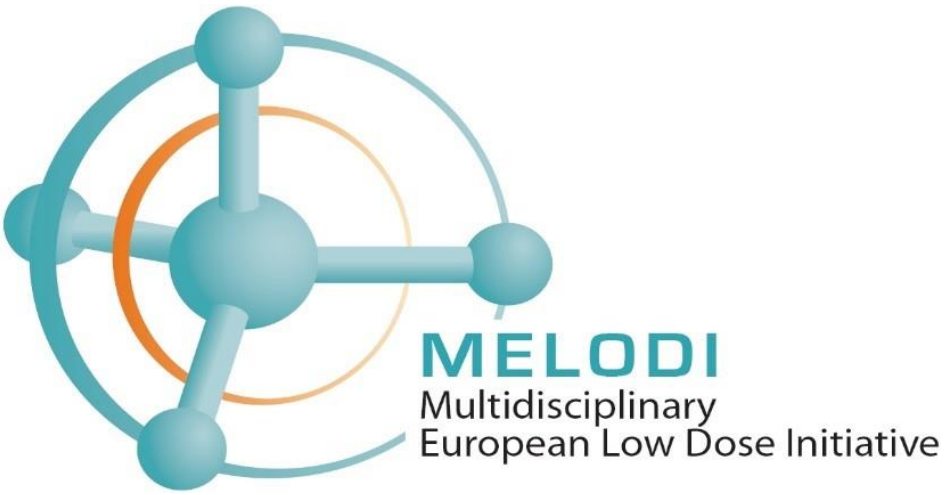

Strategic Research Agenda of the Multidisciplinary European Low Dose Initiative (MELODI) – 2022

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1. Executive Summary

The Multidisciplinary European Low Dose Initiative (MELODI) is a European Platform dedicated to low dose ionizing radiation risk research. The challenge is to improve the quantification of risks and reduce the uncertainties in the risk estimates, as well as to develop and validate risk models that best characterise health effects at low doses, drawing on both epidemiological and radiobiological understanding. In 2010, MELODI was founded as a registered association with 15 members; membership has now increased to 41 institutions.

A major activity of MELODI is the establishment and periodic revision of a long-term Strategic Research Agenda (SRA) for research on low dose risk for radiation protection (RP) in Europe. MELODI considers low doses to be those where there remains substantial uncertainty on the magnitude of health risk. The SRA is intended to guide the priorities for national and European research programmes and the preparation of competitive calls at the European level in order to fill research gaps and test the hypotheses on which the current RP system is based. The ultimate goal is to provide an improved evidence-based protection of the population. A key priority for radiation protection research is to improve and reduce the uncertainties associated with health risk estimates for exposures at low doses and dose rates that are relevant for the dose limits for occupational exposures, reference levels for the exposure of the population in emergency situations, diagnostic reference levels for medical exposures, damage to normal tissues during radiotherapy, reference levels for radon exposures in buildings and occupational compensation scheme claims, amongst others. The approaches have to be multidisciplinary and innovative to provide the best opportunities for advancing the understanding of low dose and low lose-rate effects. Incorporation of expertise outside of the conventional fields of radiation research is essential to widen the prospects for broadening approaches and adopting novel methods in health research in the assessment of health risk relevant to radiation protection. MELODI is also concerned to ensure the availability of key infrastructures as an essential basis for research activities, and to maintain competences in radiation protection research and health risk assessment in the long term via an integrated European approach for training and education. For these purposes, in February 2014, MELODI established three working groups (WGs), one on the MELODI SRA, one on Infrastructures and a third on Education and Training.

The SRA is periodically updated by the MELODI SRA Working Group (WG), systematically taking into account results of recent research and emerging radiation protection research issues. Open consultations via website and the annual MELODI workshops are regularly conducted, the results of which are taken into account in the revised SRA. Prior to calls from the European Commission (EC) or EC-funded projects in radiation protection, in addition to the SRA, a short MELODI statement presenting the top priorities is developed by the MELODI WG SRA and an open consultation process initiated.

In recent years, large parts of radiation protection research in Europe have been organized within a European Joint Programme (EJP), CONCERT. The aim of the EJP was to bring together relevant funding agencies from the EC and its Member States to integrate European research and to administer calls for research proposals in radiation protection on behalf of the EC. This activity is built upon and aimed to promote integration of the SRAs from six European radiation protection research platforms and aims to establish interaction and synergies between the different areas of expertise: MELODI (low dose and dose-rate risk research), ALLIANCE (Radioecology), NERIS (Emergency management), EURADOS (Dosimetry issues), EURAMED (Medical associations), and SHARE (social sciences/humanities). Research findings arising from projects funded by the

CONCERT calls have, along with other developments, contributed to updating the SRA. CONCERT ended in May 2020, and was not directly followed by a similar project. However, in June 2022 the PIANOFORTE European Partnership started under the EURATOM Horizon Europe scheme, and at the kick-off meeting it was suggested that this project is expected to open a call for research proposals in March 2023. Broadly, the topics anticipated will be in the areas of medical exposures and risks, low dose risk more generally and inter-individual variation in response as well as radiation emergency preparedness and response; clearly three of these areas are of direct interest to MELODI and its membership.

The activities of MELODI can be seen to be complementary to other co-ordination activities elsewhere such as the IDEA initiative in the USA, the Japanese PLANET initiative and the OECD's Nuclear Energy Agency Committee on Radiation Protection and Public Health (https://www.oecd-nea.org/rp/crpph.html) which established a High Level Group on low dose research (HLG-LDR) to co-ordinate efforts on a global scale, with emphasis on radiation and chemical Adverse Outcome Pathway (AOP) development, communication strategies on low dose risk research, and the development of a low dose research projects register/database. Most recently, in June 2022, the US National Academies of Sciences, Engineering and Medicine published a report aimed at rejuvenating low dose risk research in the USA (published here). If this programme is initiated, it will represent a major new initiative in low dose risk research.

The current 11th MELODI SRA for the year 2022 describes two research topics and two cross cutting topics (which are relevant for both of the research topics) in low dose or low dose-rate radiation risk research. The topics relate to the diseases of concern, (1) cancers and (2) non-cancer diseases. The cross-cutting topics that are relevant to both of these disease categories are (3) individual variation in risk and (4) effects of spatial- and temporal-variation in dose delivery on disease risk. Each of these is considered in detail in the SRA.

The research required to improve the evidence base for each of the four topics may be grouped into two categories:

1) Research to improve understanding of the mechanisms contributing to radiogenic diseases following low dose and dose-rate exposures
2) Epidemiological research that integrates, where possible and informative, biological and molecular markers to improve health risk evaluation of radiation exposure

The current and former versions of the MELODI SRAs and statements can be downloaded from the following website: www.melodi-online.eu. The current SRA structure is outlined in **Figure 1**.

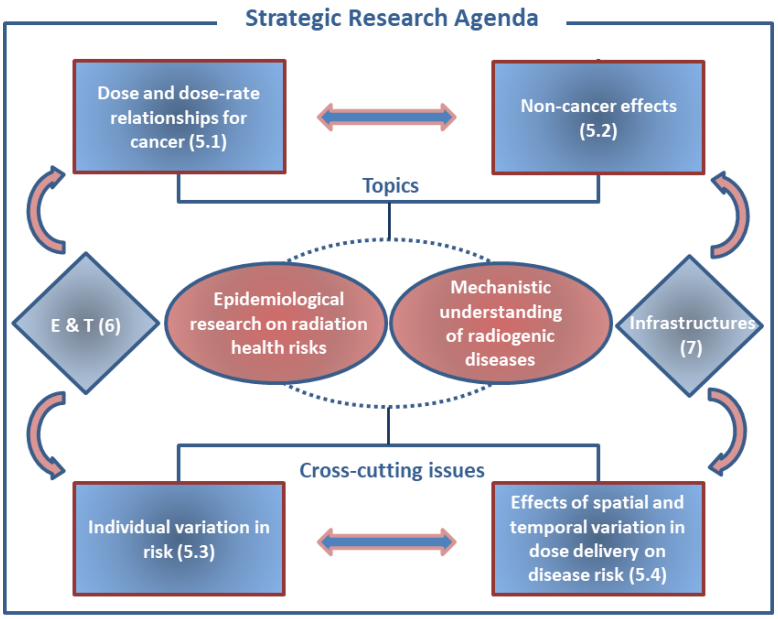

Figure 1: Outline of the structure of the Strategic Research Agenda (SRA), numbers in parentheses refer to the SRA section dealing with each topic/issue.

2. Importance of low dose radiation health risk research

Exposure to ionizing radiation is unavoidable. Everybody encounters exposure from a range of natural and artificial sources. Medical and natural sources are the largest components of the average dose received by the general public. Exposures to artificial or natural sources can vary between individuals depending on their occupation (e.g. employment in the nuclear industry, in air transport and in medicine, particularly interventional radiologists), medical exposures (diagnostic and therapeutic procedures) and in some cases due to environmental contamination. Exposure from naturally occurring radiation involves background from terrestrial and cosmic sources, and internal exposure from radioisotopes such as radon and uranium (there is notable geographic variation in radon exposure). There are many and varied uses of radiation in modern society. Nuclear power generation is viewed as a carbon neutral and efficient energy source; industrial radiography plays important roles in safety assessment; medical uses of radiation for diagnostics and therapy are extensive and rapidly increasing. Long distance air travel can lead to exposures, typically 0.08 mSv for a transatlantic flight though altitude, duration and other parameters, including latitude can affect the actual exposure level. Other sources are exposures to 'NORM' (Naturally occurring radioactive materials) in the oil extraction and other industries. Broadening access to space travel is anticipated, with both longer exploratory missions likely as well as commercial space travel that has recently commenced.

Not only is exposure to ionizing radiation unavoidable and variable in the population, but it is known to damage health at certain exposure levels. At very high doses radiation exposure can be lethal, while tissue damage can occur following more localized high dose exposures. Whole body exposures at these levels are very rare, but for localised exposures, severe tissue damage can be observed in some patients following radiotherapy for cancer.

Evidence accumulated over many decades demonstrates that radiation can cause cancer in humans following acute exposure in the dose range of a few Gy down to 100 mGy or less, with children often showing higher sensitivity. There are indications that these more moderate exposures may also be associated with other conditions such as circulatory diseases, cataracts, cognitive impairment, immunological effects – collectively described as 'non-cancer diseases' and possibly effects on future generations (hereditary or transgenerational effects). The risks to humans in terms of cancer are established down to around 100 mGy in adults, for circulatory diseases and lens opacities down to about 500 mGy and about 200 mGy for defects on brain development and cognition after prenatal exposure during neurogenesis. The risks to human health below these levels, especially following protracted or other non-homogenous exposures are less certain. Currently, the system of radiation protection aims to avoid tissue injury and minimize the risk of cancer and the possibility of hereditary disease. For radiation protection purposes, risks of cancer and possible hereditary effects below 100 mGy are regulated on the basis of an assumed linear non-threshold (LNT) relationship between dose and incidence. However, there remains uncertainty about the exact dose-response relationship for such low-dose exposures, and the impact of protracting exposures over long periods such as during a working lifetime, and vulnerabilities of specific groups that may be at higher risk.

Striking the appropriate and acceptable balance between the benefits accrued from activities involving exposure to radiation on the one hand and the health risks posed on the other is important. The regulation for protection of individuals and populations comes at a financial cost – there are, therefore, disadvantages to both under- and over-protection. This applies in all

situations – existing elevated exposure situations such as high radon areas, occupational settings such as the nuclear industry and the medical sector, and accidental situations where difficult decisions on the implementation of protective actions such as sheltering and evacuation are required. In all these contexts, it is critical to utilise robust and accurate information on the magnitude of health risks posed by given radiation doses, ranging from high to low.

The main uncertainties in radiation health risk evaluation are in the magnitude of cancer risk at low and protracted doses below 100 mGy, the magnitude of non-cancer effects below 500 mGy, the variation in individual risk within the population, and the variation in risk with dose distribution in space and time. These are therefore the key areas requiring further exploration to provide better and more reliable evidence for appropriate decision making in all areas of radiation protection. Accurate and reliable low dose human health risk estimation is an essential foundation for a robust and acceptable system of radiation protection.

2.1 *Dose and dose rate ranges to be considered*

For the purposes of this document, MELODI considers low doses to be those where there remains substantial uncertainty on the magnitude of health risk. For low LET radiations these are taken to be those of 100 mGy and below when considering cancer risks, and 500 mGy and below when considering non-cancer diseases as recognised by international organisations such as the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) and the International Commission on Radiological Protection (ICRP). In the context of cancer risk, moderate doses are those between 100 mGy and 2 Gy, with high doses being those above 2 Gy. For non-cancer diseases, MELODI considers moderate doses as those between 500 mGy and 5 Gy, and high doses those above 5 Gy. Low dose-rates are those of 0.1 mGy min^{-1} or less for low LET radiation, or one-track traversal per cell per hour for high LET radiations. These definitions apply both for organ and whole-body doses. These dose ranges are similar to many of those of interest in the medical community as set out in EURAMED documents such as the evolving research agenda under development in the EURAMED Rocc-N-Roll project (see here) and https://roccnroll.euramed.eu). Note that units of Sievert (effective dose, a radiation quality and tissue sensitivity weighted quantity) are frequently used for quantification of cancer risk. Effective dose, as defined by ICRP, relates specifically to cancer and hereditary effects, it is therefore not appropriate to use for non-cancer outcomes. Sieverts are also not directly quantifiable and so the absorbed dose units of Gray are generally used in this document; furthermore, these are the units used for dose quantification in experimental and epidemiological investigations.

3. MELODI

The purpose of the MELODI Association, as given in its Statutes, is to constitute a European Research Platform in the field of low dose ionizing radiation health risk assessment and its application for radiation protection and to coordinate and promote research and long-term competence on effects and risks to human health associated with low-dose and low-dose rate exposures to ionizing radiation.
MELODI currently has 41 institutional members including national bodies responsible for defining, funding and implementing research on low dose risk, as well as universities and research institutes committed to contribute to R&D efforts. It is a research association that contributes to the definition of priority objectives in low dose risk research, fostering of research programmes and

initiatives to achieve these objectives, assessment of results obtained, and promotion of communication on these issues between the various parties involved as well as sustainability of key research capacity, competencies and infrastructure. These functions are performed by organizing scientific and stakeholder workshops, promoting the visibility of the research area, establishing working groups on specific topics and facilitating collaborative research.

To achieve these goals, the establishment and regular updating of a long term (>20 years) SRA for research to improve protection from low dose health risks in Europe remains a major activity of MELODI. It provides guidance on the priorities for national and European research programmes and the preparation of competitive calls at the European level. Furthermore, MELODI supports the availability and maintenance of key infrastructures as an essential basis for research activities, and the retention and development of competences in radiation research and health risk assessment in the long term via an integrated European approach for training and education. As the primary aim of the MELODI SRAs is to provide Euratom, national authorities and funding agencies with scientific research agendas to guide the preparation of calls and areas for prioritization, the significance of this work should periodically be evaluated for its impact on the content of calls and research prioritizations, and advances made through funded projects. Ultimately, the research guided by the SRA is anticipated to make an impact on radiation protection policy.

Following the recommendations and roadmap established by the High Level and Expert Group on European Low Dose Risk Research (HLEG) in 2009 (full report here; for a summary see Repussard, 2018)), and supported over time by DoReMi, OPERRA and CONCERT, the latter moving to integrate SRAs covering all aspects of radiation protection research in Europe, the radiation protection research community within Europe has been progressively more deeply integrated over the past decade.

MELODI participates in the body representing all radiation protection platforms, MEENAS; this body serves to coordinate the entire range of radiation protection research areas in Europe. An important recent development has been the publication of a joint-Platforms roadmap for radiation protection research, available here.

In October 2010, the first draft of a MELODI SRA was published on the MELODI Website and opened for public consultation. The contents were based on the considerations and key priority issues formulated by the HLEG and DoReMi. In February 2014, the MELODI Board of Directors (BoD, now re-constituted as the MELODI Executive Committee) established three working groups (WG's), on the MELODI SRA, Education & Training and Infrastructures. The MELODI SRA is updated periodically by the SRA WG, taking into account recent and emerging research results and radiation protection research issues. The updated draft and a short MELODI statement (usually in years where an EC or EC-funded project call will be launched), presenting the top priorities, is posted on the public MELODI website, usually before the annual MELODI workshop - now European Radiation Protection Week (ERPW). An open consultation process is set-up via the website and the workshop to seek input from other scientists and stakeholders before the SRA´s and statement's revision. The updated SRA and MELODI statement are also sent to the independent Scientific Advisory Committee of MELODI for comment. The final SRA and MELODI statement are prepared for approval by the MELODI Executive Committee. The current edition of the SRA will be the eleventh version.

3.1 MELODI in the context of other radiation research platforms

Recently, large parts of European radiation protection research have been organized within the CONCERT European Joint Programme (EJP), and the recently started PIANOFORTE project will continue to develop this coordinated approach. The EJP and PIANOFORTE European Partnership has brought, and will continue to bring, together relevant funding agencies from the EC and Member States to integrate European research, and to administer calls for research proposals in radiation protection on behalf of the European Commission. This activity builds upon the Strategic Research Agendas from six European radiation protection research platforms, MELODI, ALLIANCE (radioecology), NERIS (emergency management), EURADOS (dosimetry issues), EURAMED (medical associations), and SHARE (social sciences and humanities), and aims to establish interactions and synergies between the different areas of expertise. Integration across the different platform areas is being fostered and developed through the drafting of a roadmap to guide all research related to radiation protection, and further integration can be anticipated in future years (available here). This roadmap is expected to be implemented as part of the PIANOFORTE project.

MELODI's activities can be seen to be complementary to other co-ordination activities elsewhere such as the IDEA initiative in the USA (see Cool, 2019, Int J Radiat Biol. 95(10):1358-1360), the Japanese PLANET initiative and others described by Cho et al (Cho et al, 2019, Int J Radiat Biol. 2019 95(7):816-840, Repussard, 2019, 95(10):1354-1357). Furthermore, in June 2022 a report that aims to reinvigorate low dose risk research in the USA was published by the US National Academies of Sciences, Engineering and Medicine (available here). The OECD's Nuclear Energy Agency Committee on Radiation Protection and Public Health (see further information here) has been working to co-ordinate efforts on a global scale. Furthermore, MELODI aims to be responsive to the key challenges in the system of radiation protection as identified by international organisations such as UNSCEAR and ICRP.

4. Summary of Developments since last SRA update

Recent advances in radiation epidemiology are starting to provide evidence of risk to health at doses below the 100 mGy level used to define low dose exposure. The INWORKS series of pooled occupational exposure studies suggests that significantly increased risks of solid cancer and leukaemia can be detected at doses of 100 mGy when delivered over a working life. Though the subject of continued debate, several studies of cancer risks associated with exposure to CT scans in childhood suggest significant increases in leukaemia and brain cancer risk at 50 mGy and above. Likewise, some studies have shown increased risk of childhood leukaemia from natural background radiation, though the evidence is not consistent and dose assessment often not based on individual measurements. Thus, this SRA edition is being written at a time of strengthening evidence of cancer risks at 100 mGy and below, even when exposures are protracted. Much of this evidence has been drawn from European cohort studies.

A notable development in recent years has been an increased interest in applying AOP approaches to assist low dose health risk assessment and to promote the integration of epidemiological and experimental evidence (see for example, NCRP, 2020, Report No. 186 – Approaches for Integrating Information from Radiation Biology and Epidemiology to Enhance Low-Dose Health Risk Assessment). Such approaches hold some promise to further embed the integrative, multidisciplinary approach, and indeed MELODI has run a workshop on the topic in 2021 (see below).

The research areas covered by current active EU funded projects are summarised here.

In 2018, a EURATOM call in radiation protection resulted in the funding of one project:

- HARMONIC is a large multi-disciplinary project to contribute to improvements in the understanding of health effects of medical IR exposure of paediatric patients, focusing on two distinct scenarios: (1) Paediatric patients undergoing modern radiotherapy (including proton therapy); (2) Paediatric patients undergoing interventional cardiology. The project explores potential effects at very early ages, exposure to a wide range of doses from photons, protons and secondary neutrons radiation. It will also build European cohorts and registries for long term follow-up in the context of very rapid technology evolution. The study will use state-of-the art dosimetry, complemented by non-invasive imaging and molecular epidemiology to assess: endocrine dysfunctions, cardio and neurovascular diseases, societal impact and cancer. The project will also investigate radiation-induced cellular responses in samples of blood and saliva, and the mechanisms involved in the processes that may lead to cancer and vascular diseases. Ultimately, HARMONIC will develop tools and allow definition of guidelines on optimization techniques to guide treatments toward reduction of patient doses in paediatric cardiology and oncology. Relates to SRA topics: dose and dose-rate dependence of cancer risk/non-cancer diseases, individual variation in risk and consideration of spatial/temporal variation in dose delivery by mechanistic and epidemiological investigations. This project runs until June 2024.

The 2019 EURATOM call resulted in the funding of two projects:

- RadoNorm aims at managing risk from radon and NORM exposure situations to assure effective radiation protection based on improved scientific evidence and social considerations. RadoNorm is designed to initiate and perform research and technical development in support of European Union Member States, Associated Countries and the European Commission in their efforts to implement the European radiation protection Basic Safety Standards. The proposed multidisciplinary and inclusive research project will target all relevant steps of the radiation risk management cycle for radon and NORM exposure situations. RadoNorm aims to reduce scientific, technical and societal uncertainties by: (i) initiating and performing research and technical developments, (ii) integrating education and training in all research and development activities, and (iii) disseminating the project achievements through targeted actions to the public, stakeholders and regulators.
  This will strengthen the scientific and technical basis for all key steps of the radiation risk management cycle for radon and NORM. The inclusive character of RadoNorm is given at different levels, by (i) targeting research and development on all steps of the management cycle, (ii) combining biomedical, and ecological research with mitigation development and social science research, (iii) integration of researchers from national radiation protection institutions, research centres, universities, and SME, (iv) incorporation of E&T activities in all undertakings, and (v) linking dissemination efforts directly to knowledge achievements and new recommendations. The project runs until August 2025.

- The SINFONIA project concerns radiation risk appraisal for detrimental effects from medical exposure during management of patients with lymphoma or brain tumours. It will develop novel methodologies and tools that will provide a comprehensive risk appraisal for detrimental effects of radiation exposure on patients, workers, carers and comforters,

the public and the environment during the management of patients suspected or diagnosed with lymphoma and brain tumours. SINFONIA runs 2020 – 2024.

The 2021 EURATOM call resulted in one successful project of relevance:

- The PIANOFORTE European Partnership is in many ways a successor to the CONCERT EJP, it started in June 2022. A first of three calls for research is anticipated for March 2023.

Additionally, MELODI has sponsored five workshops, concerning (i) individual sensitivity to radiation, (ii) non-cancer diseases, (iii) the effects of inhomogeneous radiation exposures, (iv) adverse outcome pathways for radiation pathologies and (v) transgenerational and prenatal radiation effects. Outputs and recommendations from the individual sensitivity and non-cancer diseases workshops are published, and one publication from the AOP workshop is available (Siebold et al, 2019, https://doi.org/10.1080/09553002.2019.1665209 ; Averbeck et al, 2019, https://doi.org/10.1080/09553002.2019.1704908 ; Gomolka et al, 2019, https://doi.org/10.1080/09553002.2019.1642544 ; Calman and Oughton, 2019, https://doi.org/10.1080/09553002.2019.1665210; Kreuzer and Bouffler, 2021, https://doi.org/10.1016/j.envint.2020.106286 ; Ainsbury et al, 2021, https://doi.org/10.1016/j.envint.2020.106213 ; Lumniczky et al, 2021, https://doi.org/10.1016/j.envint.2020.106212 ; Pasqual et al, 2021, https://doi.org/10.1016/j.envint.2020.106295 ; Tapio et al, 2021, https://doi.org/10.1016/j.envint.2020.106235; Chauhan et al, 2021, https://www.tandfonline.com/doi/full/10.1080/09553002.2021.1969466; Chauhan et al 2022, https://doi.org/10.1080/09553002.2022.2086716). Further publications from the latter workshops are anticipated. Key recommendations for research from the publications have been taken into consideration in developing this SRA.

Beyond the activities of MELODI, documents of relevance to this SRA have been published by UNSCEAR in recent years – most notably UNSCEAR 2019, Annex A - Evaluation of selected health effects and inference of risk due to radiation exposure and Annex B - Lung cancer from exposure to radon and the 2020/21 Annex C, Biological mechanisms relevant to the inference of cancer risks from low dose and low dose-rate radiation. In 2021, ICRP published a paper outlining its approach to review of the system of radiological protection (Clement et al, 2021) and in the same year published a paper summarising the areas of research that are expected to support the development of the system of protection (Laurier et al, 2021). NCRP have published in 2020 its Report No. 186 – Approaches for Integrating Information from Radiation Biology and Epidemiology to Enhance Low-Dose Health Risk Assessment (2020) that also places emphasis on AOPs and related approaches.

5. Strategic Research Agenda

Radiation protection is one particular area of health protection concerning the prevention of radiation induced non-communicable diseases and tissue damage, notably cancers and some non-cancer diseases in the general public, patients and workers. The health impacts of radiation generally concern diseases or biological effects that are multi-factorial in origin, with both intrinsic and extrinsic risk factors. The intrinsic, non-modifiable risk factors, include age and sex as well as less well characterised genetic and other factors, all of which, in addition to being important risk factors in themselves, may also modify the health impact of radiation. There is also a wide range of modifiable risk factors affecting the incidence of these diseases, including 'lifestyle' factors such as diet, tobacco smoking and exercise, as well as natural and human-made environmental factors including co-exposures to other environmental and occupational carcinogens and medicinal drugs.

Radiation protection research therefore needs to be viewed in this wider context where any radiation exposures and effects on health are rarely, if ever, experienced alone; rather individuals and their disease risk can be influenced by their genome, epigenome, exposome, microbiome and other factors. This wide range of influences on individual and population health risk can pose problems for discerning the impact of radiation exposures, especially when exposure levels are low. As stated earlier, radiation protection is one element of general health protection relevant in public, occupational and medical exposure setting.

The MELODI SRA is based on the key policy goals defined by the High Level and Expert Group to address the robustness of the current radiation protection system with evolution to take account of developments in the area (see **Figure 2**).

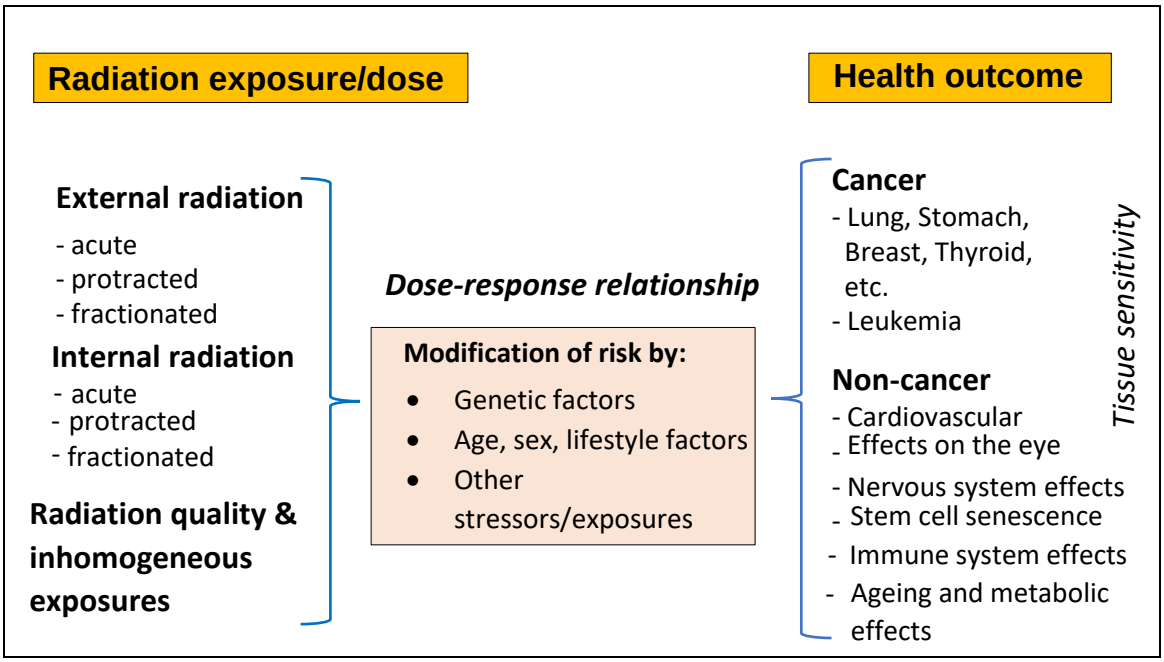

Figure 2: Key policy issues in European low dose radiation risk research defined by the High Level and Expert Group.

The key policy issues identified in the HLEG report are:

- The shape of the dose-response for cancer;
- Tissue sensitivities for cancer induction;
- Individual variability in cancer risk;
- The effects of radiation quality (type);
- Risks from internal radiation exposure;
- Risks of, and dose response relationships for, non-cancer diseases and hereditary effects.

For the purpose of the MELODI SRA, these issues were restructured into two topics relating to disease types and two cross-cutting issues (**Figure** 1):

TOPICS

(1) Dose and dose-rate dependence of cancer risk;

(2) Risk for non-cancer effects;
CROSS-CUTTING ISSUES
(3) Individual variation in risk;
(4) Effects of spatial- and temporal-variation in dose delivery

As discussed by the HLEG and confirmed by MELODI, research at low dose-rates or low doses presents significant challenges in the investigation of both radiation-related health effects and underlying biological mechanisms, because the magnitude of health risk and biological effects is expected to be low. A multidisciplinary approach is therefore essential, both epidemiological and experimental studies will also require sufficient statistical power and sample sizes to be effective, nested case-control study designs are likely to be suitable, as well as "meet in the middle approaches" for example.

For these reasons, discussion of each key question is sub-divided below into two categories:

- Research to improve understanding of the mechanisms contributing to radiogenic diseases following low dose and dose-rate exposures.
- Epidemiological research that integrates, where possible and informative, biological approaches to improve health risk evaluation.

5.1 Dose and dose-rate dependence of cancer risk

Current risk estimates used in radiation protection are based upon epidemiological studies of exposed populations. Radiation protection standards aim to avoid tissue reactions and minimize the incidence of the late developing stochastic effects of cancers and possible hereditary effects in future generations. Thus, it is of fundamental importance to radiological protection that the health risk estimates are evidence-based, robust, and credible. Most important among the epidemiological studies are the follow-up studies of Japanese populations exposed as a consequence of the atomic bombings of Hiroshima and Nagasaki that provide risk estimates per unit dose for cancer and, more recently, non-cancer effects. While the Japanese studies remain the main basis for the cancer risk estimates used in radiation protection, they relate to a specific population and a specific exposure scenario. The exposure was essentially an instantaneous, high dose rate total body gamma ray exposure with a small neutron component. Information about cancer risk from the A-bomb survivor studies is, to an increasing extent, complemented by studies of occupational, environmental and medical exposures, which allow direct investigation of effects of fractionated or protracted exposures in current European populations.

As noted earlier, epidemiological studies provide direct evidence of dose-related increases in total cancer risk after acute exposures with doses of about 100 mGy and above. Recent studies have provided better evidence of risk at doses below 100 mGy and with protracted exposure. Some reports indicate a possible increased risk of childhood leukaemia, and possibly also brain cancer from doses below 100 mGy due to natural background gamma radiation and from paediatric CT imaging.

Nevertheless, there are major uncertainties concerning (i) the magnitude of total and organ-specific cancer risks following specific exposure situations such as protracted exposure encountered in the environment as well as in occupational and medical settings, and when the

dose is inhomogeneously distributed, more particularly after internal contamination; (ii) the risk for individual cancer sites due to possibly different tissue sensitivities, and (iii) the best evidence-based models to infer risk at doses and dose-rates that are lower than those for which direct epidemiological evidence is available. In this context, there are also a number of ethical questions that need to be addressed, such as the use of the LNT model for extrapolation to very low doses, and whether other risk factors may substantially modify radiation risks.

Classical epidemiological studies will need to be continued to refine the knowledge of risk directly in human populations, particularly in the context of low dose, protracted and non-uniform exposures. Accuracy of risk estimates can potentially be increased by more precise dose estimation and outcome assessment, larger studies or pooling of data from several studies. Mechanistic and epidemiological approaches should be integrated whenever feasible to address cancer risks from acute whole-body exposures with low-dose (<100 mGy) or from fractionated, protracted and inhomogeneous exposures resulting in low-to moderate dose. Studies also need to address the impact of different radiation qualities and effects of both internal and external exposures, alone and in combination. Knowledge of health risks from low dose-rate exposures is of direct relevance for radiological protection in emergency situations, in medicine (with children, who are known to be more sensitive than adults, easily receiving doses of several tens of mGy to the brain from multiple brain CT scans), and in occupational settings, with the current dose limit of 20 mSv/year averaged over 5 years with no single year exceeding 50 mSv. Radiation protection in the medical context is particularly important as exposures have been increasing, and novel radiation modalities are both in use and under development. Clear and coherent principles for justifying the long-term risks with more immediate benefits are needed. Radiation protection in the context of long-term space travel, where radiation exposures have some very specific characteristics and differ from terrestrial exposures, is likely to grow in importance in the future. In the context of the risks associated with space travel, the formation of links to other relevant agencies with research programmes, e.g. NASA, ESA, JAXA, would be beneficial. Beyond studies of specific irradiated populations, there exist some major cohorts established and followed primarily for reasons other than the assessment of radiation risk, some consideration of the benefits of utilising such cohorts and adding radiation exposure information may be of use in the future.

Research line: Health risk evaluation

Quantification of cancer risk at moderate dose or from acute or protracted non-uniform exposure, and at low doses or dose rates from acute homogenous exposure are key challenges for improved radiation risk assessment. The large size of epidemiological studies required to detect small increases in cancer risk at low doses and dose rates, the need to capture all major sources of radiation exposure, and the potential for bias and confounding factors present practical challenges, particularly at the lowest doses. The priorities in this area include the maintenance and improvement of key cohorts by continued follow-up, pooling of different studies, collection of information on confounders and improving precision of dose and health data. Key cohorts are characterized by large populations with exposure conditions and dose distributions that are relevant for radiation protection, good individual dosimetry, long and complete follow-up with good quality of health outcome data, particularly in relation to cancer occurrence; and the possibility of collecting information on relevant potential confounders either on the whole cohort or through targeted nested case-control studies.

These studies should include, where possible and likely to be informative, the collection and appropriate storage of a large number of relevant biological samples, including tissue samples from cancer cases and somatic tissue from affected individuals; while this is generally difficult in large

scale cohorts, it can be integrated in nested case-control studies. Through identification, validation and integration of relevant biological endpoints and markers into epidemiological studies, further insights will be gained into the risks associated at the population and individual level with such exposures. The integration of both epidemiological and mechanistic studies will improve cancer risk evaluation through molecular epidemiological studies or by mechanistic modelling.

Priority research areas are:

- 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 precursor lesions of cancers 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 AOP 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 as in cohort studies, and tracing markers of susceptibility, pre-clinical changes and biological indicators of exposure in disease as in case-control studies– the 'meet in the middle' approach (Vineis and Perera, 2007, Cancer Epidemiol Biomarkers Prev. 16(10):1954-65).
- To determine the value of evaluating cancer risks through systems biology analyses and models of carcinogenesis based on mechanistic studies and epidemiological data, and integration of the two.

Research line: Basic mechanisms

An LNT extrapolation model is currently used to estimate risk at low doses from higher dose epidemiological data. An important aspect of the justification of using this model is that radiation carcinogenesis is assumed to be primarily driven by damage to DNA and subsequent mutation of growth-regulating genes in target cells. Yet, a number of other potential mechanisms contributing to and modulating radiation carcinogenesis have been proposed, including epigenetic mechanisms of gene regulation such as DNA methylation and miRNA expression, transmissible genomic instability, bystander effects and adaptive response, and it is important to determine their roles. The extent to which these modulating effects and non-mutational mechanisms challenge the validity of the LNT risk extrapolation model needs to be determined. For this purpose, the use of well validated animal and human cellular / tissue models of radiation carcinogenesis (both solid cancers and leukaemias) is required.

Priority research areas are:

- 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 qualities. 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 and ageing. 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-environmental, non-targeted and systemic processes that may promote or restrict the growth of pre-malignant cells in tissue, and 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 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. All these investigations are likely to benefit from the application of Artificial Intelligence/Machine Learning (AI/ML) approaches to analyses of multi-omics and big data sets in the future.

5.2 Non-cancer effects

It has been traditionally assumed that health effects other than cancer and hereditary diseases show a threshold (defined as the dose required to lead to 1% excess incidence) at doses that are well above the levels of exposure typically encountered in the public environment, at work or in diagnostic medical uses of ionizing radiation. Recent results from epidemiological and experimental studies indicate possible increased risks of circulatory diseases, cataracts, cognitive/neurological effects and others not only at high doses but also at down to 500 mGy and, possibly even lower. Based on these findings the ICRP issued in 2011 a statement on tissue reactions (formerly termed non-stochastic or deterministic effects) that noted evidence that the threshold in absorbed dose for effects on the lens of the eyes is of the order of 500 mGy (acute and protracted exposure). Consequently, a recommendation was made for a reduction in the annual equivalent dose limit for the eye lens to 20 mSv per year averaged over 5 years, with no one year exceeding 50 mSv. In addition, ICRP suggested that the dose threshold for circulatory diseases may be as low as 500 mGy.

Evidence for radiation-related hereditary effects is based on experimental animal studies. There is no direct evidence for hereditary/transgenerational effects from human studies, though 2nd and 3rd generation studies are likely to be feasible in specific cohorts, e.g. in the Urals. The as yet uncertain contribution of hereditary risk to overall risk is expected to be small in comparison with that of cancers. While the system of radiation protection includes hereditary effects in the calculation of low dose detriment along with cancers for risk management purposes, the range of diseases occurring among the offspring of irradiated parents includes both cancer and non-cancer diseases. There are also effects on pregnancy outcomes, and as such the pregnant mother represents a high risk group.

For all outcomes, there are uncertainties about possible effects at low doses, which may have important implications for radiation protection. Results of available epidemiological studies are not always consistent, as the risk estimates are prone to bias and confounding, and the biological mechanisms of relevance for health risks at these low doses are not known. The possibility of a stochastic nature of non-cancer effects without dose thresholds raises a wide range of questions and needs further investigation. In contrast to cancer, knowledge on the underlying biological mechanisms for radiation-related non-cancer effects in the moderate and low dose range is very sparse. Therefore, research to understand the mechanisms is necessary. In addition, epidemiological research of key cohorts with good information on potential confounding factors is needed to provide information on radiation-related risk of non-cancer diseases following low-dose, protracted or fractionated exposure, relevant for radiation protection. Individual variation in risk, mixed exposures and impact of characteristics of radiation exposure will also need to be explored.

Research line: Health risk evaluation

Quantification of non-cancer disease risk in humans at moderate or low doses or dose-rates is a key and difficult challenge for radiation protection, because the magnitude of risk due to radiation is expected to be low and the potential for bias and confounding factors is high. Informative epidemiological studies in this field will be characterized by cohorts of large size with exposure settings and dose levels relevant for radiation protection, good dosimetry, high quality of health data, long follow-up and the possibility of collecting information on relevant potential confounders either on the whole cohort or through nested case-control studies. In addition, these studies should include – where possible and informative – collection of biological samples, relevant tissue samples from the relevant organ to allow mechanistic investigations, and extensive data on the health status during follow-up.

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

Priority research areas are:

- To determine the shape of the dose-rate and dose-response relationships, 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/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), and for 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.

- 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 biology analyses and mathematical models combining and integrating mechanistic studies and the epidemiological data.

Research line: Basic mechanisms

Deterministic effects or tissue reactions are classically thought to arise as a consequence of cell killing or functional inactivation by high radiation doses. They are characterised by steeply increasing dose-response relationships at doses exceeding a defined threshold. It is unlikely that cell killing/inactivation will explain fully the effects of lower radiation doses on circulatory diseases, cataract and cognitive dysfunction. Epidemiological investigations of populations with well-characterised exposures require support from studies to identify the underlying mechanisms that lead to each of the non-cancer diseases. Each disease may have a different mechanistic basis, and it is not clear, if there will be any similarity with the mechanisms that lead to radiation related cancers.

Low dose radiation may induce cellular senescence. The occurrence of this phenomenon in tissue stem cell compartments is an event that could have profound pathophysiological consequences. Alteration of stem cell functions may impair tissue renewal and homeostasis or may promote non-cancer diseases or cancers.

Priority research areas are:

- 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 AOP for radiation-induced non-cancer effects.

- To apply a full range of analytical methods including multi-omics and multi-modal data integration (with application of AI/ML where appropriate) and consideration of the target cells and surrounding microenvironment. In this context emerging technological innovations including single cell multi-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

5.3 Individual variation in risk

Individual variation in radiation-related cancer and non-cancer disease risk is a key area to address for radiation protection; effective identification of groups at higher risk is necessary to ensure that adequate protection is provided to all. Differences in the magnitude of radiation-induced risks between individuals, or groups, may relate to sex, age at exposure and age attained, state of health, genetic and epigenetic make-up, as well as behavioural factors. Such differences, if significant, raise very important ethical and policy questions as to whether some individuals or groups are inadequately or over-protected by the present system and regulations. Similar concerns on variation in risk between individuals apply to non-cancer outcomes.

At present, there is insufficient information about the size of the differences in radiation response between individuals or groups of individuals and their consequent influence on risk estimates at low doses and dose-rates. In order to address policy questions, it is necessary to obtain better scientific information on the extent of the variations in sensitivity/susceptibility in the population, in the sizes of the variations, characteristics affecting the variation and in the sizes of the various population subgroups. Importantly, reliable and robust biomarkers predictive of individual risk need to be identified and characterised through basic mechanistic research before application in epidemiological studies.

The group of individuals who reach a high age is expanding in many countries worldwide, this may increase the need for additional considerations when estimating long-term risks after radiation exposure. Research in this field aims to improve quality of life for elder people.

Treatments with low-dose radiation for medical purposes is increasing worldwide. These procedures are beneficial to the patient. Nevertheless, there is scant awareness of health risk associated with their unjustified or excessive use. In particular, health risk may be higher in elderly patients due to increased vulnerability, the possible impact of co-morbidities and poor recovery of homeostasis following a stress such as low dose radiation exposure.

Consideration of how individual differences affect the relationship between absorbed dose (and dose distribution) and risk is required. For internal intakes of radionuclides, the dose and dose distributions can be very different in individuals for the same exposure because of anatomical and physiological differences (e.g. in airway morphology or breathing mode). These variabilities should be taken into account by accurate dosimetric and physiologically relevant biokinetic models. In addition, the nature of the interaction of ionizing radiation with co-exposures to other agents (e.g. tobacco smoke, heavy metals and, generally, environmental pollutants) and existing risk-modifying conditions (e.g. iodine deficiency for thyroid cancer) for the onset of various cancers and diseases are important in considering risk transfer between different populations.

Research line: Health risk evaluation

The quantification of the contribution that individual variation in response to radiation makes to radiation health risk on both an individual and population level is a key question. Realistic estimates of the magnitude of differences in response between individuals and groups are needed.

Priority research areas are:

- To identify and validate candidate biomarkers of individual sensitivity/susceptibility 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. Links to existing biobank resources, particularly in relation to medically exposed patients should be considered.
- 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 impact.
- 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

Basic research is needed to establish which factors and processes (including genetic, epigenetic and environmental factors/processes, co-morbidities, co-exposures and lifestyle factors) lead to greater individual risk of late effects in terms of cancer or non-cancer diseases. This includes the discovery of genetic, phenotypic and molecular markers of these pathways, and the integration of mechanistic studies in the quantitative evaluation of health risks. A major focus should be the understanding of how these different factors may modify risk, keeping in mind that the radiosensitive phenotype is likely to be multifactorial. Another important question is whether biomarkers of radiation in normal tissue reactions are related to risk of developing late effects following exposure to low and protracted doses of different LETs including internal exposures.

Priority research areas are:

- To develop 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, including the use of AI/ML approaches to predict differences in outcome at both individual (qualitative changes affecting health-relevant pathways) and population (quantitative changes in health outcomes) levels.

5.4 Effects of spatial and temporal variation in dose delivery

In the system of radiological protection, risk mainly depends on absorbed dose averaged over a given target mass. The biological outcome of the exposure is determined not only by the dose but also by the time frame of the dose delivery (dose-rate pattern), and by the specific kind of radiation responsible for the energy deposition (radiation quality). In order to account for the effects of temporal variation in dose delivery, a single dose- and dose-rate effectiveness factor (DDREF) is currently applied for low LET radiation in radiation protection; however, the evidence base for this judgement continues to be debated. Concerning spatial variation, radiation weighting factors are currently applied for radiation protection purposes to account for the difference in the spatial pattern of energy deposition at the subcellular scale, due to different radiation qualities. When it comes to high-LET exposures, particle fluence should be considered in addition to dosimetric information, as fewer cells are expected to be hit but with high deposited energy. At a larger scale, the effects of intra-organ (but supra-cellular) variation in dose delivery are not considered: the same health risk is assumed for all exposure types if they result in a given amount of absorbed energy, independently of whether the energy is absorbed by a single target cell or homogeneously distributed among all target cells of the same organ. However, the biological effects and so the health consequences are unlikely to be the same.

Inhomogeneity in dose delivery, both at the temporal and spatial level, is a real feature of many environmental, medical and occupational exposure scenarios. Mechanisms responsible for biological effects of different dose-rates or of inhomogeneous dose deposition are not fully characterized: at the cellular level they can be investigated with in vitro studies, but when it comes to how they finally affect health risk (both for cancer and non-cancer diseases) few relevant experimental models or valid datasets exist. In many situations, mixed field exposures are also relevant, but again there are few studies that consider risk in such exposed populations.

The effects of spatial and temporal variation in dose delivery are also gaining importance because of the more wide-spread availability of external beam hadron therapy, where out-of-field doses by scattered neutrons are of concern, the increasing clinical use of radionuclides, and the perspective of longer duration space travel (as well as space tourism) in the future. There is also a need to characterize how internal exposure, dose inhomogeneity and radiation quality influence the formation of candidate biomarkers so-far identified in response to low LET external exposure.

Research line: Health risk evaluation

Quantification of health risk at low/moderate dose or dose-rates from internal exposures and from inhomogeneous dose distribution from external exposures is a key challenge for improved radiation risk assessment. As exposures frequently involve all three features noted above (effects of dose rate, radiation quality, and intra-organ dose distribution), relevant cohorts have to be identified or consolidated, where the separate effects of these three variations can be studied. In addition, collection and maintenance of relevant biological sample collections, including tissue samples from cancer cases and somatic tissue from affected individuals may also help to estimate the contribution of the effects of these three exposure characteristics. Sound individual dosimetry is particularly important in case of internal exposures.

Priority research areas are:

- To determine cancer and non-cancer risks related with 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

Effects of radiation quality and dose-rate on individual cells and at the cell population level are well documented. Many biological endpoints show a dose-rate dependence (notably DNA damage response) and data supporting an inverse dose-rate effect also exist. This raises the question of the effects of protracted exposures, particularly at low dose and low dose-rate. It is recommended to consider fluence (in addition to dosimetric information) when dealing with exposures to charged particles (particularly for high LET). Concerning spatial variation at the sub-cellular level, the biological outcome is clearly modulated by radiation quality indicators such as LET. Using *e.g.* microbeam irradiations, mechanisms determining the response to a highly inhomogeneous energy deposition can be addressed under controlled conditions.

To provide further insights in the effects of intra-organ dose distribution, experiments with organotypic tissue models and animal models are required. The effects of locally high doses, when small parts of the tissue/organ are irradiated with high doses while the average dose remains low have to be quantified and compared to homogeneous exposures. Whether and how effects of the locally high dose propagate in the less exposed tissue also deserves investigation. Organotypic tissue models and animal models also allow to study the changes in tissue architecture in order to analyse the effects of intra-organ dose distribution.

Priority research areas are:

- 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.

- 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 AOP approach, determining those operating in case of inhomogeneous exposures.

6. Education and Training

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

The HLEG Report of 2009 (https://op.europa.eu/en/publication-detail/-/publication/47c88945-aec3-4730-ad75-e1f9173e5c09) identified a problem with the maintenance in Europe of the range of expertise essential to an effective programme of research into the risks to humans from low-dose radiation. The report advises that specific programmes aiming at knowledge management across generations have to be designed in order to achieve sustainable continuity and development.

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

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

6.2 Priorities for strategic support of E&T

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

Support for students and young scientists

- Students need to be able to find places at universities and placement with research groups for project/dissertation work. This requires that the places must be available, but also that there are sufficient incentives to attract students. Universities are autonomous and develop new courses in response to a perceived need, taking account of staff expertise and specialization. Financial support from outside is not needed to achieve this end, although there is a role for influencing the perceived need. On the other hand, increasing the access of 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. Coordination with existing schemes (eg EU Marie Curie, IAEA Marie Sklodowska-Curie Fellowship Programme) could be useful in this respect.
- 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.
- The MELODI Mobility Programme is established and offers travel award support to early career scientists, PhD and MSc students, as the groups identified with greatest need for this form of support. The intention of the MELODI Mobility Programme is to financially support participation in conferences, courses, visits, internships 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.

Promotion of E&T for dissemination

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

Coordination and collaboration of E&T providers

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

- Continuation and extension of the MELODI Education and Training Forum in order to bring together all 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.
- There should be an active cooperation among groups promoting and supporting E&T in the radiation protection and research area (EURAYS, ENEN, etc.) and possibly use of mailing lists or social media to advertise programmes, courses, scholarships, fellowships, etc.

7. Infrastructures

One of the roles of MELODI is to promote and facilitate access to the state-of-the-art research infrastructures to support the research efforts in the radiation protection field which are prioritized in this SRA. In order to identify, characterise and quantify health risks accurately, the quality of raw data and final results produced from research projects is essential. So, the harmonization of practices amongst multiple facilities is 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.

Infrastructures include exposure facilities, observatories as well as databases (including cohorts) and biobanks and many analytical platforms (e.g. for omics) and specific tools especially developed for the domain.

Within DoReMi, a first extensive list of relevant infrastructures was generated for low dose research, in particular irradiation facilities for internal and external exposure. Within projects OPERRA and more recently CONCERT, infrastructures were highlighted via AIR² bulletin and AIR²D² database. A web-handbook has been produced, describing exposure facilities, cohorts, databases, biobanks and analytical platforms.

STORE, an Internet-based platform for storage and sharing data from previous studies, 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 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.

In order to assess the most appropriate infrastructures that meet the needs of the various priorities described in this SRA and so the future specific linked projects, it is necessary to develop and apply quality criteria for selection through the future calls. Supporting financially those infrastructures can be included through future calls in which they are clearly identified answering to specific services under guarantees such as protocols, criteria about harmonization and quality of results, data storage and sharing.

The use of bio-banked materials, where applicable, should be encouraged by including their use in future calls either indirectly for all relevant proposals or by specific topics dedicated to its use. In addition, funding should be included to support the biobanking of samples arising from Euratom/Horizon Europe funded projects where appropriate.

Next steps will rely on further 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 infrastructure. Huge efforts will be dedicated to sample/data acquisition and sample/data storage with the aims to re-use of archived materials. There is a need of 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.

Priority areas are:

- Develop easy access and improve the common organisation of the existing network of infrastructures, using feedback from approaches applied for infrastructures networks issued from past initiatives within Europe,
- Improve the awareness of existing relevant infrastructures through E&T courses, and promote their use implementing on site practical courses,
- 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,
- Develop inter-comparisons and harmonization activities to guarantee the quality of data and results issued from funded projects.

8. Research priorities (MELODI Statement)

The purpose of the MELODI Association is to define priority scientific goals and to encourage the implementation of research on health risks from low-dose and low-dose-rate radiation with the aim to improve radiological protection. A robust understanding and quantification of human health risks is the fundamental basis of radiological protection; the system of protection for public, occupational, medical and emergency exposures flows from this basis. The Strategic Research Agenda of MELODI identifies these priority goals and the specific resources, infrastructures and training capabilities needed to further develop low-dose risk research within a time frame of 20 years. MELODI statements aim to inform on priority topics for forthcoming EU and National calls; the EU issued a call for a European Partnership project in 2021, the resulting PIANOFORTE Partnership started in June 2022, and anticipates opening a call for research in March 2023. This Statement should facilitate setting priorities for both the EU and any subsequent European

Partnership calls. The high-level priorities of all European radiation protection research platforms have been identified within the CONCERT Joint Roadmap.

The key priority for radiation protection research is to improve health risk estimates for low dose and dose-rate exposures encountered in occupational, medical and public/emergency situations. The approaches will need to be multidisciplinary and innovative, including where appropriate the application of artificial intelligence and machine learning approaches. The integration of expertise outside the conventional fields of radiation research will widen the possibilities to integrate modern health research technologies in the assessment of health risk relevant to radiation protection. The priorities identified for the 2022 – 2027 period listed below take into account the feasibility and impact of the topic area (see MELODI Roadmap document) and the amount of related ongoing work on the topic

Several relevant European projects are ongoing, focused on particular topics. The HARMONIC project investigates short to medium-term health outcomes (endocrine dysfunction, cardiovascular toxicities, second primary cancers and neurovascular damage) in paediatric patients undergoing interventional cardiology or proton therapy. The RADONORM project considers the risks associated with radon and other sources of NORM exposure, the risks arising from combined exposures and elements of radon dosimetry. The SINFONIA project started in 2020 and considers cancer risks associated with medical exposures, including those at low doses.

Priorities for the 2022 – 2027 period:

The overall priority is as given in the Joint Platforms Roadmap (available to download here), Challenge A, *Understanding and quantifying the health effects of radiation exposure.* The following points provide more specific priorities within this overarching aim in light of recent developments:

- To understand the health effects of inhomogeneous exposures, various types of radiation including internal emitters and differences 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 fields and experiments with organotypic tissue models.

- In relation to tissue reaction and stochastic health effects (cancer and other diseases): Characterisation and quantification of variation in response and risk between population sub-groups/individuals due to host factors including genetic and epigenetic factors, sex, co-morbidities, environmental and lifestyle factors, co-exposures and the interactions between these depending on dose levels.

- To evaluate the risks of, and dose-response/dose-rate response relationships for, non-cancer diseases at low and intermediate dose levels (100 - 500 mGy and below): in particular cardiovascular, neurocognitive 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 microenvironment, cell-to-cell interaction (as mentioned in ICRP publ 131), the role of epigenetics, metabolic status, ageing, and immuno-senescence amongst others, in single and multiple stressor exposure situations.

- To identify, develop, validate and, where feasible, implement the use of biomarkers of exposure, and for early and late effects for cancer or/and non-cancer diseases and variation in susceptibility. The relationship between these radiation biomarkers and those emerging biomarkers of various pathophysiological processes and health outcomes needs to be considered and explored.

- 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 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 at higher levels of exposure, and when the triggering of an AOP is sufficient to disrupt normal homeostasis and lead to pathologies.

The current and previous MELODI statements, providing information about short-term research priorities for specific calls, can be found on the MELODI website. The definition of research priorities for the medium and long-term is described in the CONCERT Joint roadmap.

MELODI encourages, where appropriate, (1) the use of archived biological materials from prior EU funded research, (2) the integration of experienced laboratory networks (such as e.g. RENEB), (3) the consolidation and use of important epidemiological studies (both radiological and non-radiological) where feasible, (4) the integration of expertise from outside the conventional fields of radiation research; (5) the use of shared infrastructures and (6) continued availability of targeted education and training opportunities (such as e.g. Student Mobility Support) to share and spread technical skills.

9. Abbreviations, Websites

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

DoReMi Network of Excellence (Low Dose Research towards Multidisciplinary Integration), https://melodi-online.eu/doremi/

CONCERT https://concert-h2020.eu

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

EURAMED (European Alliance for Medical Radiation Protection Research)
http://www.eibir.org/scientific-activities/joint-initiatives/european-alliance-for-medicalradiation-protection-research-euramed/

HLEG (High Level expert group)
https://op.europa.eu/en/publication-detail/-

/publication/47c88945-aec3-4730-ad75-e1f9173e5c09

MEDIRAD **(**Implications of Medical Low Dose Radiation Exposure**)** http://www.medirad-project.eu/

MEENAS (MELODI, EURADOS, EURAMED, NERIS, Alliance, SHARE) an organisation coordinating the work of all European radiation protection research platforms.

MELODI (Multidisciplinary European Low Dose Initiative) http://www.melodi-online.eu/

NASEM (National Academies of Sciences, Engineering and Medicine, USA) report on low dose research: Leveraging advances in modern science to revitalize low dose radiation research in the United States

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

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

SHARE (platform on social science and humanities) http://sites.exeter.ac.uk/nuclearsocieties/shine/

STORE (platform for the archiving and sharing of the primary data outputs from research on low dose radiation) https://www.storedb.org