



DoReMi -
Low Dose Research towards
Multidisciplinary Integration

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Low dose Transitional Research Agenda

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Purpose of this document

The Transitional Research Agenda (TRA) is a DoReMi document, the primary purpose of which is to guide the planning, prioritization and facilitation of research activities. The existing DoReMi work plan will be taken as the starting point. The TRA also provides an overview of new areas in which the project hopes to develop research activities within its 6 years time span. While this is primarily a document for internal project use, it is anticipated that it is likely to provide an important input into the MELODI Strategic Research Agenda (SRA) and quite possibly into the prioritization of issues to be addressed in longer terms by institutions and organizations in the field including relevant funding bodies.

1 Introduction

The HLEG identified as the main relevant research areas for improving low dose risk estimation (1) the shape of dose-response curve for cancer, (2) individual radiation sensitivity for cancer, and (3) non-cancer effects together with three important cross-cutting issues (1) radiation quality, (2) tissue sensitivity and (3) internal emitters. Based on the recommendations by the HLEG report (www.hleg.de), a Network of Excellence (NoE) of Low Dose Research towards Multidisciplinary Integration called DoReMi has been established in line with the EURATOM Fission-2009-3.1.1 (FP7 call) stipulating ‘an integrated approach to low dose risk research in Europe’. The Network is coordinated by Prof. Sisko Salomaa, STUK, Finland and comprises 7 work packages: WP1 concerned with coordination and management, WP2 with structuring and setting up of the operational tool for the development of the MELODI platform (Multidisciplinary European Low Dose Initiative) to ensure long term commitment (> 20 years) to low dose risk research in Europe, WP3 with Education and Training in radiation biology and protection, WP4 with essential infrastructures and three scientific work packages concerned with research on the shape of dose response for cancer (WP5), with individual radiation sensitivity for cancer (WP6) and with non-cancer effects (WP7). These latter WPs will all include work on the three cross-cutting themes, radiation quality, tissue sensitivity and internal exposures.

WP2 has the particular task to establish and update the Transitional Research Agenda (TRA) on the basis of the proposed Joint Research programme of Integration. The HLEG has already prepared a basic outline of the SRA in February 2009. The overall goal of both research agendas is to stimulate and co-ordinate low dose research on the basis of established integrated national, bi-and multilateral research programmes within an agreed Agenda focussing research on issues that are important for radiation protection. The agendas will need to be regularly evaluated and updated.

The time-scales of both research agendas, TRA (DoReMi) and SRA (MELODI) and the corresponding Road Maps are overlapping. In fact, DoReMi is involved in the structuring of MELODI. Thus, the two strategies have to be considered differently in terms of their operational life-spans the TRA will be mainly implemented early, during the 6-year period of DoReMi, whereas the SRA will reflect and shape long-term MELODI activities extending far beyond DoReMi (over 20 years or more). Here, we focus first on the relatively short term

TRA and the corresponding Road Map for DoReMi taking into account feasibility issues of the research in the actual European context and the likely achievements of results in a reasonable time-frame with available and evolving human and financial resources.

Thus, the TRA not only outlines approaches to address the critical scientific questions but also how to overcome institutional or organisational barriers for effective low dose radiation research in Europe and beyond.

2 Questions waiting to be answered

The HLEG recognized two high priority questions to be considered: How robust is the current system of radiation protection and risk assessment? How can it be improved? The answers are likely to come from a better understanding of (1) the shape of dose responses for cancer and the validity of the linear non threshold LNT hypothesis used in radiation protection, (2) individual radiation sensitivity including factors such as genetics, age, gender, life style and other confounding exposures, (3) non-cancer effects including vascular effects (both cardiovascular and cerebrovascular), neurological/cognitive effects and lens opacities, (4) effects of radiation quality and the definition of radiation weighting factors, (5) the effects of internal emitters including biokinetic and dosimetric models, and (6) tissue sensitivities including the definition of tissue weighting factors. The current system of radiation protection has a number of underlying assumptions that need to be addressed by the strategic research agenda in order to reduce the uncertainties currently in the system of radiation protection. These assumptions are described in the HLEG report and illustrated in Figure 1.

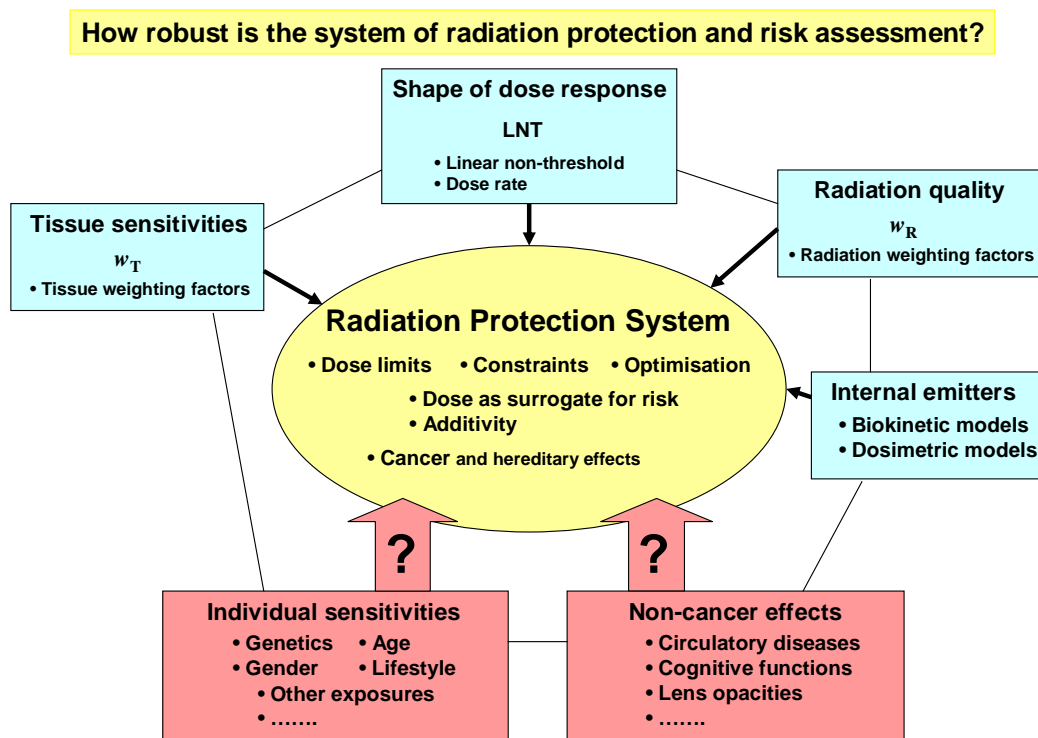


Figure 1. The basic elements of the system of radiation protection and the underlying assumptions (taken from the HLEG report).

Figure 2 illustrates how the scientific questions will be addressed by DoReMi. The interconnection between research themes is schematically illustrated in the figure below of the joint program of DoReMi activities (see Annex 1 of DoReMi for details).

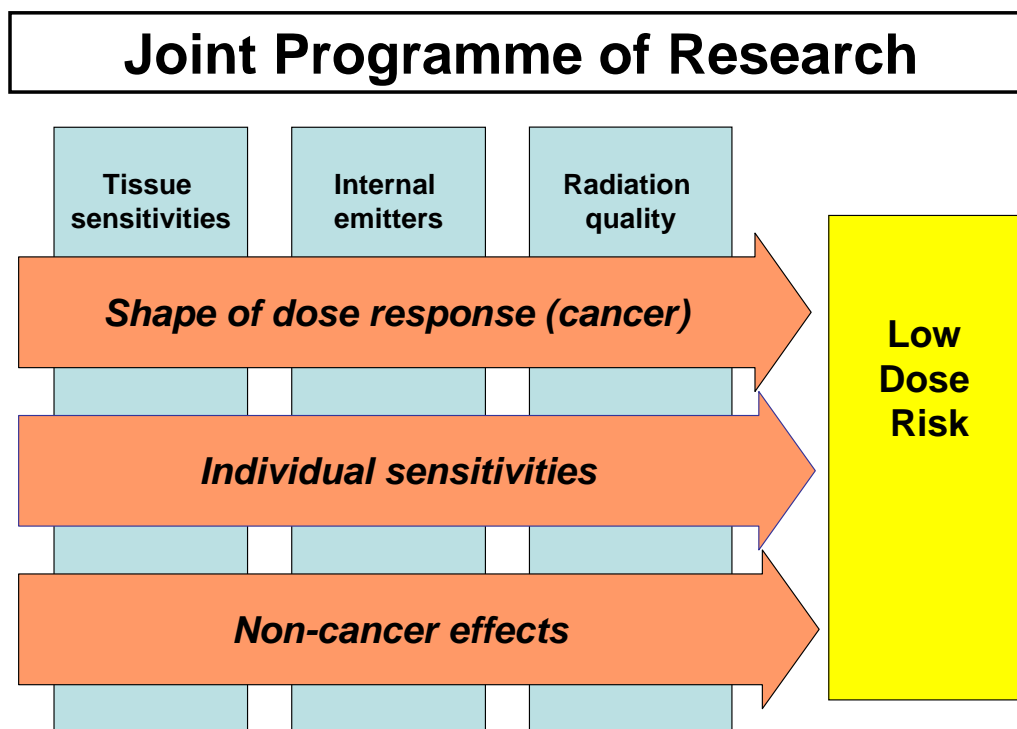


Figure 2. Joint Program of Research of DoReMi involves three main research questions that are addressed in RTD work packages 5, 6, and 7. Each of these work packages includes the cross cutting themes tissue sensitivities, internal vs. external exposure and radiation qualities.

3 Methodology of the TRA

DoReMi (and MELODI) were established at the European level to promote interdisciplinary, highly interactive and integrative research on low dose health risks. In order to attract and involve new and existing scientific expertise and to create new dynamism in this domain, the TRA is open to new incoming research directions and the development of new scientific partnerships. An effective TRA requires the identification of critical scientific questions, the associated research needs and clear priority setting.

The TRA should correspond to societal needs for radiation protection. According to the Council Directive 96/29 Euratom, the limit of the effective dose from occupational exposures is 100 mSv within 5 years. Medical diagnostic exposures can easily lead to effective doses summing up to the order of 100 mSv although dose limits do not apply to those medically exposed. The health risks from such exposures and far below (<100mGy of low LET radiation) are not well quantified. It is a main objective of DoReMi to provide data to improve

quantification of radiation health risks at low (<100 mGy) and very low (<10mGy) doses in terms of low LET radiation. Thus, DoReMi is bound to examine radiation doses down to environmental background in order to define the doses where radiation health effects can be initiated. This cannot be achieved by epidemiology alone (that forms the basis for current risk estimates), because the statistical power in the low dose range is limited. Indeed, the human population studies have to be accompanied by mechanistic studies to provide a fundamental understanding of health risks, to identify actual risk factors involved and to help establish quantitative risk estimates for humans. Only a well coordinated, multidisciplinary integrative research approach will allow the derivation of the improved risk estimates needed for radiation protection.

Open mindedness together with regular updating of the TRA will ensure that the research recommendations made and potential impact on EU calls remain relevant for the scientific and general community, and correspond to genuine and achievable research priority issues. Obviously, the success of the TRA and the promoted research rely heavily on the timely development of new research lines, concepts and opportunities. The establishment of recommendations for research priorities implies taking into account the current context of the research domain and its shortcomings as well as selection criteria such as feasibility, expected duration and sustainability.

3.1 Setting the priorities

The criteria for the evaluation of the relevance of research activities in the light of European Low Dose Risk Research Strategy (HLEG) have been developed by the DoReMi Management Board.

First of all, it is important to evaluate the potential impact for radiation protection and the scientific interest based on current scientific knowledge on low dose radiation effects and a current consensus between research and regulatory bodies (see also HLEG recommendations). Also the financial, technical and organisational feasibility within the prospected time-scale should be taken into account. This includes the availability of financial support, possibly reinforced by additional specific calls; availability of competent human resources (interested partners, recruitment of master students, doctoral and post-doctoral

fellows), availability of suitable infrastructures, relationship between projected time-scale and time available and foreseeable deliverables and outcomes. The urgent needs for short and long term sustainability, such as specific infrastructures, education and training should also be taken into account when setting the roadmap for research.

The evaluation of proposed research should be based on scientific and technological quality. Multi-disciplinarity is essential, involving, where appropriate, fully integrated dosimetry, mechanistic, epidemiological and modelling approaches. The integration and interactivity of research partners, the possibilities for developing new partnerships and interactions and for the extension towards joint, long-term sustainable ventures will be in key points in the evaluation process. The originality and innovative features of the proposed research in the international context includes expected outcomes and scientific, practical and/or societal impacts (publications, regulatory measures, patents etc).

3.2 Process for the updating and the implementation of TRA

The Transitional Research Agenda (TRA) is a strategic document guiding the research activities of DoReMi and describing the early research areas of MELODI. This first version of the TRA is prepared at month 6 (June 2010). Thereafter, major TRA updates will take place at months 36 (December 2012) and 72 December 2015 as deliverables to EC. In addition, project internal updates of TRA are foreseen at months 18 and 54. The TRA is the main strategic document of the Management Board. Implementation of TRA takes place via:

- DoReMi Joint Programme of Research work described in Annex I (Description of Work)
- DoReMi Call Plan which describes the topics for the open and internal calls for research and training activities. The Call Plan will be updated each 18-month period.
- Initiatives for annual EC calls (jointly with MELODI)
- Initiatives for bi- and multilateral projects

Input for the updating of TRA will be collected systematically by:

- Following on-going research
- Arranging exploratory workshops and hearing meetings

- Analysing the outcome of surveys on on-going research (MELODI), infrastructures (DoReMi) and training and education (DoReMi)
- Development and analysis of a table of key questions and research areas/projects
- Taking into account WP strategic reviews and outcome of feasibility studies
- Participating in MELODI workshops
- Consulting MELODI
- Consulting External Advisory Board
- Consulting other relevant Euratom projects and scientific community

The main forum for the TRA development and updating are dedicated TRA (WP2) meetings, typically arranged in connection of MB meetings. Each MB meeting will have a specified programme section devoted to the analysis of input information from the prior project period. This should include short summaries of relevant DoReMi Work Package and Task activities and planning for the coming occasions.

The first version of the TRA is based on Annex I as well as working meetings of the Management Board. The overall approach is to continue from the policy level report by HLEG by expanding the scientific content within the previously identified key research areas:

1. Identifying key questions and more detailed scientific questions and possible approaches to address them
2. Prioritizing the questions and research areas/potential projects according to relevance and potential impact
3. Considering the feasibility of the research approaches/ projects
4. Considering the roadmap of actions, taking into account the feasibility and resources available

The first version of the TRA will be presented to MELODI, EC and EAB at month 6 (June 2010).

During early 2010, the MB met four times to discuss the content of the first version of TRA (Barcelona kick-off January 27, Brussels March 25, phone conference April 29 and WP2 meeting in Sant Feliu de Guixols May 16-17). The exploratory workshops and hearing meetings have an important role in the further development of TRA. During the first six

months, two consultation meetings are arranged related to non-targeted effects (Task 5.2) in order to consider research needs for the first open call. In March 24, the Management Boards of NOTE and DoReMi met in Brussels, and on June 14, there will be NOTE workshop - DoReMi Forum organised in connection of the Third European IRPA Congress in Helsinki. A review of cohorts (WP4 meeting in San Feliu de Guixols May 18-19) that could be available for molecular epidemiological studies is another early activity providing input to the first version of TRA.

To review systematically and update relevant research lines related low dose risk, DoReMi has prepared a list of key questions and related subquestions that are in common to both cancer and non-cancer effects. The key questions relate to:

- The dependence on energy deposition (dose, LET)
- The dependence on dose rate
- Tissue sensitivities
- Modification of risk by genetic and epigenetic factors and gender
- Effect of age
- Effect of lifestyle
- Effect of physiological state and environmental exposures
- Possible radiation-induced hereditary contribution
- The role of non-targeted effects in low dose risk

Related to each of the key questions, there are subquestions that further define the research needs and outline possible projects that could provide answers to them. The subquestions address both epidemiological issues related to the quantification of effects at population level and mechanistic issues at cellular and tissue level addressing the causality. General structuring of the list of key questions and subquestions is presented in Table 1.

Table 1. Structuring the key questions and subquestions addressing low dose risk

	Cancer (1)		Non-cancer (2)	
Key question	Subquestions		Subquestions	
	Epidemiology	Mechanisms	Epidemiology	Mechanisms
1. What is the dependence on energy deposition?				
2. What is the dependence				

on dose rate?				
3. What are the tissue sensitivities?				
4. What is the modification of risk by genetic and epigenetic factors and gender?				
5. What is the effect of age on risk?				
6. What is the effect of lifestyle and/or other exposures on risk?				
7. What is the effect of physiological state?				
8. Is there a hereditary component in risk?				
9. What is the role of non-targeted effects in health risk?				

Once the research needs are identified, their relevance can be reflected against HLEG and DoReMi objectives, and the potential impact evaluated by considering if and how much the new information could change the existing radiobiological or radiation risk paradigms and, potentially, the system of radiation protection. Another step is to evaluate the feasibility of approaches, which would determine if the research can be implemented short term (from the beginning of DoReMi), medium term (during the lifetime of DoReMi) or will need long-term implementation (possibly starting with DoReMi but necessitating long term sustainability by MELODI). The feasibility assessment, together with assessment of relevance and potential impact, will set the roadmap for research in DoReMi and beyond. The overall process of generation of the DoReMi Roadmap is shown in Figures 3 and 4.

It is already evident that the three main scientific work packages WP5, WP6 and WP7 have common scientific themes such as the systems biology approaches. Moreover, individual sensitivity, as well as radiation quality are relevant for both cancer and non-cancer diseases. Addressing such themes is likely to benefit from enhanced networking and a careful analysis of the key questions and subquestions set by MB. The next TRA at month 18 should address the common themes in more detail. Meanwhile, the three WP leaders will discuss this and prepare a proposal on the update plan for the MB. Such update would potentially lead to more unified multidisciplinary approach that would support the formulation of MELODI SRA as well..

DoReMi TRA process (1)

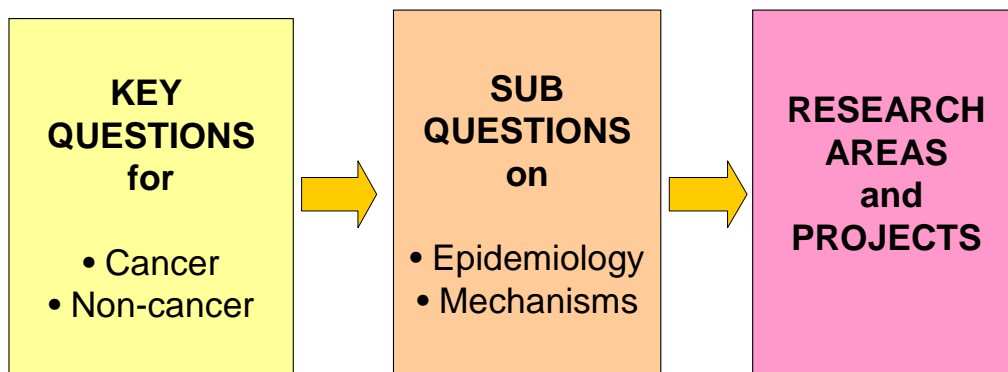


Figure 3: The process for the TRA starts with identification of key questions addressing risk of cancer and non-cancer diseases and defining more detailed questions and research areas.

DoReMi TRA process (2)

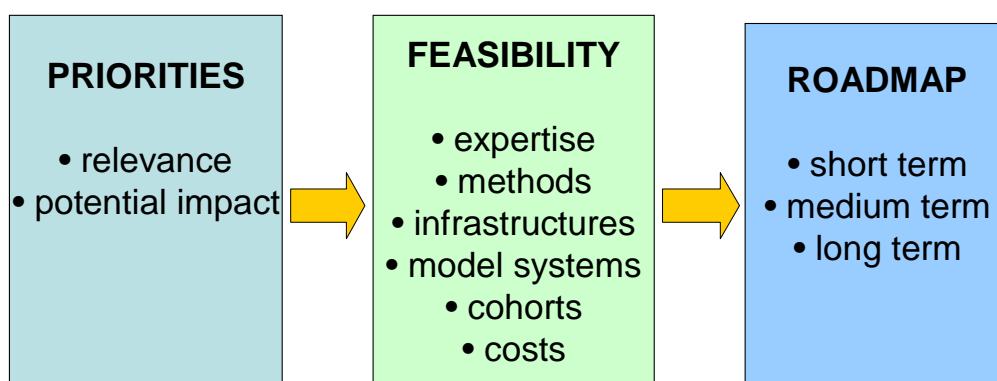


Figure 4: The process for the creation and updating of DoReMi TRA. Depending on the importance and feasibility, the projects are implemented short-term (in the beginning of DoReMi), medium-term (during the life-time of DoReMi) or long-term (possibly starting with DoReMi but implemented by MELODI).

Criteria for the evaluation of relevance, potential impact and feasibility of approaches are provided in Tables 2 and 3. In the first step (Table 2), ranking of approaches and projects according to the relevance and potential impact will be performed by providing a numerical score for each of the criteria. The high priority projects and approaches are then evaluated according to the feasibility, such as availability of expertise, technologies, infrastructures, experimental models and epidemiological cohorts as well as the estimated costs (Table 3). The feasibility analysis of high priority projects will set the foundation for a roadmap for low dose risk research in Europe.

Table 2. Evaluation form for prioritizing lines of research (relevance and potential impact). Total priority score of 8-10 is considered high priority, 6-7 medium priority and less than 5 low priority.

Topic number			
Proposed project:			
	Evaluation and score:		Scoring:
Relevance: - Is the project in line with HLEG strategy and DoReMi TRA; - Relevance of the topic for radiation protection; - Repeating old or creating new? - Multidisciplinarity of approach			1= not at all in line with HLEG or DoReMi strategy; does not bring new knowledge / this knowledge is not needed 2= relevant to high doses only; narrow scope 3= well supporting HLEG and DoReMi objectives 4= a strong societal demand; directly relevant for human health risk 5= addressing a key strategic aim; a major issue for radiation protection and low dose risk; innovative, a new international approach
	Score:		
Potential impact: - Prospects for improved protection of citizens, workers or patients; - Addressing needs of stakeholders; - Applicability of the knowledge to RP - Change in paradigm? - May change RP system? - May change RP procedures?			1= no impact on radiation biological or risk paradigms or radiation protection system 2= limited applicability to RP 3= a limited public health question but very important to a specific group; good applicability to a specific RP question 4= likely to change current paradigms in human health risk; significant societal impact 5= an important public health issue; large potential impact on RP system, addresses needs of stakeholders
	Score:		
PRIORITY SCORE	Total score:		

Table 3. Preparing the DoReMi Roadmap

Evaluation form for the assessing of feasibility of approaches in short term (total score 19-24), medium term (total score 14-18) or long term (total score 13 or less).

Topic number		
Research area / project:		
	Evaluation and score:	Scoring:
Availability of expertise:		1= not foreseen within 6 years 2= relevant expertise exists outside DoReMi consortium but has not been surveyed yet 3= available in 2-3 years, networking has not been started yet, no recruitment yet 4= most expertise is available within DoReMi consortium and additional contacts to outside experts have been made 5= all necessary expertise is available within the DoReMi consortium
	Score:	
Availability of technologies and methodologies:		1= not foreseen within 6 years 2= available in 2-3 years 3= available in 2-3 years for feasibility studies at moderate costs 4= available now and costs for large scale studies are modest 5= all necessary methodologies are routinely available within DoReMi consortium
	Score:	
Availability of infrastructures:		1= not foreseen in 6 years 2= relevant infrastructures are available only outside Europe and access is limited 3= relevant infrastructures are available outside Europe with good access 4= relevant infrastructures are available in Europe 5= all necessary infrastructures are available within DoReMi consortium
	Score:	
Availability of relevant experimental models or epidemiological cohorts:		1= not foreseen in 6 years 2= relevant models could be developed or cohorts identified in 6 years 3= relevant models could be available in 2-3 years; suitable cohorts exist outside Europe 4= relevant models / cohorts already exist but outside DoReMi 5= relevant models / cohorts are readily available within DoReMi
	Score:	
Cost of proposed work	Score:	1 = very high (>5ME) 2= high (1-5ME) 3 = reasonable (200KE – 1ME) 4 = low (<200 KE)
ROADMAP SCORE	Total score:	

3.3 Schedule for TRA updating and implementation

During the first project year, the methodology for the updating of the TRA will be tested and consolidated. The key questions are defined at month 6. The lists for more detailed subquestions addressing epidemiology and mechanisms will be developed by month 9. Testing the evaluation tools for priority setting and feasibility assessment will be carried out at month 10. The first version of the roadmap will be developed by month 12. The updating of the TRA will be carried out at months 18, 36, 54 and 72.

To implement the TRA, there will be one external call and one internal call per 18-month period so that the implementation (access of new partners and new RTD projects) will start at months 18, 36 and 54. The internal calls would be for integrative RTD between the consortium partners (old and newcomers). The different tasks and milestones of the external-plus-internal call are presented as Gantt chart 1. In addition to this major two-step RTD call, internal calls for access to infrastructures and for small feasibility projects may be arranged. The call plan for training will be prepared as part of Joint Plan for Spreading of Excellence by UNIPV. A more detailed description of the calls and the project evaluation by the EAB will be provided in the Call Plan (month 6).

Initiatives for the annual EC calls as well as nationally funded projects will be prepared in collaboration with MELODI. The complementarity of MELODI and DoReMi is illustrated in Figure 5.

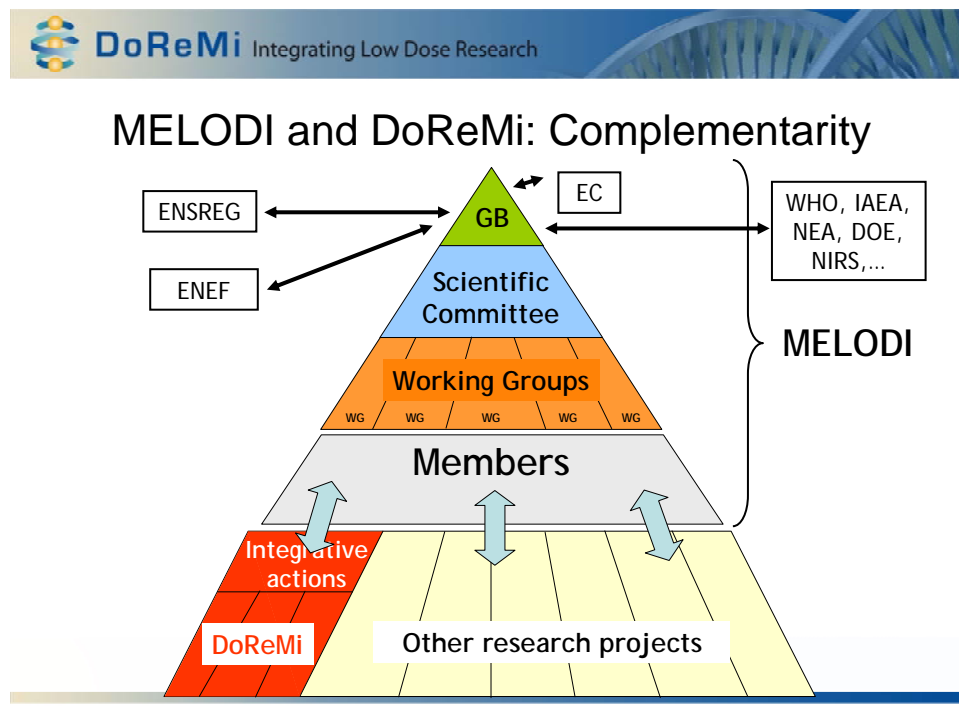
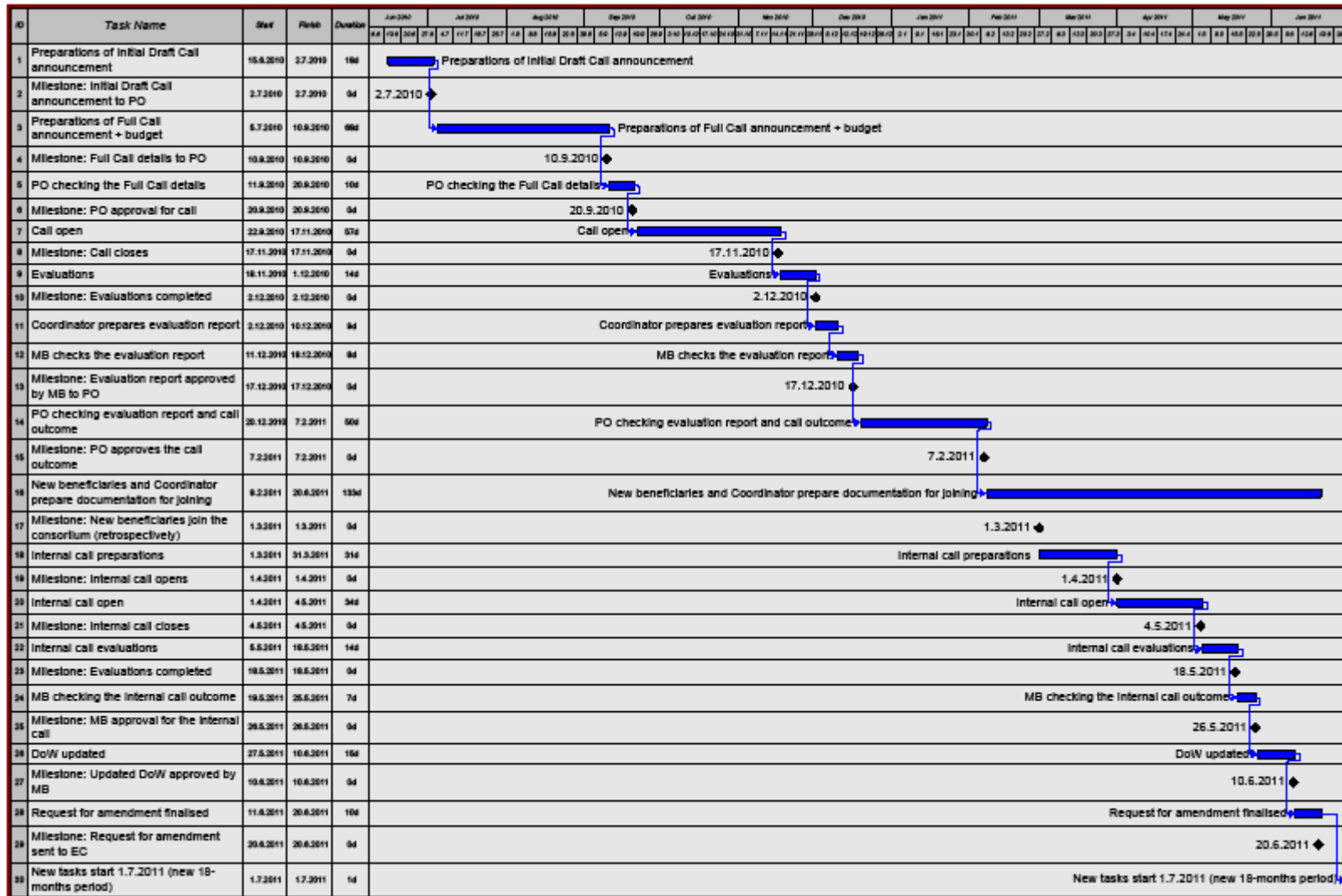


Figure 5. MELODI platform and DoReMi Network of Excellence complement each other.

Gantt chart 1: Sequence of steps for the implementation of competitive calls and linked internal calls



4 Transitional Research Agenda

4.1 Basic Research Issues

For individuals and human populations, exposures to ionizing radiation (IR) are unavoidable. With rare exceptions (e.g. the Hiroshima and Nagasaki atomic bombings, Chernobyl...), human exposures to IR are mostly due to natural radiation (radon, terrestrial and cosmic radiations), medical (diagnosis and therapy) and/or industrial activities (nuclear power plants etc.). Reports on the occurrence of cancers due to occupational exposures and due to environmental contamination such as that from the production of plutonium for nuclear weapons have alerted the public that not only exposures to high doses but also exposures to lower dose radiation may be harmful and cause human health risks. As already pointed out by the High Level Expert Group (HLEG), the risks from high IR doses are already well established, whereas this is not the case for low IR doses where still many uncertainties exist.

As far as the research themes are concerned, in recent years, it has been shown that radiation effects can be observed in living systems already at low (100 mGy) and very low (<10 mGy) doses and dose rates (< 100 mGy/h) of low LET radiation. For high LET radiations, dose and dose-rates of interest are clearly lower, e.g. for alpha radiation by an order of magnitude. It is as yet unclear to what extent these effects are detrimental to health and related to defined pathologies in animals or human beings. Furthermore, radiation qualities as well as environmental, developmental and genetic factors serve to modulate short and long term health impact of such exposures.

Epidemiological studies are to varying extents limited by their statistical power to evaluate human health risks at radiation doses much below 100 mSv. Studies of the fundamental mechanisms involved in biologically relevant low dose responses and appropriate model systems are thus necessary to address existing uncertainties, to get a better understanding of low dose radiation effects and to define potential human health risks of low radiation exposures. For radiation protection and societal purposes, it will be of particular importance to define any possible borderlines between non pathological and pathological radiation responses.

DoReMi (in line with MELODI) intends to put special emphasis on **integrated** and well coordinated studies combining mechanistic (molecular, cellular *in vitro* and *in vivo*), human health related (epidemiological) and mathematical modelling approaches. In the long run, the systems biology as well as the molecular epidemiology approach are recognized as important factors of integration in the DoReMi project but also to promote radiation protection issues.

4.2 The response of DoReMi to the 6 key research issues identified by HLEG

Three scientific work packages (WP5, WP6 and WP7) have been established in DoReMi in order to address the key research areas (shape of dose response, individual sensitivities, non-cancer effects) and cross cutting issues identified (radiation quality, internal emitters and tissue sensitivity) by HLEG (see Introduction). In addition, two work packages treat the related issues of education and training (WP3) and infrastructures (WP4). The objectives and actual tasks of each WP have been described in DoReMi Annex I.

Obviously, in the time-frame allotted DoReMi cannot cope with all important low dose research issues at the same time. Thus, the TRA of DoReMi should be taken as an important starting point attempting to outline the most urgent and the most feasible research lines to be considered to obtain relevant results and further scientific progress in this research domain and also to scope new calls directly supporting multidisciplinary and integrated low dose research in Europe. Regular updating of the TRA (at least every 18 months) will ensure effective evolution of the projected research lines, reconsideration of projected time schedules, inclusion of new forthcoming approaches and adjustments to incorporate significant research developments.

4.2.1 Shape of dose response and tissue sensitivities for cancer (WP5)

From the outset DoReMi WP5 was established to address the scientific question: What is the general shape of the dose-response for radiation-induced cancer and to what extent do dose response relationships depend upon tissue (tumour) type? To answer this question the main aims can be defined as the following:

1. To improve knowledge of low dose cancer risk in humans
2. To improve risk projection models based on knowledge of processes that drive carcinogenesis.

The current approach used in radiation protection holds that (1) Risk estimates are firmly based on human population studies which provide evidence of cancer risk after acute exposure with doses in the order of 100 mSv (effective dose, A-bomb survivor studies) and at 10mSv *in utero* (UK *in utero* diagnostic radiation/childhood cancer studies) (2) cancer risks follow a linear relationship with dose and the mechanisms involved are at all doses similar (3) there are no thresholds below which the linear assumption no longer holds (4) weighing factors (w_R and w_T values) are employed to estimate effects of doses of different radiations to different tissues (5) dose-rate effects are approximately taken into account by application of the dose and dose-rate effectiveness factor (DDREF with a value of 2 as currently recommended by ICRP), (6) the impact of non-targeted effects if they operate will be incorporated into epidemiologically based risk estimates. Although there is now epidemiological evidence for an increase in cancer risk after low-dose-rate exposures with doses in the order of 100 mSv, the dependence of the risk on cancer site and type, age at exposure, age attained, dose, dose rate and other factors remains unclear. Further, among humans compelling direct evidence is missing for the assumptions (2)-(6) made for radiation protection.

As already pointed out by the HLEG group, the question is whether the actual scientific basis of these radiation protection issues can be improved by decreasing existing uncertainties through a better understanding of the mechanisms involved.

To achieve the above mentioned aims, a profound understanding of the biophysical interactions of radiation with biological targets, molecular mechanisms of carcinogenesis in humans (including proteomic, metabolomic, physiological responses that can be combined in systems biology approaches) and intra- and intercellular signalling mechanisms as well as the role of specific cell types (including stem cells) and the influence of genetic variability and predisposition (see WP6) is essential. Knowledge of the molecular mechanisms involved and the corresponding development of suitable biomarkers should also provide a new and more solid basis for interpreting low dose epidemiological data.

Defined animal models should allow confirmation of the relevance of these molecular approaches at the level of whole organisms.

The following **priorities concerning research on the shape of dose-response curve for cancer** have been identified and included in the WP5 work plan:

1. In order to get an answer to the question “are processes underlying or contributing to radiation-induced carcinogenesis uniform over the entire dose range” an examination of cellular stress responses in fibroblasts and stem cells and possible phase shifts in responses (or non-linear responses) over a wide dose range has been initiated (WP 5 Task 5.1). We can foresee that this task could be extended to include new endpoints all of which require a rationale for contributing to carcinogenesis in humans and also to consider high-LET radiation/radiation quality dependence.
2. To find out whether non-targeted and systemic processes (inflammation, immune function) contribute to radiation-induced carcinogenesis, non-targeted phenomena are foreseen to be examined in cellular 3-D tissue and in vivo models (WP5 Task 5.2). Initial activity focuses on discussion and consideration of NOTE outputs and conclusions. An external call to establish research activity in this area more firmly in the network is foreseen after a workshop planned for June 2010 to identify the priorities. Studies on immune response and inflammation will be of relevance to WP7 also.
3. In order to provide quantitative data to develop and test biologically realistic mathematical models of risk projection, studies of pre-neoplastic development have been started. These studies aim to identify the key events that convert normal cells into tumour cells, initially using a mouse model of radiation leukaemogenesis (WP 5 Task 5.3). Future work on a solid cancer system is anticipated along with continuation of leukaemia studies. Such work may also be expected to identify potential biomarkers of exposure, risk or susceptibility (see WP6) that could be of use in future molecular/biomarker epidemiological studies (see WP6 Task 6.1)
4. To prepare integration of mechanistic studies in the evaluation of epidemiological data, in Task 5.4 feasibility studies are being performed on intercellular communication, lung cancer after incorporation of alpha emitters and the analysis of data from the UK National Registry on Radiation Workers with models of carcinogenesis.
5. To assess the health risk from internal emitters on the basis of a combination of epidemiological and experimental approaches (WP5 Task 5.5). Similar to task 5.2 initial work will focus on discussions to establish the best design and approach of

such a study, followed by a call in 2011 to bring the required expertise and resources into the NOE.

Anticipated additions to the WP5 work plan

Some of the tasks already underway anticipate the need to include new resources and areas of expertise into DoReMi, especially in tasks 5.2 and 5.5. But there is likely to be a sound rationale for expanding and developing all tasks 5.1-5.5

In addition three areas ripe for development within the timeframe of DoReMi have been identified:

1. In order to investigate the likely important role of stem cells in carcinogenesis the mechanisms of radiation responses of various types of stem cells is foreseen as a timely and important development.
2. In order to answer the question whether specific DNA damages (types and distribution of damages) and cellular responses (intra- and intercellular signaling, genetic and physiological responses) are induced by radiations of different qualities there is a need to examine the particular biophysical interactions of radiation with cellular targets, the induction and processing/repair of damage involved at different dose levels and dose-rates in human cells possibly differing in genetic cancer predisposition and repair capacity (see WP6). Workshops are planned to give these two issues (radiation quality and cancer predisposition) more detailed consideration before defining the topic for a call and most appropriate endpoints and biological systems to employ.
3. Integrated studies can already be anticipated in the 100 mSv order of dose including measurements of genomic instability in members of large radioepidemiological cohorts and integration of the mechanistic results in models of carcinogenesis for the evaluation of organ/tissue specific cancer mortality or incidence in these cohorts. This is likely to be funded through the recent EC EURATOM call through the EpiRadBio project, and if such funding is secured DoReMi will seek to enter into a Memorandum of Understanding with EpiRadBio.

The main goal of this WP is thus to improve knowledge on low dose/low dose-rate cancer risk in humans and low dose/low dose rate risk projection models, also as a function of radiation quality, based on knowledge of the mechanisms and processes that drive radiation-induced carcinogenesis.

Longer term developments

It is of course more difficult to predict longer term developments and so anticipate future research directions. However, DoReMi partners have identified the following as being strong candidates for future multidisciplinary research initiatives:

1. Much experimental work has the potential to identify novel biomarkers of radiation exposure or effect (cancer risk). Consideration needs to be given to establishing suitability powered molecular/biomarker epidemiological studies to establish the value of these markers. A future large study can be envisaged that incorporates:
 - a high standard of radiation dosimetry
 - a high degree of attributability of cancers observed to radiation
 - appropriate and ethical sampling and storage of biological materials.

In principle, improved quantitative biomarkers of radiation exposure could be of value in providing sufficiently robust dosimetry in existing cohorts where reliable dosimetric data are not available. In addition to biomarker approaches the application of recent and developing 'Next generation' (or 'deep') sequencing methods is predicted to be valuable. These approaches could reveal signatures of radiation exposure (and even attributability) that would be of tremendous value in future studies and approaches.

2. Further understanding of stem cell biology and the ability to reprogram cells is likely to impact on future priorities. This area should be kept under review.
3. Advances in imaging at the cellular, molecular and atomic scale could provide powerful new tools to study, inter alia, DNA and cellular lesions directly, damage response processes in real time, genetic, epigenetic factors and other events (stem cell differentiation.etc.) that drive radiation tumorigenesis in real time *in vivo*. All such technical advances have the potential to move radiation cancer risk research forward significantly. Again these areas should be kept under review and appropriate applications considered.

4. Integration of systems biology in models of carcinogenesis to evaluate radioepidemiological data on cancer in order to achieve an extrapolation of risk assessment to doses in the order of 10 mSv.

4.2.2 *Individual variability in cancer risk (WP6)*

WP6 was set up in DoReMi to find answers, taking into account the results of WP7 concerning non-cancer effects, to the question “Does individual variability significantly affect low dose radiation and radiation quality responses such as the induction of cancer and non-cancer diseases?” To achieve this it is thought that a profound molecular inventory of genes and proteins is needed that are influencing low dose radiation responses, and, in particular, radiation sensitivity, radiation-induced cancers and non-cancerous diseases. In this way, also mechanisms and factors involved in one or the other phenomenon may be identified. Intimate knowledge on genes and genetic polymorphisms (i.e. DNA repair genes, cell cycle checkpoint genes, oncogenes, genes controlling DNA and general metabolism, hormonal and immune responses etc.) should help to define their role in low dose radiation responses. Relevant genes and polymorphisms identified can be employed in newly designed epidemiological studies (with access to biological, i.e. blood, tissue samples) to define sensitive subpopulations in the cohort and possible specific effects of confounding factors (sex, age, lifestyle, reproductive factors, concomitant exposure to chemical and different types of physical agents, and other factors affecting the response (age, gender, radiation quality). In line with this line of research, new genes and polymorphisms have been recently described that are related to cancer predisposition and/or radiation sensitivity (and this may also apply to non-cancer diseases).

Furthermore, it is the aim of WP6 to explore the question “What is the importance of individual radiation sensitivity for acute versus chronic or fractionated radiation exposures with regard to the induction of carcinogenic or non-cancer effects?” For this latter research line, defined animal models should allow confirmation of the relevance of these molecular approaches on the level of whole organisms.

The main goal is thus to quantify how the sensitivity of individuals to (late) health effects depends on gender, age, genetic and epigenetic factors, lifestyle and co-exposures to other agents. The use of suitable biomarkers in molecular epidemiological studies could help to

determine different types of exposures (radiation, chemicals..). Better knowledge on this should allow better protection of particular subgroups in the general population.

The following priorities concerning research on the individual variability in cancer were so far identified to be realized in WP6:

1. In order to respond to anxiety and questioning in the general population concerning low dose radiation effects for the development of cancer and non-cancer diseases molecular epidemiological studies (such as a prospective children CT scan cohort or another diagnostic related cohort such as mammography) are going to be designed. This may involve close interaction with other European projects. The launching of such prospective lifetime studies will allow assessing long term risks. The design of such cohorts may include lifetime risk assessments from working places, imaging devices and natural radiation sources together with access to full health evaluation and health records and may be taken over in the long run by MELODI directed projects. The cohorts are meant to include parameters such as the induction of cancer and non-cancer diseases, radiation quality and several confounders and modifiers. The suitable follow up of other already existing or reconstituted cohorts (uranium miners, Mayak cohort, and nuclear workers) is considered as well (WP6 Task 6.1). (For non-cancer effects see also WP7)
2. The Chernobyl accident revealed an extreme sensitivity of children for the development of radiation-induced thyroid cancers. In order to get a better understanding of the radiation-induced thyroid cancers in relation to individual susceptibility (radiation sensitivity) the mechanism of thyroid cancer induction is foreseen to be studied with suitable mouse models. This analysis does include the identification of modifier genes by classical linkage analysis, high throughput analysis (mRNA, miRNA, protein, metabolites) in appropriate in-vitro multicellular models of radiation responses 4 and 24/48 hrs after exposure. As a complementary approach, the radiation response of human cell model systems with variants in genes that have been associated with varying degrees of IR sensitivity will be studied (WP6 Task 2).
3. In order to assess the importance of individual human variability in radiation responses it is foreseen to select appropriate epidemiological cohorts for modeling individual radiation responses. Knowing that for risk estimates genetic modifiers are likely to play an important role it is foreseen to explore low dose rate effects using

well-defined mouse models for radiation-induced osteosarcomagenesis (Rb1), mammary tumors (APs) (involving interaction with Euratom WP 2010) and medulloblastoma (Ptch1) (WP6 Task 4). (For this, the availability of suitable low dose rate facilities in Europe is crucial and some of this work will rely on collaborations with infrastructures outside Europe (Canada, Japan) until WP4 has put into place a genuine European facility for this).

4. Recent work in fundamental research revealed that also epigenetic mechanisms may contribute to the development of cancer. It is thus foreseen to examine RI induced cancer susceptibility not only from the genetic point of view but also from the point of view regarding the contribution of more specific epigenetic factors (for example, those interfering with DNA repair and chromatin restructuring) This will also include aspects of mathematical modeling (WP6 Task 5).

Anticipated additions to the WP6 work plan

It is planned to model radiosensitivity for cancer and non-cancer predisposition in mice taking into account radiation quality and the effects of dose and dose-rate (Task 6.3). Cancers are generally clonal in nature and so single cell level events must contribute. Cellular aging and its epigenetic modifications may contribute to the penetrance of radiation-induced mutations. It is proposed to examine IR induced cancer susceptibility according to individual variation in cellular aging and epigenetic modifications (for example telomere maintenance, histone marks, DNA damage signalling).

1. In order to answer the question whether specific genetic factors influence individual susceptibility to low dose radiation- induced cancers a pilot study is foreseen consisting of a well-designed molecular epidemiological study (WP6 Task 6).
2. In order to answer the question whether an individual susceptibility exists also for IR induced non-cancer diseases it is foreseen to develop specific models to analyze low dose radiation-induced non- cancer pathologies such as cataract formation, neurological and cardiovascular disorders (in collaboration with WP 5 and 7).

The possible openings and future perspectives of this work are expected to include the integration of genomic and epigenetic processes relevant for carcinogenesis in the evaluation of organ/tissue specific cancer mortality or incidence in large and good-quality

radioepidemiological cohorts with information on physiological parameters (e.g., hypertension, obesity), reproductive factors (e.g., number of children, age at first birth of children), familial predisposition (e.g., cancer among parents and siblings), or lifestyle (e.g., smoking and alcohol consumption).

4.2.3 *Non-cancer diseases (WP7)*

WP7 in DoReMi has been designed with the aim to find answers to the following questions:

1. What is the biological impact of different radiation qualities and radiation dose levels in terms of the perturbation of homeostasis and induction of pathological non-cancer effects (cardio and cerebrovascular diseases, neurological and cognitive effects, lens opacities)?
2. What is the importance of acute versus chronic or fractionated radiation exposures for non-cancer effects?
3. What is the molecular basis to expect that low dose radiation can cause or modulate pathological, non-cancer effects?
4. Can molecular alterations of cellular homeostasis, redox potential and energy metabolism induced by low dose radiation induce or promote non-cancerous diseases?

To achieve this, an extensive knowledge of the molecular alterations and behavioural changes of disease-relevant cell types (epithelial cells, cells of the central nervous system, and specific types of stem cells...) after ionizing radiation exposure is needed. It is likely that oxidative damage (and, to a minor extent, genetic damage) will play a role. As in the case of cancer, transcriptomic, proteomic, metabolomic changes at the cellular, tissue, organ and population level will probably allow to relate radiation-induced molecular changes to pathological effects, and to develop relevant biomarkers. Research using already available biomarkers for the detection of radiation-induced metabolic and physiological changes as well as the detection of alterations in intra-and intercellular signalling may be a good starting point.

Recently, several metabolic networks have been described by systems biology approaches able to explain specific disease responses. In most cases, low dose radiation responses have not yet been explored in these systems.

Stimulated by recent epidemiological findings, the main goal of this work is to analyze the impacts of low doses of radiation on the occurrence of a variety of non-cancer effects such as circulatory diseases, cognitive dysfunctions or lens opacities etc.

The following **priorities concerning research on non-cancer effects** have been identified to be realized in the context of WP7:

It is recognized that among the non-cancer effects three are of outmost importance and will be explored as a first priority: vascular effects, cognitive effects, lens opacities (cataracts). Accordingly, the WP7 Task 7.1 work plan has foreseen three respective hearing meetings at month 12, month 18 and month 24 that are expected to serve for the preparation of further calls and the launching of RTD projects.

1. Vascular effects: in order to investigate the role of (low dose) ionizing radiation in the development of vascular diseases, epidemiological as well as fundamental studies are needed. The epidemiological studies will focus on the determination of a possible threshold or if a LNT relationship with dose exists and the importance of radiation quality for vascular diseases. Clinical and fundamental studies will try to elucidate the nature of vascular diseases as a function of radiation dose, the mechanisms of tissue and inflammatory responses, the involvement of cellular signaling and senescence, and the role of endothelial, smooth muscle cells and bone marrow progenitor cells and stem cells. From the start, in DoReMi, emphasis will be put on molecular epidemiological studies on vascular radiation damages (Task WP7.2) (see for example, the CT children project). A systems biology approach based on high throughput 'proteomic' technology will be used to get mechanistic insights in the radiation response of the endothelium after acute and chronic exposure including internal contamination with radio-nuclides (Task WP7.3). Also, modelling studies to investigate the effects of low doses of ionising radiation on the formation of cardiovascular and cerebrovascular diseases and study the related dose-response curves will be performed.
2. Cognitive effects: ionizing radiations are known to affect neurogenesis of the hippocampus and hippocampus-dependent learning and memory processes and thus can cause cognitive impairment, neuro-inflammation, alterations in brain electrical activity and neuro-chemical responses, and disruption of the blood brain barrier. It is felt that more knowledge on the molecular mechanisms of cognitive effects

following acute and chronic radiation exposures is needed. Thus, research on brain and spinal cord radiotoxicity from chronic gamma-radiation or internal emitters will first be undertaken exploring the possible mechanisms involved (oxidative stress, alterations in neurotransmission and neuromodulation). The different pathways of radionuclide entry to the brain will be also explored, such as a possible olfactory pathway. The use of high throughput techniques proteomics and gene expression data are expected to yield important information for the identification of relevant biomarkers that may be useful in future molecular epidemiological studies (Task WP 7.5).

3. Lens opacities (cataracts): ionizing radiations are generally although not exclusively associated with cortical and posterior sub capsular opacities. Recent data sets indicate that cataract formation occurs after relatively low doses of ionizing radiation, and that there is a threshold probably below 1 Gy. Thus, it is felt that a follow-up of the major cohorts is needed to better evaluate latency and cataract progression issues and to better characterize risk at low doses to the lens. In this situation, an epidemiological study on interventional radiologists who are chronically exposed to ionizing radiation to >150 mSv per year and an unexposed control group is expected to be useful (Task WP7.4). Of course, also mechanistic studies on the involvement of DNA damage, protein-cross linking and disruption of membrane channels and ion pumps as well as the importance of genetic components such as Rad9 and ATM in radiation-induced cataractogenesis need to be launched as well. These will be probably further specified after the WP7 hearing meeting on lens opacities in 2012 (month 24).

Anticipated additions to the WP7 work plan

The experimental approaches will rely on existing and the development of suitable irradiation and contamination facilities for chronic and protracted low dose exposure of cells and rodents with different types of radiation quality (see WP4). Furthermore, in addition to the existing platforms of high throughput “omics” technologies genomics and proteomics for vascular effects, there will be a need for a metabolomic platform concerning vascular and cognitive effects. Moreover, the set-up of an in vitro model for the study of the differentiation of epithelial lens cells (according to the Blakely model) is highly desirable. The use of a suitable

imaging platform to follow low dose radiation effects (vascular, cognitive effects and evolving lens opacities) can be anticipated.

Suitable cohorts for classical and molecular epidemiological studies have to be sought that allow to study low dose groups from <5 Gy down to <100 mGy. Medical cohorts with whole body or partial body exposure will be useful because of good dosimetry data.

The importance of confounding factors including lifestyle and environmental risk factors such as cigarette smoking, alcohol consumption, other dietary factors (cholesterol levels, diabetes, BMI etc.) for this type of cohort has to be stressed. It will be desirable to use morbidity rather than mortality registers because of the more accurate diagnostic information. The possibility to gather adventitiously blood samples for genotyping, exploration of the inflammation and general biomarker assays could serve to find convenient markers for radiation etiology and age related effects.

Cohorts for studying circulatory diseases such as A-bomb survivors, Mayak and Chernobyl populations and others may be used for advanced follow-up studies.

Experimental studies on lens opacities are likely to be extended in order to investigate the whole network of signaling (for example, ATM, RAD9) and repair proteins (for example, BRCA1) and its involvement in the formation of lens opacities. Moreover, studies on radiation-induced molecular changes and mechanisms involved in the response of epithelial lens cells acute and chronic exposure to low and high LET radiations will have to be undertaken. Depending on the mechanistic insights obtained and the identification of suitable biomarkers, appropriate molecular epidemiological studies have to be put into place.

An obvious long term future evolution for all three research issues concerns the further development of suitable cellular and animal models, research on senescence, stem cells research, molecular and cellular in vivo imaging, molecular physiopathology, analytical and molecular epidemiology as well as modeling, computational biology and systems radiobiology.

4.2.4 Radiation quality (cross-cutting issue)

Three important cross-cutting issues, (tissue sensitivities, internal emitters and radiation quality), were identified by the HLEG group and constitute an essential part of the Joint Programme of Research of DoReMi. They were defined as “cross-cutting” because they have implications for all categories of radiation risk, and therefore must be addressed in a coordinated way across each of the 3 scientific workpackages. In particular there is a need for dedicated studies on the mechanisms of the biological response to radiation at low doses and dose rates (modelling different radiation qualities, inhomogeneous distributions from internal emitters, different tissue types, etc) to be integrated with the experimental and epidemiological studies in the scientific workpackages.

For a better understanding of the role of radiation quality in carcinogenesis and non-cancer diseases experimental and theoretical mechanistic studies are needed on radiation-quality dependence of the relevant end points, starting from track structure and physical interactions with various biological “targets”. A critical question is how radiation quality affects the initial damage (DNA and non-DNA) and its evolution with time (considering both faithful repair and misrepair processes), the intra- and intercellular signalling, and in general non-DNA-targeted effects. A deeper understanding is necessary on the relevance in chromosome aberration, mutation induction and carcinogenesis of clustered DNA damage induced by a single track. Also the possible role of dose-rate should be better understood, together with the mixed field effects (including possible synergistic and adaptive phenomena).

Topics related to radiation quality have been addressed explicitly in WP7:

- To investigate the influence of dose rate and of radiation quality on the inflammatory response, an integrated approach, from cells studies to mathematical modelling, is planned as a feasibility study in task 7.3. Also, some radiation quality issues are addressed in WP5.4 and WP5.5.
- A call is foreseen for understanding the contribution of individual genetic variation including studies of different cell types and tissues, effects of age and of radiation quality (task 6.2)

Anticipated additions of radiation quality issue to WP5, WP6 and WP7:

1. Partially from 4.2.1 (WP5): In order to answer the question whether specific DNA damages and cellular responses are induced by radiations of different qualities there is a need to examine the particular biophysical interactions of radiation with cellular targets, the induction and repair of damage involved at different dose levels and dose-rates in human cells of different origin (also related to WP6 and 7).
2. For a better understanding of the contribution of individual genetic variability on cancer development a call is foreseen in 2012, taking into account studies on different cell types and tissues, effects on age and radiation quality (see task 6.2)
3. From (WP 6): in order to clarify if individual sensitivity for cancer and non-cancer effects is influenced by radiation quality, dose and dose-rate, it is planned to model individual radiosensitivity

Quite a few other topics need to be addressed, implying expansion of the existing tasks in the three scientific workpackages and the corresponding allocation of new resources:

1. Mechanistic (experimental and modelling) studies on the relationship between early physical/chemical/biological processes, as a function of radiation quality, and pathological effects (cancer and non-cancer)
2. A better evaluation of radiation quality influence on inflammatory response in cells and animal model.
3. Determination of the effects of mixed fields, for both cancer and non-cancer effects, and of the criteria to predict biological effects need further investigation. These studies include consideration of the role of dose/fluence rates, of the role of time sequence in the effects of exposure to different radiation types, and of the conditions that might produce synergistic/additive phenomena or adaptive responses.

DoReMi partners have identified longer term developments that may include:

1. Even more closely integrated studies between experimental and theoretical approach with the aim of a “complete” understanding of the mechanisms related to low dose, low dose-rate, and radiation quality effects
2. Microbeam (with low and high LET radiation) facility coupled with in vivo imaging to analyze a single cell knowing exactly the irradiation it has undergone
3. A more systematic development of a systems biology approach. This should include a full consideration of radiation quality.

4.2.5 *Internal versus external exposure (cross cutting issue)*

It is obvious that contaminations with internal emitters are distinct from external exposures by differences in dose distribution, exposure duration (chronic versus acute or fractionated or low dose rate radiation exposure) and by the fact that internal contamination with radioactive isotopes of heavy metals (eg. uranium) often exhibit an important additional chemical toxicity in cells, tissues and organs. Thus, dosimetric and chemical issues are of particular importance and need to be concomitantly studied.

Topics related to internal versus external exposure have been addressed in WP 5 and 7:

1. To further examine the effect of dose rate for α -particle lung cancer induction an epidemiological study is foreseen as second step in task 5.4
2. To assess the risk from internal exposure a multidisciplinary collaboration is foreseen in task 5.5
3. To determine if neurogenesis is differently affected by external versus internal exposure, a feasibility study is planned in task 7.5

Anticipated addition to internal versus external exposure study:

- The macroscopic distribution and biokinetics of radionuclides within tissues and organs are generally well known, but the microscopic distribution at the cellular level and dependence on molecular and chemical forms need further study. Mechanistic studies are needed on the effects of different microscopic radionuclide distributions on the energy deposition within cells from short-range emissions (alpha particles, low energy beta particles (as from tritium), Auger electrons, very low energy photons, etc.).
- Studies on factors that influence the uptake and retention of radionuclides and concentrations and distributions at the microscopic level.
- A combined epidemiological and experimental study of internal emitter risk is planned to extend task 5.5 through competitive calls.

4.2.6 *Tissue sensitivity (cross cutting issue)*

It is established that different tissues (or organs) of the body have different sensitivities for the induction of cancer by radiation. This is reflected in the use of tissue weighting factors in the current system of radiation protection (ICRP 2007). The biological bases of these recognised

differences, e.g. between different solid tissues, are not well understood and current judgements are largely based upon empirical epidemiological observations after relatively high dose acute exposures to low-LET radiation. Epidemiological studies of sufficient power should be able to yield more information on these tissue sensitivities and the potential for modification by dose, dose-rate, radiation type, gender and age.

Topics related to tissue sensitivity have been addressed in WP5:

1. Several different cancer (tissue) endpoints are included in the currently implemented workplan. For example myeloid leukaemia (task 5.2), lung cancer (task 5.4), thyroid cancer (task 6.2), bone and brain cancer (task 6.4).
2. Planned epidemiological studies will follow cancers at a number of sites. Therefore a wide range of tissues are under consideration.

Longer term issues might include:

1. Meta-analysis studies of epidemiological data to consider issues of tissue specific risk
2. Mechanistic studies (experimental, modelling etc.) on different tissue types to investigate the reasons behind different sensitivities to radiation.

5 Training and education to support the TRA (WP3)

Workpackage 3 will provide a coordinating centre for networking training institutions/facilities, and generating training and education initiatives. Through an advisory Training and Education Committee it will be continuously responsive to the needs of the low-dose research community, and policies will evolve with in parallel with any new directions taken by the TRA. Key elements of the planned work programme are:

1. Formation of an advisory Training and Education Committee (TEC) to set priorities and propose new training and education initiatives;
2. Creation of a web-based database and information resource for the facilitation of networking, and the promotion of new courses and funding opportunities;
3. Open calls for training modules of 1-2 weeks at the MSc or PhD level to be offered in topics identified by the TEC by institutions that have special expertise and research programmes in the relevant areas;

4. Open call for a university to develop and host a multi-disciplinary, multi-national Bologna-accredited MSc course. This would target high-level graduate students from both the physical and biological sciences, and would provide a valuable supply of career research scientists in the field.
5. Continuous calls for ad hoc workshops and one-off specialist courses. These would be offered on a responsive basis when there is a perceived need to facilitate access to new scientific methodology, or infrastructure. They should also include a training and/or Network workshop dedicated to enhance integration and sustainability.

In the longer term the centre will need to become incorporated into the MELODI structure, and achieve sustainable funding.

6 Infrastructures to support the TRA (WP4)

Infrastructures are essential in order to fulfil low dose risk research objectives. Many types of facilities are required ranging from radiation facilities like large accelerators to data bases, human cohorts, tissue banks and platforms for sample analysis.

The first priority is to produce a review of the current status of infrastructures for radiobiology in Europe.

External radiation facilities:

- > Facilities providing low dose and dose rate gamma and neutron irradiations;
- > Specialized facilities such as charged particle beams, synchrotrons;
- > Microbeams for low dose research.

Internal irradiation facilities:

Available facilities investigating the effects of internal radioisotopes, especially with respect to animal experiments, taking into account that some of them are at high risk to be dismantled in the next future.

Data bases and tissue banks:

Many of them exist although rather dispersed, heterogeneous and frequently dormant. Indeed an optimal utilisation of the banks and access to data and material would need 1) a survey of

the “existing” 2) a characterization of the quality of the samples 3) a validation of their storage condition 4) open/restricted accessibility. The European project STORE (Sustaining access to Tissues and data frOm Radiobiological Experiments) funded by the European Commission in the framework of the 7th EURATOM Framework Programme (7FP) is already engaged in a short term programme that mainly concerns tissue and data banking for animal radiation experiments. DoReMi WP4 will interact with STORE in order to reinforce and promote tissue and data banking from human radiation studies and to seek together with DoReMi WP2 longer term sustainability.

Epidemiological cohorts:

There are a number of existing epidemiological cohorts that have the potential to constitute a key infrastructure for low dose risk research. The key cohorts will be identified

Platforms for analysis:

Most of those platforms are not dedicated to radiobiology but many of them exist. Accessibility to low dose risk researchers remain to be improved. Information related to these infrastructures will be made available on the public NoE website. Cartography of accurate infrastructures with open access will be performed.

The second priority is to define the future needs in each of the above areas in order to achieve the TRA goals. Should new kind of shared facilities emerge, working groups will studied those requests in order to identify which facilities are needed by several European partners and how DoReMi and Melodi could facilitate their implementations

The third priority is to implement the support and accessibility to infrastructures that will be performed within the NoE and those within MELODI (in collaboration with WP2 and to define and to envisage adapted ways of financing. Portal and tools will be implemented on public website in order to facilitate access to the infrastructure requested for low dose research for each lab (in or out radiation research field).

7 Roadmap

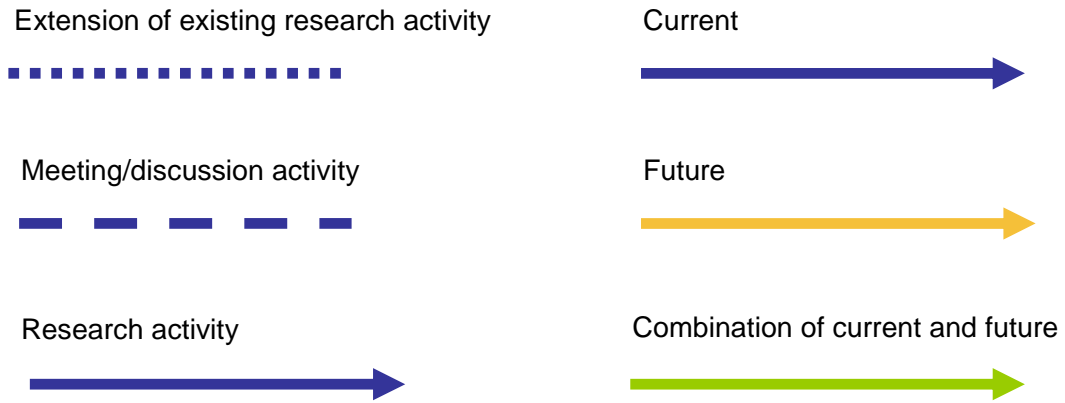
The roadmap defines the projected progression of each research line in time and indicates the possible input from other outside research domains and new partners. The roadmap is an important requisite for projecting future internal and external calls (time schedules) in low dose radiation research. It helps to set time schedules and call plans.

Table 4. Scientific discoveries and technological innovations that pave the way to understanding of radiation effects - and vice versa

	Past	Recent and present	Future
Scientific discoveries and key disciplines	X-rays, radioactive decay physics and biophysics genetic effects DNA helix DNA repair molecular biology oncogenes and tumour suppressor genes	sequencing human genome: less genes than proteins non-targeted effects intra- and intercellular signalling tissue responses single nucleotide polymorphisms epigenetics	molecular epidemiology systems biology stem cells; reprogramming of cells synthetic biology
Technological innovations	therapeutic applications dosimetry cell culturing computers	microbeams IT technologies molecular imaging omics, high throughput analysis bioinformatics	whole genome chips high throughput sequencing live cell imaging tissue scaffolding, culturing of organs

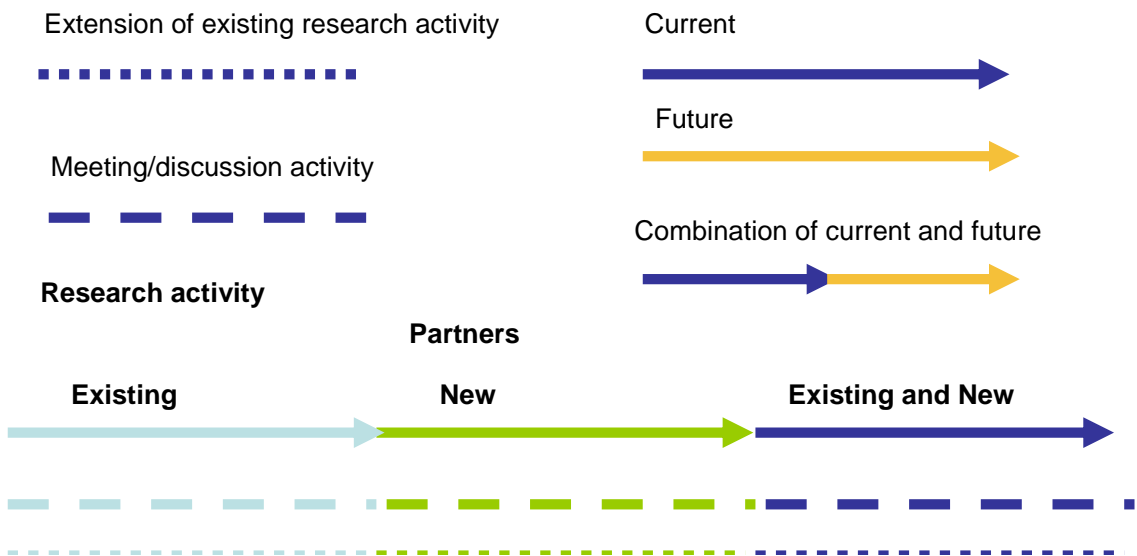
WP5: TRA Shape of Dose-Response Curve for cancer

Key



WP5: TRA Shape of Dose-Response Curve for cancer

Key



WP5: TRA Shape of Dose-Response Curve for cancer

Mechanistic studies (1)

Task 5.1 Phase shifts in responses at high/low doses



Task 5.2 Assessing the contribution of non-targeted and system effects



Task 5.3 Dynamics of pre-neoplastic change - AML



Task 5.3 Dynamics of pre-neoplastic change - solid cancers



WP5: TRA Shape of Dose-Response Curve for cancer

Mechanistic studies (2)

Task 5.4 Mathematical models to link experiments and epidemiology:



Task 5.5: Assessing the risk from internal exposures



Anticipated new Task 5.? Stem cell radiobiology



Anticipated new Task 5.? DNA lesion distribution/damage/rrepair at low doses



WP6: TRA Individual variability (1)

Classical and Molecular Epidemiology (6.1)

Design of molecular epidemiology cohort studies

Prospective CT scan cohort (lifetime study?)



Epidemiological studies:

Cancer (uranium miners, Mayak cohort)
 Non cancer (uranium miners, Mayak cohort)
 Radiation quality
 Confounders & modifiers



WP6: TRA Individual variability (2)

Mechanistic studies

Genetic susceptibility to thyroid cancer (mouse models) (Task. 6.2)



Identification of modifier genes by classical linkage analysis

High throughput analyses: mRNA, miRNA, protein, metabolites

In vitro multicellular models: responses at 4 hrs/24-48hrs

Analyses of DNA repair defects/IR sensitivity



Modeling individual human variability (Task 6.3)

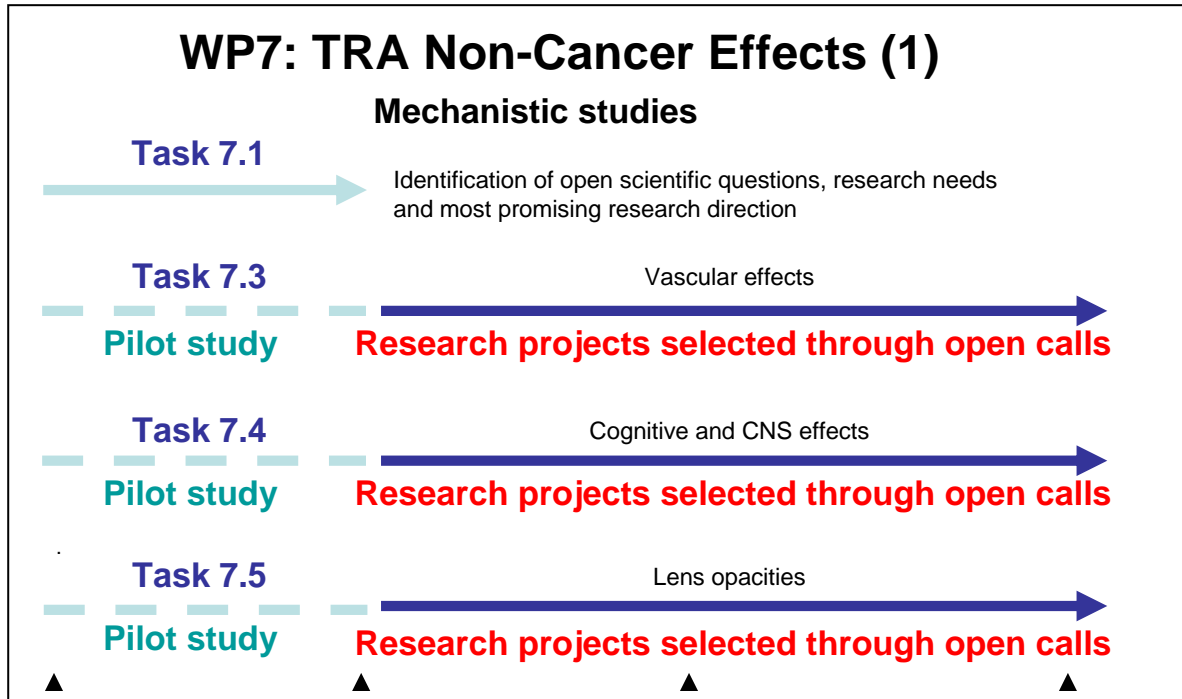


Modeling individual radiosensitivity/ cancer and non cancer predisposition in mice
 (radiation quality, dose and dose-rate dependency)

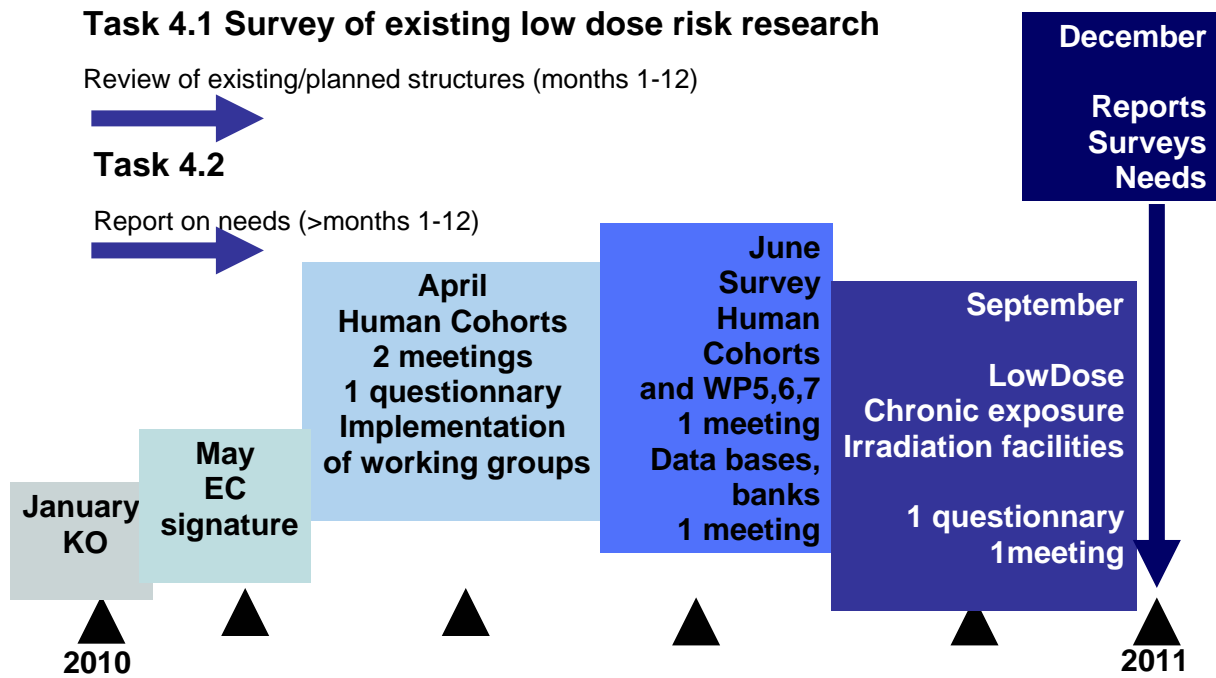


Genetic modifiers of carcinogenesis /low dose & low dose-rate effects Task 6.4)





WP4: Infrastructures (1)



WP4: Infrastructures (2)

Task 4.1 Survey of existing low dose risk research

Review of existing/planned structures (months 1-12)



Task 4.2

Report on needs (> months 1-12)



Task 4.3

Establish Roadmap for infrastructure



Task 4.4

Toolboxes for infrastructure (IS) access (month 36)



Task 4.5

Call Agenda and budget for IS access months 24 and 36)



EXECUTIVE SUMMARY

Although much is known about the quantitative effects of exposure to ionizing radiation, considerable uncertainties and divergent views remain about the health effects at low doses. Many of the European states have institutional or national research programmes in this area, however, beyond the Euratom research program, little has been done to integrate these programmes in the past. The European High Level and Expert Group (HLEG) recently recommended the establishment of a Multidisciplinary European Low Dose Research Initiative (MELODI) that would create a platform for low dose research under a jointly agreed Strategic Research Agenda (www.hleg.de; MELODI platform). The research agenda would focus on the key policy questions to be addressed and provide a road map for such research in the coming years and decades.

In 2010, a Network of Excellence called DoReMi was launched by the Euratom FP7 program. DoReMi will act as an operational tool for the development of the MELODI platform over six years, 2010-2015. The joint program for research focuses on the areas identified by the HLEG as the most promising in terms of addressing/resolving the key policy questions, namely: the shape of dose response curve for cancer, individual susceptibilities and non-cancer effects. Radiation quality, tissue sensitivities and internal exposures will be addressed as cross cutting themes within the three main research areas.

One of the early activities of DoReMi is to develop the Transitional Research Agenda (TRA) with a short to medium term scale, which will attempt to capture the essence of the HLEG strategy and begin its implementation. Strategic planning will be carried out in collaboration with MELODI DoReMi research priorities are thus based on the short- and mid-term Transitional Research Agenda (TRA), focusing on goals that are feasible to achieve within the 6 year project and areas where barriers need to be removed in order to proceed to the longer term strategic objectives. The long-term Strategic Research Agenda (SRA) will be developed by MELODI.

The present transitional research agenda (TRA) is the first step in the roadmap of joint European low dose risk research program. The TRA describes a methodology to identify and prioritize pertinent research lines and a way to open up low dose research to other disciplines. It describes how program priorities are set, how the research strategy will be implemented and

how the updating of the TRA will be carried out in the future. The TRA provides details and some refinement of the scientific questions addressed, the actual research issues covered and a forecast of forthcoming additional research needs. The Roadmap and a Call plan give an initial view of identified future research priorities and likely further developments.

Since epidemiological studies are limited in statistical power to assess risk at low doses it has been proposed to link these with molecular and mechanistic studies in order to get an understanding and a better definition of low dose health risks. The identification and development of suitable biomarkers should facilitate the way toward molecular epidemiology. Concerning the shape of dose response for cancer, among others, emphasis is placed on the development of molecular biomarkers that allow the detection of relevant low dose effects and the identification of cancer initiating or early events in the carcinogenic process. To achieve this, new approaches using 'omics', stem cell research, cell, 3-D tissue and suitable animal models are proposed. This work together with well designed molecular epidemiology and modelling should bring us closer to understanding radiation-induced carcinogenesis and improve the robustness of judgments on risks associated with low dose risk exposures.

Concerning the individual variability in radiation responses, the first priority is to develop suitable molecular biomarkers (genetic and epigenetic and physiological markers) allowing the identification of radiation sensitive and /or cancer prone individuals among patients medically exposed (diagnosis, low dose CT scans, mammography, out-of field effects of modulated conformational radiation therapy etc.). This will rely on the setting up of suitable cohorts. How the degree of individual variability at low dose rates can be assessed will attract special attention. Selected animal models will be used to further investigate the molecular pathways involved.

Current knowledge concerning the non cancer health effects of low dose radiation exposures is limited. The TRA thus proposes research lines that can already be envisaged on the basis of present knowledge and before getting the conclusions of the forthcoming exploratory workshops. It is clear that the first aim will be to find out which of the three research areas so far identified, cardiovascular effects, cognitive (CNS) effects and cataracts will be the most susceptible to low dose radiation. Research on possible involvement of physiological, inflammatory and immunological biomarkers is foreseen from the start. Using proteomic methodology some of these markers can be developed as markers for exposure and disease

onset and development, and thus serve to set up well-designed suitable molecular epidemiological studies (using cohorts where the physical and biological dosimetry can be easily assessed and biological samples are accessible, see for example, radiotherapeutic units, interventional cardiovascular therapy etc.). From this line of research, we can expect valuable indications on the dose dependency of these effects and whether the observed effects can be considered as stochastic and/or deterministic.

The cross-cutting issues (radiation quality, tissue sensitivity and internal emitters) are considered in all three main research lines. Some specific feasibility studies are envisaged that will guide future research activities in those domains.

It has to be recognized that DoReMi is just a starting point for most research issues and only part of the relevant research can be addressed in the initial plan. The lines of research need to be further developed by allocating resources from internal DoReMi calls and in particular open calls bringing in new expertise from diverse disciplines. The TRA includes the envisaged Roadmap and the associated Call Plan. It does also point out areas of research that should be expanded by additional funding from EC or national programmes.

The TRA is seen as a valuable tool to follow and implement recent developments in research while maintaining a focus on low dose health risk assessment. Substantial support for this work in terms of long term sustainability is expected from the SRA of the MELODI platform.