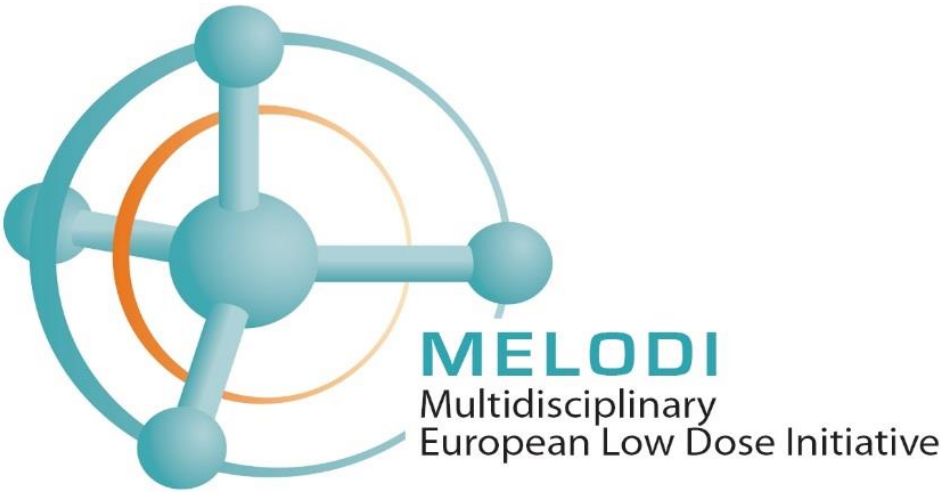

Roadmapping – results of a Feasibility and Impact assessment of MELODI topics

Status: 16th December 2020

Approved by MELODI Executive Council: 4th March 2021

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1. Abstract

This report presents the methodology used within MELODI in an analysis to assist in longer term planning and prioritization, and the results of the analysis. The approach adopted considered the feasibility and impact of conducting productive research in each area identified in the MELODI SRA at a given dose range and at a given future point in time; three dose-ranges and three-time frames were considered. As such the feasibility and impact analysis reflects the expert opinion of the authors. This report reflects work carried out by the SRA Working Group (SRA WG) of MELODI in 2016 and has been completed by the current SRA WG membership to enable documentation and publication of the methodology and its findings to inform current and future road mapping and prioritization that is important in developing ideas for a future EJP in radiation protection within Horizon Europe and beyond. Some of the limitations of the approach are considered to aid interpretation. Notwithstanding the limitations, this analysis indicates that the topics of 'susceptibility', 'epigenetics' and 'shape' are the most promising avenues of research to consider in the near-term. The analysis helped develop MELODI input to the development of the European joint platforms' roadmap for radiation protection research.

2. Objectives of the roadmap

MELODI is the European research platform for low dose ionizing radiation health risk research. The organization is one of many platforms addressing aspects of radiation protection research; as of 2020 there are six interrelated platforms, MELODI covering low dose risk, EURADOS which covers radiation dosimetry issues, NERIS which concerns emergency preparedness and response, ALLIANCE which addresses radioecology, EURAMED which concerns medical aspects of radiation protection and SHARE which has a focus on stakeholder engagement issues. A key activity for each platform is the identification of research priorities for European research within their respective areas. MELODI produces a Strategic Research Agenda (SRA) and associated annual Statement that document priorities for low dose health risk research. As the platforms have matured and worked together in the context of the CONCERT European Joint Platform for radiation protection research, the importance of longer term planning and prioritization became apparent. Within CONCERT a Joint Platforms roadmap for research over the long term, 2030 and beyond, was prepared: (https://www.concert-h2020.eu/Document.ashx?dt=web&file=/Lists/Deliverables/Attachments/206/D3.7_Second%20joint%20roadmap_draft_reviewed_%20052020_approved03062020.pdf&guid=01b5ac77-b2ec-4cda-9c98-917dba396f0f). This document published in June 2020 drew on experience of developing individual platform roadmaps.

This report presents the methodology used within MELODI in an analysis to assist in longer term planning and prioritization, and the results of the analysis. The approach adopted considered the feasibility and impact of conducting productive research in each area identified in the MELODI SRA at a given dose range and at a given future point in time; three dose ranges and three time frames were considered. As such the feasibility and impact analysis reflects the expert opinion of the authors. This report reflects work carried out by the SRA Working Group (SRA WG) of MELODI in 2016 and has been completed by the current SRA WG membership to enable documentation and publication of the methodology and its findings to inform current and future road mapping and prioritization that is important in developing ideas for a future EJP in radiation protection within Horizon Europe and beyond.

3. Importance of low dose radiation research

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

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

Thus, striking the appropriate and acceptable balance between the benefits of use of/exposure to ionizing radiation on the one hand and the health risk posed on the other is important. The regulation of exposures and protection of individuals and populations come at a cost – there are, therefore, disadvantages of both under-protection and overprotection. This applies in all situations – existing elevated exposure situations such as high radon areas, occupational settings such as nuclear industry and the medical sector, and accidental situations where difficult decisions on countermeasure implementation such as sheltering and evacuation are required. In all these contexts it is critical to have robust and accurate information on the magnitude of health risks posed by given radiation doses, ranging from high to low.

The main uncertainties in radiation health risk evaluation are listed below and illustrated in Figure 1

(1) in the magnitude of cancer risk at low and protracted doses below 100 mSv,
(2) the magnitude of non-cancer effects, such as circulatory disease, cataracts, neurological effects and other age-related diseases, below 500 mSv,
(3) the variation in disease risk between individuals in the population.
(4) the variation in risk associated with spatial and temporal variation in dose delivery

These are therefore the key areas requiring further exploration to provide better and more secure evidence for appropriate decision making in all areas of radiation protection. Accurate and reliable low-dose risk estimation is an essential foundation for a robust and acceptable system of radiation protection.

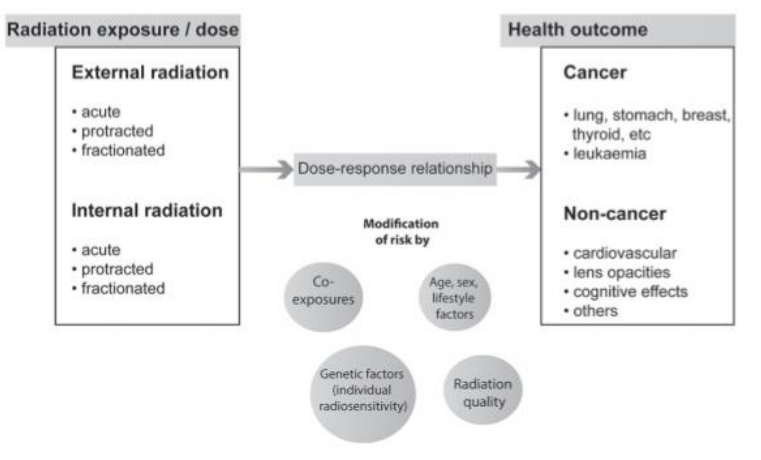

Figure 1. Illustrating the relationships between radiation exposures and health outcomes and the key issues that relate to radiation protection policy and its refinement.

The MELODI Strategic Research Agenda (SRA), which can be downloaded at http://www.melodi-online.eu/sra.html, includes these four key questions: (1) the dose and dose-rate relationship for cancer; (2) non-cancer effects; (3) individual radiation sensitivity and (4) the variation in risk associated with spatial and temporal variation in dose delivery. For each key question, several priorities for research areas in each of the following sub-sections were defined:

- Research to improve understanding of the mechanisms contributing to radiation risk.
- Epidemiological research in humans that integrates, where possible and informative, biological approaches for health risk evaluation.

Next to the development and regular update of the SRA, another activity of MELODI is to develop a roadmap, which could guide future calls in the next 10 to 20 years. While in technical sectors, a roadmap can be relatively easily constructed, this is more difficult in research. The low-dose radiation field research 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 are expected to be low.

A roadmap defines the way in time how the key policy issues are solved. This includes the definition of open questions to be answered in radiation protection in the low-dose- and dose-rate range, the evaluation of these questions with respect to the impact and relevance for radiation protection and the feasibility of achieving these aims in a given time period. In order to identify the short-term, mid-term and long-term priorities for research in the next 10 to 20 years, six topics which cover the key questions of the MELODI SRA were defined and a feasibility-impact assessment of these MELODI topics was performed. The scores of this feasibility-impact assessment can guide the selection of short-term priorities for the next call, but also the planning of long-term activities. The assessment can therefore be used as a surrogate for a roadmap and has regularly to be updated.

4. Methods

The following six major MELODI topics were defined:

1. To explore the shape of the dose-response relationship for radiation-induced health effects (Abbreviation: Shape)
2. To explore and define the role of epigenetic modifications in radiation-induced health effects (Abbreviation: Epigenetics)
3. To identify, develop and validate biomarkers for exposure, early and late effects for cancer or/and non-cancer diseases (Abbreviation: Biomarkers)
4. To explore the roles of specific target cells for radiation-induced late developing health effects (Abbreviation: Target cells)
5. To understand the potential impact of individual susceptibility on radiation-induced health effects (Abbreviation: Susceptibility)
6. To understand the health effects of inhomogeneous dose distributions, radiation quality and internal emitters (Abbreviation: Inhomogeneity)

The priorities were evaluated with respect to feasibility and impact in three different **time periods** (<5, 5-10 and 10+ years) and three different dose ranges. **Feasibility** is defined as the availability of relevant methods and techniques, infrastructures, laboratory capacity and appropriately trained researchers within Europe to do the work. **Impact** defined as the likelihood that results on the topic will bring new scientific information to inform judgements in the radiation protection system in this time period under consideration. Both feasibility and impact were scored on a three point scale (3 – high, 2 – medium, 1 – low) The **dose range** categories were defined as an external exposure of 0-10 mGy (very low), 10-100 mGy (low) and 100+ mGy (moderate) with respect to the first five topics and as an effective dose of 0-10 mSv (very low), 10-100 mSv (low) and 100+ mSv (moderate) for the topic ("dose inhomogeneity"). The scores presented in this document were arrived at through initial scoring by members of the SRA Working Group (WG) followed by discussion to reach consensus amongst the entire WG. The final feasibility and impact score is defined as the feasibility score multiplied by the impact score (range: 1 to 9); the use of addition of the scores could have been adopted but it was thought that using the product of feasibility and impact provided a clearer distinction amongst the final scores. The scores provided should therefore be viewed as the expert judgements of the SRA WG and therefore should not be seen as fully objective and are likely to change over time as results from future studies accumulate and consensus develops within particular areas.

Clearly the topics above will require support from other areas, most notably radiation dosimetry and studies of the effects of medical irradiation amongst others, including developments in understanding and technology outside the field of radiation protection research.

5. Results

The six MELODI topics have been evaluated with regard to feasibility and impact for three different dose ranges and three time frames (short-, mid- and long-term). The results are given in Table 1 and illustrated in Figure 2.

Table 1: Evaluation of feasibility and impact of six MELODI topics for three dose ranges and three times frames

Evaluation	Feasibility			Impact			Score		
Time scale	**Short -term**	**Mid -term**	**Long -term**	**Short-term**	**Mid -term**	**Long -term**	**Short-term**	**Mid -term**	**Long -term**
100 – 1000 mGy									
Shape	3	3	3	2	2	2	6	6	6
Epigenetics	3	3	3	2	2	1	6	6	3
Biomarkers	2	3	3	2	2	2	4	6	6
Target cells	2	3	3	2	2	2	4	6	6
Susceptibility	3	3	3	3	3	2	9	9	6
Inhomogeneity	2	3	3	2	3	2	4	9	6
10 – 100 mGy									
Shape	1	2	3	3	3	3	3	6	9
Epigenetics	2	3	3	3	3	2	6	9	6
Biomarkers	2	2	3	2	3	2	4	6	6
Target cells	1	2	3	2	2	3	2	4	9
Susceptibility	2	2	3	3	3	3	6	6	9
Inhomogeneity	2	2	3	3	3	3	6	6	9
0-10 mGy									
Shape	1	1	2	3	3	3	3	3	6
Epigenetics	1	2	3	3	3	3	3	6	9
Biomarkers	1	2	2	2	2	2	2	4	4
Target cells	1	2	3	3	3	3	3	6	9
Susceptibility	1	2	3	3	3	3	3	6	9
Inhomogeneity	1	1	2	3	3	3	3	3	6

TIME SCALE: SHORT-TERM: < 5 YEARS, MID-TERM: 5 -10 YEARS, LONG-TERM: 10 OR MORE YEARS
FEASIBILITY (1= LOW, 2=MEDIUM, 3 =HIGH)
IMPACT (1= LOW, 2=MEDIUM, 3 =HIGH)
SCORE: FEASIBILITY SCORE TIMES IMPACT SCORE (RANGE 1 TO 9)

The justification for the feasibility-impact assessment for all six topics is given in the following text.

1) "To explore the shape of the dose-response relationship for radiation-induced health effects"

Background: There are major uncertainties concerning the magnitude of the risk of stochastic effects following (1) protracted exposures in the order of 100 mSv (effective dose) or less, and (2) organ specific risks following acute or protracted doses of a few hundred milli-sievierts. Another major uncertainty is related to the magnitude of risk of non-cancer diseases (notably the late developing conditions such as circulatory diseases, neurological effects and cataract) at doses below about 500 mGy. Research is required to quantify the magnitude of risk by quantitative and mechanistic studies such aswell-designed experimental animal studies and large informative (molecular) epidemiological studies. An improved knowledge on the shape of the dose-response-relationship for cancer and non-cancer diseases will strengthen the robustness of present radiation protection system.

Dose range	Feasibility across time	Impact across time
100 – 1000 mGy	*"High" at all times*: Key informative cohort studies with	*"Medium" at all times*: The impact is evaluated as medium, because

	sufficient statistical power, sufficient information on confounders and improved dosimetry have been identified for different study questions (cancer and non-cancer diseases). In addition, experimental animal studies may be useful.	the shape of the dose-response relationship is largely known for total cancer down to about 100 mGy. However, uncertainty exists above this value for non-cancer diseases (e.g. circulatory diseases) and for individual cancer sites ("tissue sensitivity"). Reducing these uncertainties will strengthen the robustness of present radiation protection.
10 – 100 mGy	*"Low" in the short-term*, *"Medium" in the mid-term and "High" in the long-term:* Low feasibility in the short-term, because epidemiological studies have limited statistical power and high potential for bias and confounding. Low statistical power may also hold for animal studies. Through improvement of key cohorts (pooling, nested case-control studies to get information on confounders, improved dosimetry) and availability of suitable animal models the feasibility is judged to be steadily increasing over time. Studies of 'off-target' effects, supported with good dosimetry, in irradiated patients are also likely to be informative on this topic and in relation to individual susceptibility.	*"High" at all times:* There are major uncertainties concerning the magnitude of cancer risk following protracted exposures encountered in occupational settings and in the environment in the order of 100 mSv or less. The same holds true for non-cancer diseases. The impact for radiation protection in this dose-range is thus very high. This will especially be the case for (i) regulating occupational exposures, deciding about appropriate diagnostic applications of radiation in medicine, (3) regulating emergency situations (involving reference levels from a few tens to 100 mSv).
0 – 10 mGy	*"Low" in the short- and mid-term, "Medium" in the long-term*: Very low statistical power, high chance of uncontrolled confounding and bias in epidemiological studies and low statistical power and noise in animal experiments. In the long-term feasibility might increase through availability of pooled cohorts with good dosimetry, integration of valid biomarkers and mechanistic modelling.	*"High" at all times:* The impact of knowing the magnitude of risk in this dose-range is very high for radiation protection in the short and long-term, because currently the knowledge is very poor. See arguments above.

2) "To explore and define the role of epigenetic modifications in radiation-induced health effects

Background: Research addresses the question whether endpoints in addition to DNA mutation need to be considered in selection of risk extrapolation models for cancer, and if epigenetic effects are important for judgements on risk extrapolation for non-cancer diseases. In both cases there is a need to quantify the relative contribution of the genetic (mutational) component and the epigenetic component. The proposed research will provide evidence to inform judgements on one of the most fundamental aspects of the system of radiation protection, namely the best model for risk extrapolation for cancer and non-cancer diseases. Epigenetic effects may be of particular importance in relation to radiation effects in foetal and embryonic development. The research thus informs judgements on dose limits and emergency reference levels.

Dose range	Feasibility across time	Impact across time
100 – 1000 mGy	*"High" at all times*: The technology to assess DNA methylation, histone modifications and micro RNA levels, all at reasonably good resolution, is available. In principle studies can be carried out in cell models at high dose easily, likely in some animal models of radiation cancer and non-cancer disease too, human studies are of course more challenging.	"*Medium" in the short- and mid-term and "Low" in the long-term*. The impact is medium in the next years, assuming it is established that radiation at high dose does or does not affect epigenetic process – and there is some evidence already that it does. This prompts the need to look over dose- and dose-rate ranges, and to consider epigenetic modifications in the context of LNT justification (in addition to damage – mutation – cancer). As time goes on and the early findings become clearer, the impact of further high dose studies drops
10 – 100 mGy	"*Medium" in the short-term, "High" in the mid- and long-term*: Techniques may need to become more quantitative to detect more modest effects in the 10-100 mGy range, especially for histone modifications. Also, statistical noise will be greater so feasibility starts lower but increases.	*"High" in the short- and mid-term. "Medium" in the long-term*: See arguments above…
0 – 10 mGy	*"Low" in the short-term, "Medium" in the mid-term and "High" in the long-term:* At low dose, even more work will be needed to ensure methods are robust, reliable and quantitative but can be expected to improve over time, hence low becoming high feasibility.	*"High" at all times*: Impact remains high throughout, as the identification of another low-dose mechanism for cancer (and maybe other diseases) will require re-examination of the arguments behind LNT for cancer and other models for circulatory diseases, cataract etc.

3) To identify, develop and validate biomarkers for exposure, early and late effects for cancer or/and non-cancer diseases

Background: Identifying biomarkers for radiation-induced stress responses, as well as for early and late stages of diseases induced by radiation will provide a platform for a mechanistic understanding of the cellular responses to ionizing radiation. If persistent biomarkers for exposure and radiation-induced diseases can be identified, the integration of them in epidemiological studies will have significant implications for risk estimates of low-dose/dose-rate exposures. The proposed research will provide evidence to inform judgements on one of the most fundamental aspects of the system of protection, namely, the best model for risk extrapolation for cancer and non-cancer diseases. The research thus informs judgements on dose limits and emergency reference levels.

Dose range	Feasibility	Impact
100 – 1000 mGy	*"Medium" in the short-term, "High" in the mid- and long-term*: Many methods that can carry out high-throughput "omic" analyses (including transcriptomics, proteomics, and metabolomics amongst others) have been developed. The bioinformatics needed for the transfer of these results into a mechanistic understanding is developing. Therefore, the feasibility is evaluated as high in the mid- and long-term in this dose range, but in the next 5 years still medium.	*"Medium" at all times*: The potential usefulness of identifying biomarkers of exposure to and health effects of ionizing radiation is recognized, but the conditions of their implementation and use in daily practice are still questionable and need to be defined clearly. The issue of inter-individual variation in response may also impact upon the utility of biomarker approaches.
10 – 100 mGy	*"Medium" in the short- and mid-term, "High" in the long-term*: Developing and identifying biomarkers in this dose range may be feasible; however, validation may take more time. Therefore, the feasibility is estimated to be medium in the next ten years, but will increase at the long-term.	*"Medium" in the short-term, "High" in the mid-term, "Medium" in the long-term*: The potential usefulness of identifying biomarkers of exposure to ionizing radiation is recognized, but the conditions of their implementation and use in daily practice are still questionable and need to be defined clearly. The issue of inter-individual variation in response may also impact upon the utility of biomarker approaches.
0 – 10 mGy	*"Low" in the short-term, "Medium" in the mid- and long-term*: Although biomarker identification techniques are available, it is not certain that it would be possible to identify biomarkers at such low dose levels given the associated uncertainties and confounding factors. Improvements of existing techniques are certainly needed, so the feasibility is judged as low in the short-term, and medium at medium and long-terms anticipating	*"Medium" at all times:* The usefulness of identifying biomarkers of exposure to ionizing radiation is recognized, but the conditions of their implementation and use in daily practice are still questionable and need to be defined clearly.

	technological progresses in the future.	

4) "To explore the roles of specific target cells for radiation-induced late developing health effects"

Background: It is important to identify the cells at risk of conversion into the disease state, and enumerate these. For the case of cancer, it is generally assumed that stem and early progenitor cell populations are relevant, but these are not generally well characterised, understood in their responses to low-dose/dose-rate radiation or enumerated. Research is required to clarify these aspects, and similarly to identify, enumerate and define radiation responses of target cell populations for non-cancer diseases. It is also important to establish if radiation damage in non-target cells can propagate to target cells and contribute to disease development. An improved mechanistic understanding of radiogenic disease processes can inform mechanistic approaches to cancer risk extrapolation. The proposed research will provide evidence to inform judgements on a fundamental aspect of the system of protection, namely, the best approach for risk extrapolation for cancer and non-cancer diseases. The research thus in the long term informs judgements on dose limits and emergency reference levels.

Dose range	Feasibility	Impact
100 – 1000 mGy	*"Medium" in the short-term, "High" in the mid- and long-term*: Feasibility is medium/high as we can identify target cells in many radiologically important tissues, and easily investigate effects above 100 mGy.	*"Medium" at all times*: The impact might not be great for cancer as we have good data on the magnitude of cancer risk above 100 mGy, but high for non-cancer effects where information on targets and mechanisms are needed. However, for both cancer and non-cancer diseases the impact is gained through use of data in mechanistic modelling of risk, and even in the case of cancer at this dose level proof of principle work is still needed – stem cell numbers and the frequency of disease-related effects will be critical.
10 – 100 mGy	*"Low" in the short-term, "Medium" in the medium-term, "High" in the long-term*: Stem cell identification methods are available but seeing relevant effects at this dose level is more difficult, so over time feasibility should increase.	"*Medium" in the short- and mid-term, "High" in the long-term:* Impact for cancer and non-cancer effects in this dose range can be greater, applying information gained in modelling as outlined above.
0 – 10 mGy	*"Low" in the short-term, "medium" in the mid-term, "High" in the long-term*: Detecting relevant effects at this dose level is very difficult, and feasibility is expected to improve with time.	*"High" at all times*: Impact for cancer and non-cancer effects is potentially high at this dose level for the whole time period.

5) To understand the potential impact of individual susceptibility on radiation-induced health effects

Background: Studies of carriers of BRCA1/2 mutations and studies of cancer patients have shown that single nucleotide polymorphisms (SNPs) in a number of genes can modify the radiation responses – either in the long-term (risk of cancer) or in the short to medium terms (adverse reactions to radiotherapy/interventional radiology procedures). Differences in sensitivity have also been observed in relation to gender, age-at-exposure (ie the young and the elderly [in light of the frailty of the elderly and increasing numbers in the populations, some receiving frequent medical exposures], the embryo and foetus), health status, genetic and epigenetic make-up, lifestyle, co-exposure to other no radiological agents and age attained. In case of internal contamination dose values and dose distributions may strongly depend on anatomical and physiological diversities. At present, there is insufficient information on the influence of individual radiation sensitivity on health risk estimates at low-doses/dose-rates. Research is required on the extent of variation of radiation-related individual sensitivity in the population, on the factors contributing to this variation, as well as integration of mechanistic studies in the quantitative evaluation of health risk.

Dose range	Feasibility	Impact
100 – 1000 mGy	*"High" at all times* In this dose range, different approaches are available, including (molecular) epidemiological studies of cancer patients or cohorts of genetically predisposed individuals, system modelling, studies of biomarkers, animal models. In the short-term, case-control studies of specific outcomes among cancer survivors might be a good approach (e.g. contralateral breast cancer among breast cancer survivors).	*"High" at all times:* In this dose range, the knowledge on the variation of radiation-related individual sensitivity is still poor. The impact of gaining more information on the basic mechanisms or extent of variation in health risk would thus be high in the short- and long-terms. Results are important for future medical applications and for the integration in the radiation protection system.
10 – 100 mGy	*"Medium" in the short- and mid-term, "High" in the long-term*: In this dose range subjects showing phenotypic markers of radio-sensitivity, will be rare. A focus might be given on cohorts of susceptible individuals (e.g. AT heterozygotes, carriers of specific mutations for example in BRCA 1 or 2). The feasibility will go up as the basic understanding and number of useful biomarkers goes up.	*"High" at all times:* In this dose range impact will still be high as the basic understanding and prevalence of radio-sensitivity will allow for considerations in radiation protection.
0 – 10 mGy	*"Low" in the short-term, "Medium" in the mid-term, "High" in the long-term*: Feasibility will be low in the short-term, but will go up as the basic understanding and number useful biomarkers goes up.	*"High" at all times:* Impact is high because of possible implications for radiation protection. Understanding basic mechanisms and with biomarkers available screening of prevalence will be possible motivating a high impact for radiation protection perspective.

6) To understand the effects of inhomogeneous dose distributions, radiation quality and internal emitters

Background: Many of the exposures to radiation encountered in the environment, occupationally and in medical settings can be to internal contamination, often to radiations of differing quality or involve other aspects of dose inhomogeneity (for example the use of charged particle radiotherapy). The current system of radiation protection makes use of radiation weighting factors to reflect spatial dose distribution differences between radiations of differing quality. However, the spatial dose distribution within the tissue is not considered. The risk associated with all forms of dose inhomogeneity, internal contamination and radiation quality is not well understood. Research is required to determine the extent to which these radiation exposure characteristics modify dose-response relationships for health effects. Findings will improve the scientific evidence base for judgements in radiation protection.

Dose range	Feasibility	Impact
100 – 1000 mSv	*"Medium" in the short-term, "High" in the mid- and long-term:* The feasibility to determine the effects of inhomogeneity in cell cultures, tissues and animal experiments in the short-term is "medium". The same holds true for the estimation of risk due to internal contamination in epidemiological studies. In the mid- and long-term systems biology approaches and large epidemiological cohorts with good dosimetry will present high feasibility.	*"High" in the short- and mid-term, "Medium" in the long-term"*: Knowing the extent to which the above mentioned exposure characteristics modify the dose-response relationships for health effects in this dose range is very important for radiation protection. It has therefore a high impact in the next 10 years. As time goes on and findings are clear, the impact of high-dose studies drops.
10 – 100 mSv	*"Medium" in the short- and mid-term, "High" in the long-term:* The feasibility in the first five year is medium. In the second time interval feasibility will increase.	*"High" at all times:* The description of the effects of dose inhomogeneity within tissues in the low dose range is one of the most important tasks of current radiation protection. It is expected that the effect is strong and up to the present it is not quantified. Thus, the impact is always high from the radiation protection system perspective.
0 – 10 mSv	*"Low" in the short- and mid-term, "High" in the long-term:* The feasibility in the first five years is low. Both in the second and third time intervals feasibility will increase.	*"Medium" in the short-term, "High" in the mid- and long-term:* In this dose range, the concomitant effects may disturb the description of the effects of dose inhomogeneity. However, the impact is always significant from the radiation protection system perspective. A more exact characterization of radiation quality is similarly important and difficult task.

Figure 2: Feasibility and impact score for six MELODI research topics for three different dose ranges for the short-term (<5 years) (upper figure), mid-term (10-15 years) (middle figure) and long-term (10+ years) bottom figure. The scores represent the collective consensus judgement of the SRA WG; the F&I score is defined as the product of the individual feasibility and impact scores as shown in Table 1

6. Conclusion and future perspectives

The score of the feasibility-impact assessment of the six major MELODI topics provides a tool to plan research for the next years for different dose ranges. A separate assessment could be made for different diseases (cancer, circulatory diseases, cataracts, neurological effects etc.) if needed. The approach adopted drew on the expertise and experience of members of the MELODI SRA working group and is therefore consensus judgement of the authors. The results informed the development of the Joint Platforms roadmap within CONCERT (https://www.concert-h2020.eu/Document.ashx?dt=web&file=/Lists/Deliverables/Attachments/206/D3.7_Second%20joint%20roadmap_draft_reviewed_%20052020_approved03062020.pdf&guid=01b5ac77-b2ec-4cda-9c98-917dba396f0f). The approach is a scientific assessment of priorities and did not take into account other factors such as societal concerns for example.

As noted the scores are consensus expert judgements of those SRA WG members involved and thus have to be treated as approximations rather that absolute values, other groups may have arrived at different scores. The choice of using the product rather than sum of the feasibility and impact scores has the effect of exaggerating differences and leads to step changes in scores as opposed to a six-point continuous scale. Score ranges of, for example 1 – 5 or 1 – 10, could have been adopted but the WG considered that this would lead to a false sense of precision in the relative scores.

Notwithstanding the above considerations, this analysis indicates that the topics of 'susceptibility', 'epigenetics' and 'shape' are the most promising avenues of research to consider in the near-term. Decisions on priorities for next calls, may additionally take into account, (1) whether specific topics have been recently funded and results are not yet available, and (2) potential synergy with topics of other platforms.

Looking to the future, it is clear that the workshops organized by MELODI will provide an important additional input for further development of a roadmap, and research planning/prioritization more generally. There have now been three workshops, the first held in 2018 considered individual sensitivity and susceptibility, the second focused on non-cancer diseases and was held in 2019 and the third, held in 2020, considered the effects of inhomogeneous radiation exposures. Review papers based on the first two workshops are now available (Salomaa and Jung, https://www.tandfonline.com/doi/full/10.1080/09553002.2019.1704107, Averbeck et al, https://www.tandfonline.com/doi/full/10.1080/09553002.2019.1704908, Gomolka et al, https://www.tandfonline.com/doi/full/10.1080/09553002.2019.1642544, Seibold et al, https://www.tandfonline.com/doi/10.1080/09553002.2019.1665209, Kalman and Oughton, https://www.tandfonline.com/doi/10.1080/09553002.2019.1665210, Kreuzer and Bouffler, https://www.sciencedirect.com/science/article/pii/S0160412020322418?via%3Dihub, Tapio et al, https://www.sciencedirect.com/science/article/pii/S0160412020321905?via%3Dihub, Ainsbury et al, https://www.sciencedirect.com/science/article/pii/S0160412020321681, Pasqual et al, https://www.sciencedirect.com/science/article/pii/S0160412019317076?via%3Dihub, Lumniczky et al, https://www.sciencedirect.com/science/article/pii/S016041202032167X?via%3Dihub). These publications summarize relevant literature and provide thoughts on roadmapping and research prioritization in the respective areas, as such they will be useful in future development of the MELODI roadmap as well as the European roadmap for radiation protection research and probably other research roadmaps internationally.