancer/non-cancer diseases detection, early exposure and long term follow up,

(b) what type of research would be needed?
b) identification of biomarker of individual sensitivity, response and morbidity
b) Identification of biomarkers of exposure
b) improve multiscale models, update of dose concepts and quantities, production of biological data for mechanistic models validation
b) biomarkers (genetic and epigenetic) for individual sensitivity
b) long term epidemiological studies and animal experiments
b)Diagnostic and treatment regimen, epidemiology
b) molecular epidemiological research to identify prospective biomarkers. These could include biomolecules like RNA, protein, metabolites; functional assays like cognitive tests; medical imaging. Would require large patient cohorts
b) Large studies to correlate clinical and biological parameters with toxicity grades,
b) Detailed evaluation and development of effective and robust extraction of biomarkers features from medical images from different vendors (generalization), also in combined modalities; exploitation and advancing of modern Artificial Intelligence based techniques for image processing and feature extraction; development of dedicated instrumentation for medical imaging with higher sensitivity and higher specificity, also able to be integrated/operated in multimodality devices.
b) In vitro studies on relevant human cells and tissues (3D cultures) and in vivo in patient samples such as blood
b) focus on the role of non-clonogenic radiation effects and potential bystander reactions
b) basic cytogenetic research on populations both occupationally exposed and patients relating doses and cancer risks
(b) Development of effective and robust extraction of biomarkers features from medical images from different vendors and acquisition modalities (also combining modalities); exploitation and advancing of modern Artificial Intelligence based techniques for image processing and feature extraction; development of dedicated instrumentation for medical imaging with higher sensitivity and higher specificity, able to be integrated/operated in multimodality devices.
b) to verify robustness of biomarkers identified for low LET homogenous exposure in case of inhomogeneous exposure/different radiation quality; perspective epidemiological studies;

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(c) what are the expected outcomes?

c) less frequent usage of ionizing radiation related diagnostic procedures in sensitive patients
c) improve knowledge on early radioinduced effects
c) Early and long term effects, adverse outcome pathways, d)individualized treatment
c) relationship among dose and dose-rate and non-cancereffect risks in medical patients
c) mechanistic studies, adverse outcome pathways, Individual dose assessment
c) Identification of prospective biomarkers of sensitivity and side effects;
c) Improvedand personnalised treatments,
c) Use of research results for the optimisation of individualised medical exposures
c) improved identification of biomarkers which are more sensible to risk variation at patient level;
c). Improved understanding of mechanisms of individual responses and risks to radiation exposure in terms of toxicity (side=effects) and long term risks such as radiotherapy induced second cancers
c) the role of non-clonogenic effects and bystander reactions in the development of radiation-induced late sequel
c) scientific papers, guidelines, recommendations
c) earlier identification of radiation induced “health” anomalies; improved identification of biomarkers with sensitivity at the personal level;
c) use of appropriate biomarkers for different radiation treatments; (d) improvement in the selection of patients to be addressed to the different types of treatment; (e) personalized treatments.

(d) what would be the relevance in terms of increased radiation protection for medical applications within 10 years

d) improved risk models
d) better radiation protection of patients
d)individualized treatment
d) Difficult to say. Benefits of RT should normally outweigh drawbacks;
d) Decrease of radiation induced side effects (toxicity and long term adverse effects such as therapy related second cancers
d&e) Optimised medical exposures in terms of radiation protection and safety.
d) better trade-off between lower radiation and improved diagnosis and therapy;
d). Identification of individuals/patients sat risk
d) application of biomarkers in RP
d) possibility of identification of high-risk populations e) legislative regulation of procedures
d) better trade-off between lower radiation and improved diagnosis and treatment.

From my opinion these two priorities overlapped and are of major importance for the next years. This question is still unsolved, and no robust biomarkers of radionsensitibity/radiosusceptibility are clearly determined.

(e) what would be the relevance in terms of increased radiation protection for medical applications after 10 years

e) identification of biomarkers, better radioprotection
e) toward truly personalized therapy; e.g. treatment plan based on personalized dose delivery response in radiation therapy
e). Identify those at risks and provide personnalised treatments with radiation free options or specific treatment plans with lower total doses, more targeted approahes and normal tissue sparing.
e) application of biomarkers in RP
d&e) Optimised medical exposures in terms of radiation protection and safety.

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e) toward truly personalized therapy

8.4.1. MELODI SRA and JRM priorities

8.4.2.1. Text from SRA

Research line: Health risk evaluation

- To identify and validate candidate biomarkers of individual sensitivity identified from mechanistic or clinical studies in cohorts of exposed and non-exposed subjects who have developed cancers or non-cancer diseases. As few suitable large cohorts with biological samples are currently available, proof-of principle studies with higher dose exposed cohorts should be conducted to refine methodologies and to extrapolate to low doses.
- To improve or set-up molecular epidemiological cohorts or case-control studies to determine factors (host and environmental) that modify individual risk of radiation-induced cancer and non-cancer effects and quantify their effects.
- To quantify the variation in risk between different population groups and the impact of different factors, for example, age at exposure, and attained age, as well as co-exposures and host factors, including anatomical and physiological differences. Knowledge of the nature of possible interactions between ionizing radiation and these factors on health risk (e.g. multiplicative, additive) is important in considering risk transfer between different populations.
- To develop mechanistic or other mathematical models of radiation-induced disease pathogenesis that can account for individual risk factors.

Research line: Basic mechanisms

- To develop an understanding of the cellular, organ and systemic responses determining individual susceptibility to radiation-induced health effects including, for example, inflammatory processes and immunological states) so that differences between individuals in the response pathways can be predicted, and biomarkers be identified.
- To investigate mechanisms by which age at exposure, attained age, sex, lifestyle and other factors, including co-exposures to other agents and diseases affecting dose from a given exposure may modulate radiation risk.
- To investigate the impact of anatomical and physiological differences between individuals on radiation dose and dose distributions.
- To start to explore modelling methods to predict differences in outcome at both individual (qualitative changes affecting health-relevant pathways) and population (quantitative changes in health outcomes) levels.

8.4.2.2. Text from JRM

The individual variation of risk has been identified as a joint priority in the joint roadmap. In the joint roadmap it is suggested to identify predictive factors as a priority feasible on the short-term. In the field of medical irradiations this could potentially allow a more individualised cancer treatment.

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Game Changers	Potential impact on the radiation protection system and/or practice
A3. For deterministic and stochastic cancer and non-cancer outcomes: **Characterisation and quantification of variation in response and risk between population sub-groups/individuals due to genetic factors, sex, co-morbidities, dedicated exposure of disease areas in patients, environmental and lifestyle factors and the interactions between these depending on dose levels.** Priority with highest potential to make progress in understanding in the short term: Evaluation of potential predictive factors and correlating them with health outcomes. To improve the understanding in the difference of the dose response curve shape between males and females, as observed in the LSS cohort Longer term research topics: Integrative radiobiologically oriented systems biology, setup of	If a robust (specific, sensitive) predictive metabolic status and biomarkers or radiomic markers for radiosensitivity (tissue reactions) were found, this would allow more individualised cancer treatment. Knowledge on the range of variation in susceptibility to stochastic effects in populations would be informative for public health and development of the system of radiation protection. A better understanding of the mechanisms involved in long term effects of ionising radiation may be integrated with mechanisms resulting from exposure to other stressors or from combined exposures. On the longer term, an integrative protective system could be established to cover realistic multi-exposure scenarios. A confirmation of the difference between sexes in the shape of the dose response (males: linear-quadratic and females: linear) may lead to changes in levels of exposure limits.
adverse outcome pathways related to ionising radiation and in combination with other stressors including diseases. Seeking biomarkers of individual risk through cellular/molecular and systems biological approaches as well as radiomics investigations	Moreover, a better understanding and validation of the impact of life-style factors on the risk of stochastic and tissue effects could contribute the reduced risk by modifying life style. The dedicated response of diseased organs are of primary interest in taking care of patients since in diagnostic as well as therapeutic procedures mainly diseased organs will be exposed.

8.4.3. MELODI workshop on the topic

A MELODI workshop entitled 'Individual Radiosensitivity and Radiosusceptibility which took place in 2019, resulting in a special issue published in the International Journal of Radiation Biology (Volume 96 issue 3 2020). A synthesis and a MELODI view on the research needs for the future is presented in the editorial by Salomaa S, Jung T. "Roadmap for research on individual radiosensitivity and radiosusceptibility – the MELODI view on research needs" [7]

In this special issue the term radiation sensitivity / radiosensitivity is used for individuals who are at higher risk for early or late reactions in normal tissue after radiation and the term radiation susceptibility / radiosusceptibility is used for individuals who exhibit higher cancer risk after radiation than the general population.

The first paper in this issue is entitled "Clinical and epidemiological observations on individual radiation sensitivity and susceptibility" by Seibold *et al*. [8]. This paper concludes with the following recommendations: " *(a) there is need for large (prospective) cohort studies; (b) build upon existing radiation research cohorts; (c) use data from well-defined cohorts with good exposure assessment and biological material already collected; (d) focus on study quality with standardized data collection and reporting; (e) improve statistical analysis; (f) cooperation*

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between radiobiology and epidemiology; and (g) take consequences of radiosensitivity and radiosusceptibility into account."

The paper stresses also the need for good screening assays. In the medical context, this is important as the first question prior to treatment of patients is how to identify those that might be sensitive to radiation. Also, for exposure of workers and the public identification of radiosensitive and radio-susceptible individuals might be useful. The existing assays for individual radiosensitivity / susceptibility are reviewed in the special issue by Gomolka *et al*. [9] providing the requirements for assays and an overview of reliable and robust screening. The paper recommends the *setup of common retrospective and prospective cohorts/biobanks to validate current and future tests*.

The special issue paper of Averbeck *et al*. "Establishing mechanisms affecting the individual response to ionising radiation" [10] describe mechanisms related to individual radiosensitivity and susceptibility: Next to DNA damage response there are other mechanisms influencing radiosensitivity and radiosusceptibility, which in turn may be different in different humans depending on sex, genetic variance, co-exposure to other stressors. Concerning medical applications, co-exposure may be interpreted as co-exposure to other than radiation treatments, mixed chemical and radiation toxicity. The medical history of patients may also alter the individual sensitivity / susceptibility.

Radiotherapy of individuals under the same radiation setting may result in different dose patterns by differences in morphology, physiology (e.g., breathing rate), metabolisms, diseases impacting functions of organisms and tissues, nutrients deficiencies, internal contaminations, and lifestyle. Therefore, radiosusceptibility can be considered as a function of the exposure and not only of the dose and dose-rate, and should then also *take into account dose inhomogeneity , fractionation, radiation quality and internal versus external exposures* (MELODI Topic 4 in this deliverable).

Averbeck et al. recommend a *prospective study to assess radiosensitivity following radiotherapy as the most tractable group of patients suffering enhanced radiosensitivity.* It is proposed to analyse the inflammatory, stress and immune responses as well as mitochondrial function and lifestyle factors.

Identification of individual susceptibility / sensitivity raises complex ethical questions. "Ethical considerations related to radiosensitivity and radiosusceptibility" by Kalman *et al* [11] demonstrate the complexity of the use of the knowledge of individuals' susceptibility / sensitivity in clinical practice and in radiation protection. may have large consequences in the social and psychological sphere.

8.5. Topic 4 – Information sources for identification of priorities for EURAMED rocc-n-roll SRA

8.5.1. Answers to the questionnaire

(a) which field of medical application would benefit from this research?

a) Radiotherapy (side effects to healthy tissue, external and internal) (8);
a)Dosimetry, Radiobiology,
a) radon therapy
a) I consider inhomogenous dose distribution as a risk factor only in the case of radiation therapy where homogenous dose distribution is important in tumour cure. It is not important

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for low dose research. In the case of radiation quality and internal emitters see my answers above.

Radiation therapy not only including external radiation but also considering nuclear medicine would gain from the study of inhomogeneous dose distribution.

(b) what type of research would be needed?

b). molecular epidemiological research to identify prospective biomarkers. These could include biomolecules like RNA, protein, metabolites; functional assays like cognitive tests; medical imaging. Would require large patient cohorts;
b) studies to verify the robustness of biomarkers identified for low LET homogenous exposure in case of inhomogeneous exposure/different radiation quality;
b) epidemiology considering dosimetry and microdosimetry ,
in vitro experiments with organotypic tissue models, in vivo experiments, quantitative mechanistic risk models (adverse outcome pathways)
b) Tissue and cell type related sensitivity,
b) improve multiscale models, update of dose concepts and quantities, production of biological data for mechanistic models validation
b)experimantal data to help to understand the health effects of inhomogeneous dose distributions, including out-of-target effects, and radiation quality, and related investigations on radiobiological molecular mechanisms employing multiomic approaches;
b) In vitro and in vivo systematic studies on healthy tissue damage from: Hadrontherapy, FLASH therapy (electrons, protons, …) and molecular radiotherapy;

In terms of tools: mutliomic approaches, mechanistic models, quantitative risk models (AOP), organotypic tissues models. Molecular epidemiology of exposed population to different treatments should allow to validate biomarkers developed after low LET radiation exposures.

Dosimetry and microdosimetry are of high importance

(c) what are the expected outcomes?

c). Identification of prospective biomarkers of sensitivity and side effects;
c) identification of appropriate biomarkers for different radiation treatments;
c) improve knowledge on early radio-induced effects
c) indicators or biomarker of tissue and cell sensitivity,
c) to improve the use of ionizing radiation in radiation oncology;
c) better knowledge of the mechanisms underlying the healthy tissue response after different irradiation modalities;
c) therapeutic and diagnostic procedures can be optimized to get the higher benefit with lower risks for patients (and in some cases the society)

From mechanistic knowledge to the improvement of treatments. Identification of Biomarkers able to predict side effects and sensitive patients.

(d) what would be the relevance in terms of increased radiation protection for medical applications within 10 years

d). Difficult to say. Benefits of RT should normally outweigh drawbacks; e. See d.
d) improved protection of patients and limit side effects
d) improved risk models

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d) improvement in the selection of patients to be addressed to the different types of treatment
d) A good feasibility in 10 years;;
d) morbidity reduction -> optimization of the treatment protocols;
d) reduction of risk in case of some applications (I assume that a lot of progress could be made in nuclear medicine)

Personalised radiation therapy

(e) what would be the relevance in terms of increased radiation protection for medical applications after 10 years

e) personalized treatments
e) A good impact, intended as the probability that the new scientific information to inform judgements in the medical radiation protection after 10 years.
e) personalized treatments.
e) same as (d) but only achievable after 10 years" same as (d) but for more applications :-)

8.5.2. MELODI SRA and JRM priorities

8.5.2.1. Text from SRA

Research line: Health risk evaluation

- To determine cancer and non-cancer risk related acute and chronic internal emitter exposures in epidemiological studies, incorporating detailed dosimetric assessment and evaluation of dosimetric uncertainties and, where appropriate, microdosimetric considerations. Where feasible and informative, these studies should include collection of appropriate biological samples and analysis of biomarkers of dose.
- To determine the Relative Biological Effectiveness (RBE) for selected endpoints in epidemiological studies for specific cancer sites through comparison of risk related to low-and high-LET radiation exposure.
- To better determine the risk (as well as possible countermeasures) associated with protracted exposure to the space radiation environment, in view of future interplanetary missions, both for cancer and non-cancer diseases (e.g. targeting possible impairments of cognitive and cardiovascular functions).
- To develop and apply more detailed biokinetic and dosimetry models in order to better characterize dose distributions

Research line: Basic mechanisms

- To conduct experimental studies in vitro and in vivo to test exposure scenarios where dose/fluence modulation plays a role, e.g. localized versus uniform exposures, acute versus protracted exposures, to inform specific biomarker development and risk quantification.
- To further develop suitable tissue and in vivo models for the quantification of the impact of dose inhomogeneity and radiation quality.
- When addressing the effects of internal contamination, specifically consider the role of chemical speciation in determining spatial distribution (at all scales) and biokinetics of radionuclides.

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- For all adopted experimental models, to develop in parallel modelling approaches able to tackle and quantify inhomogeneity at all scales: nano- (radiation track structure) and microdosimetric, dosimetric and biokinetic models at different levels of biological organisation.
- To study mechanisms elicited by inhomogeneous dose deposition, integrating "dynamic" dose assessment and identification of relevant pathways (both for cancer and non-cancer diseases) in a systems biology approach, in order to characterize the response of the complex system as a whole.
- To develop innovative ways in experimental studies to determine the Relative Biological Effectiveness (RBE) at low doses to determine/compare the effects of to low- versus high-LET exposure. To characterize how internal exposure, dose inhomogeneity and radiation quality will affect the nature of candidate biomarkers so-far identified in response to low LET external exposure.
- To develop experimental and modelling strategies to characterize the effects of exposures to mixed fields.
- Build on knowledge acquired from basic mechanisms to identify relevant pathways for the quantification of the risk for cancer and non-cancer diseases, also using an adverse outcome pathway approach, determining those operating in case of inhomogeneous exposures

8.5.2.1. Text from JRM

Health risk related to various doses inhomogeneities and dose rates has been identified as a joint priority in the joint roadmap. In the joint roadmap it is suggested to improve the understanding of the effects of intra-organ dose distribution through observations in patients exposed to inhomogeneous dose distributions on the short-term. In the field of medical irradiations this could potentially allow a more individualised approach.

Game Changers	Potential impact on the radiation protection system and/or practice
A4. For stochastic cancer and non-cancer outcomes: **Define how the temporal and spatial variations in dose delivery affect the risk of health effects following radiation exposure.** Priority with the highest potential to make progress in understanding in the short term: Addressing the difference between risks from acute and chronic exposures through the integration of experimental and epidemiological data applying biologically-based risk models To improve the understanding of the effects of intra-organ dose distribution through observations in patients exposed to inhomogeneous dose distributions and experiments with organotypic tissue models. Longer-term research topics: Addressing the difference between risks from internal and external exposures through the integration of new knowledge on the effects of chronic exposures, intra-organ dose distribution and radiation quality considering energy deposition at different scales (from intra cellular to organs).	A strengthened evidence base may impact on judgements on dose rate effectiveness factors and radiation weighting factors (potentially including those for non-cancer outcomes) as well as in the introduction of new weighting factors accounting for the effects of modulation of intra-organ dose distribution. Changes in these factors would lead to reconsideration of dose limits, reference levels, conversion coefficients and dose coefficients for intakes of radionuclides.

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8.6. Text from MELODI SRA for E&T

Support for students and young scientists

1. Students need to be able to find places at universities, placement with research groups for project/dissertation work and build their own research network. These require that the places and,sufficient incentives to attract top students and economical support for networking through for example joining congresses, scientific visits etc must be available. 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.
2. 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

3. It should be explicitly in the wording for RTD calls that proposals will be judged favourably if a plan is included that explains how E&T will be integrated into the overall research programme, providing workshops or training courses dedicated to the presentation of new science/technology which is being used or developed in the project.
4. 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

5. Continuation and extension of the MELODI Education and Training Forum in order to bring together all platforms and other 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, EURAMED etc.) in order to share mutual experience and resources.

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6. 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.

8.7. Text from MELODI SRA for Infrastructures

Priority areas are:

1. Improvement of the access to infrastructures
2. Favour open access to radiation research data within STORE
3. Re-use of archived materials and existing epidemiological studies using specific retrospective approaches
4. Enlargement and sustainability of RENEB including inter-comparison exercises
5. Improvement of the awareness of existing infrastructure via E&T courses

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