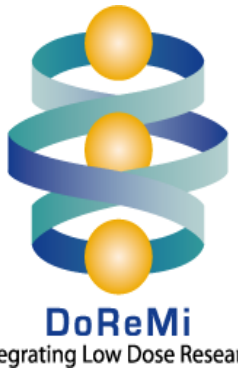


DoReMi - Low Dose Research towards Multidisciplinary Integration

TRA Statement
Version 2

Status: Publishable 6 March 2013

Table of Contents

1. Introduction and purpose of this statement

The DoReMi Network of Excellence (www.doremi-noe.net) was established on January 1st, 2010 based on principles set out in the High Level and Expert Group (HLEG) report (www.hleg.de) as an important step in the implementation of the Multidisciplinary European Low Dose Risk Research Initiative, MELODI (www.melodi-online.eu).

This statement, version 2 of the DoReMi Management Board, updates the DoReMi Transitional Research Agenda, prepared in April 2010, submitted on July 1st 2010 to the EC and published in September 2010, as well as the TRA Statement – Where are we now – published on 22 September 2011. The purpose of the TRA is to guide the planning, prioritization and facilitation of DoReMi research activities. DoReMi has been running for 36 months, held its first periodic meeting in July 4-6, 2011 and the second on 22-24 January 2013. Consequently, this revision of the original statement (version 2) provides a summary of the progress made within DoReMi and other relevant initiatives, and then uses this information to formulate our research priorities for the forthcoming 18 months. It thus serves for the DoReMi Joint Programme of Research (JPR) and also provides guidance for future internal and external calls proposed by DoReMi.

2. Progress to January 2013

The scientific work of DoReMi falls into work packages (WPs) 5-7 while capacity building is facilitated in WPs 3 and 4. DoReMi ran two successful external calls since its starting date, and as a consequence 10 new partners joined on 1 July 2011 and 10 others on 1 January 2013.

In particular, the extension and completion of competences should be noted:

As a consequence of the 1st competitive call in 2010, the following topics lead to the inclusion of:

Task 1: Non-targeted and systemic effects
- Modulation of Inflammation by low and moderate dose Ionising Radiation (ModinIR) in sub-task 5.2.1 and Task 7.6.

Task 2: Facility for low dose rate exposure
- Open Access to the UMB low dose irradiation facility (FIGARO) in Task 4.5
- Dose/Dose-rate Radiation Effects in Brain Cancer Risk (DDRE-BrainCancer) in Task 4.6

Task 3: Vascular effects
- No proposals selected under this topic

Task 4: Novel approaches
- Low-dose Gene Expression signature (LoGIC) in sub-task 5.1.1 and Task 7.7
- Predicting individual radiation sensitivity with Raman spectroscopy (PRISM) in Task 6.8

As a consequence of the internal RTD call in 2011, the following topics lead to the inclusion of:

Integration activities Task 1, Integration studies of radiation quality, with investigation of radiation induced initial events led to the inclusion of:
- Track structures and initial events: an integrated approach to assess the issue of radiation quality dependence (INITIUM) in sub-task 5.6
- Methodology implementation (ELDO) in sub-task 7.4.1;

Integration activities Task 2: Integration studies on epidemiology and low dose radiobiology:
- Integrating radiation biomarkers into epidemiology of post-Chernobyl thyroid cancer from Belarus (INT-Thyr) in Task 6.9

Infrastructures task 3: Development and utilization of Infrastructures:
- Low dose/dose rate gamma irradiation facility for in vitro biological systems (LIBIS) in task 4.7

As a consequence of the 2nd competitive call 2012, the following topics lead to the inclusion of:

Task 1: Studies which will lead to better understanding of the underlying mechanisms of radiation-induced optical changes, e.g. lens opacities at low doses, both in animals and humans:
- Study on contribution of low dose X-irradiation in induction of cataractogenesis and influencing genetic and cell communication factors (LDR-OPTI-GEN) in Task 7.8

Task 2: Mechanistic insights into epigenetic and genetic regulatory processes and their role in cancer and non-cancer effects:
- Low and moderate dose radiation effects on brain microvascular pericytes: epigenetic mechanisms and functional consequences (PERIRAD)

Task 3: Integrated studies of cancer risk following exposure to internal emitters:
- Internal Emitters in Uranium miners (INTEMITUM) in sub-task 5.5.1
- Assembly of internal radiation dose for UKAEA and AWE epidemiological cohorts (AirDoseUK) in sub-task 5.5.2

Task 4: Novel approaches:

- Induction and facilitation of chromothripsis by low dose ionizing radiation (In-FaCT-IR) in Task 5.7
- Characterization of DNA lesions in the nuclear ultrastructure of differentiated and tissue-specific stem cells after protracted low-dose radiation (Zif-TEM) in Task 6.10

Task 5: Provisions of infrastructures:

- Provision of ion microbeam irradiation facility SNAKE (MicroRAD) in task 4.9

Altogether, research priorities and scientific approaches have been discussed in 16 scientific meetings and workshops during the second project period (see list in Annex 2)

3. Assessment of current outstanding research and identification of capability needs

In WP5 – Shape of the dose response and tissue sensitivities for cancer - work continues to be focused on low dose/dose-rate radiation cancer risk in humans and on low dose/dose-rate risk projection models based on knowledge of the processes driving carcinogenesis. Dedicated workshops identified priorities for research on systems biology (October 2011, September 2012) and stem cell biology (December 2011). The work programme now also includes track structures and initial events (an integrated approach to assess the issue of radiation quality dependence), internal emitters in uranium miners (INTEMITUM), modulation of inflammation by ionizing radiation (ModInIR), assembly of internal radiation dose data for UKAEA and AWE epidemiological cohorts (AIRDoseUK) and the induction and facilitation of chromothripsis by low dose ionizing radiation (In-FaCT-IR).

Links to other EC initiatives such as EpiRadBio, EPI-CT, SOLO, and ANDANTE have been established as well to avoid overlapping efforts and promote collaborations.

In the 19-36 month period new work on inflammatory reactions, immune modulation and biophysical modelling of radiation track structures has been added following internal and external calls. Interesting dose-rate effects have been observed concerning cellular senescence, cellular stress responses and changes in protein regulation that allow mechanistic modelling. Low dose gene expression changes are to be followed in vitro and in vivo (see WP5 task 5.1). The involvement of targeted, non-targeted and systemic processes in radiation carcinogenesis are analyzed taking into account 2D- and 3D tissue models as well as inflammatory and immunological responses (see WP5 task 5.2). Modulation of inflammation by low and intermediate doses shows a discontinuous dose relationship, although effects on signalling molecules and functional aspects may not always be consistent. Studies on the dynamics of pre-neoplastic change and clonal developments have started to be analyzed by a joint systems analysis approach for radiation-induced myeloid leukaemia (see WP5 task 5.3). Mechanistic modelling revealed that intercellular apoptosis can counterbalance proliferation of pre-cancerous cells and this effect can be increased by low dose radiation. On the other hand, modelling of radiation effects in Eldorado Miners showed that radiation has a strong promotional effect for lung cancers, and bystander effects may be involved (see WP5 task 5.4). The assessment of the risk from internal exposures in WP task 5.5 has been supported by dedicated workshops and follow-up discussion on on-going research projects on uranium miners and workers in Europe and the integration of two sub-tasks through the second external call focusing on cancer risk (leukaemia and non-melanoma skin cancers) in Czech uranium miner cohorts and on dosimetric evaluation of UK (AWE and UKAEA) workers. Early-post irradiation events in relation to radiation quality are the focus of WP5 task 5.6. Effects on DNA, mitochondria, proteins and lipids are taken into account.

In WP6 – Individual variability in cancer risk - work has been concentrating on the importance of individual radiation sensitivity for acute or chronic exposures with regard to carcinogenic effects. This has led to the publication of a comprehensive status report on the possibility of using molecular biomarkers in epidemiology and to the completion of the survey of epidemiological cohorts suitable for molecular epidemiology (Task 6.1). Experimentally, we have shown that inbred mouse strains show different susceptibilities to radiation induced thyroid cancer, and have identified a role of the nucleotide excision repair pathway in contributing to individual sensitivity (Task 6.2).

The future plans of the WP include the design of a pilot study to determine the feasibility of molecular epidemiological studies, identification of genetic modifiers, the inclusion of genetic variability in risk prediction models, and the effects of genetic modifiers on carcinogenesis at low dose rate exposures (see WP6 tasks 6.1-6.6). In the second 18-month period, workshops on Epigenetics (June 2011) and Modelling and systems biology (October 2011) were held in Stockholm as well as two MELODI workshops (Rome 2011, Helsinki 2012). The results from the second external call lead to amendments that incorporated task 6.8 (Prediction of individual radiation sensitivity with Raman spectroscopy (PRISM), task 6.9 integration of radiation biomarkers into epidemiological studies of post-Chernobyl thyroid cancer from Belarus (see also INT-Thyr kick-off meeting in Barcelona May 2012), and task 6.10 the characterization of DNA lesions in the nuclear ultrastructure of differentiated and tissue-specific stem cells after protracted low-dose radiation (Zif-TEM).

Links to other European projects PROCARDIO and CEREBRAD were established.

In WP7 – Non-cancer effects - significant progress has been made through an epidemiological pilot study showing lens opacities among interventional radiologists and cardiologists. Dedicated and exploratory workshops (WP7 task 7.3, Warsaw 2 September 2011, WP7 task 7.1 Bombon 19-23 September 2011, WP7 task 7.2 Munich 19-20 October 2011) identified research approaches and priorities. In fact, the research efforts on non-cancer effects have been well-structured. Clear evidence has been obtained for the induction of lens opacities, cardiovascular and neurological effects. Now emphasis is put on a well-defined epidemiological study including suitable biomarkers and in particular, on mechanistic studies on transcriptional and proteomic responses of vascular endothelial cells to low-dose exposures as well as on neurological effects in rodents. Following the external call in the last 18-month period, studies on low dose Gene Expression signature and its impact on cardiovascular disease (LoGiC), lens opacities/methodology implementation (ELDO) and on the contribution of low dose X-irradiation on the induction of cataractogenesis and the influence of genetic and cell communication factors (DR-OPI-GEN), as well as low and moderate dose effects on brain microvascular pericytes: epigenetic mechanisms and functional consequences (PERIRAD) were also included.

WP7 now focuses on the design of molecular epidemiological studies (with markers for low dose-non-cancer health effects and for confounding risk factors (blood markers)) and pertinent mechanistic studies on the implication of oxidative damage, signalling, and metabolic dysfunctions, and the influence of the immune system.

Links to other complementary EC projects (SOLO, PROCARDIO, CEREBRAD…) need to be established.

In WP3 – Education and training – this has been recognized as an essential part of all European projects and initiatives in radiation protection. In radiation research and radiation protection significant expertise and competences must be developed and sustained to ensure that the research capacity is prepared to face the future challenges in this domain. Since the

resources in E&T are concentrated in Europe in a few centres of excellence, we need to facilitate collaboration between the centres and remove barriers due to the different demands of national education systems. The provision of sustainable long-term support is essential and must be an integral part of all radiation protection research funding at the national and international levels (WP3 tasks 3.3 and 3.4 together with WP2).

The different WP3 tasks are involved in the assessment of available resources and requirements, the setting up of training courses investigating the potential for multi-institutional multi-national degree courses and with creating a continuing entity able to maintain E&T support not only in the short term (within DoReMi) but also in the medium and long terms (in MELODI within HORIZON 2012). The courses are particularly concerned with maintaining scientific expertise and knowledge in radiation research, radiation health risk evaluation and radiation protection issues. WP3 has been particularly effective in both consensus building and in setting up joint European training courses (2 November Rome, and 11 September 2012 Helsinki). Six local courses were run last year. Nine additional courses have been set up for the forthcoming year (details http://doremi-noe/training and education.html) hosted by and involving main partner institutions of DoReMi. The establishment of these courses has largely benefited from the 2nd Training call and the 3rd Course invitation round for new courses.

Main future objectives are: to continue Europe wide investigations to create an Integrative Education and Training Network (ITEN), to seek support and organise E&T initiatives, work in collaboration with MELODI to ensure support future initiatives in the field of radiation research and radioprotection, and develop a strategic plan to meet future training and education needs. The courses are complementary to courses in Europe dealing with the organisational and technical aspects of radiation protection.

In *WP4 – Infrastructures* – Suitable infrastructures, such as irradiation facilities, databases-and biobanks, cohorts and analysis platforms, are essential to meet DoReMi objectives. WP4 has assessed available facilities, needs for new facilities and for suitable funding (DoReMi WP2), and access to infrastructures (including to the UMB facility). It has also been involved in the launching of calls for infrastructure access in collaboration with WPs 1, 2-7. In fact, as a consequence of the first competitive calls the infrastructure programme now includes open access to the UMB low dose irradiation facility (FIGARO) and the IES facility in Japan, a low dose/dose rate gamma irradiation facility for *in vitro* biological systems under development (LIBIS), the integration of STORE into DoReMi (a solid and viable database and/or pointer to biobanks and ascertained sustainability) and the provision of the ion microbeam irradiation facility SNAKE (MicroRAD).

The 4th MELODI workshop in Helsinki 2012 has revealed a marked interest in gaining access to both microbeam as well as heavy ion beam facilities. The importance of access to data and tissue banks has been underlined by the DoReMi-STORE meeting in Rome January 2012 that formed the basis for two publications (Nature 82:5, Nature 485:126, 2012). The discussion of the preparation and integration of the STORE database into DoReMi in connection with MELODI resulted in full integration of STORE into DoReMi (WP4) after October 2012. The databank provides very useful links to other databases and archived biomaterials (see also European Radiobiology Archives ERA). Links to the forthcoming Biobanking and Biomolecular Resources and Research Infrastructure (BBMRI) to be accredited by the European Research Consortium (ERIC) are foreseen (see 4th MELODI workshop in Helsinki 2012).

WP4 has been involved in the San Feliu de Giuxols meeting in 2010 and in Barcelona 2012 where cohorts and molecular biomarkers suitable for molecular epidemiological studies were discussed. A publication in Mutation Res./Reviews June 4, 2012 has been released on biomarkers. Several workshops discussed the identification and set up of suitable cohorts with

WP5, WP6 and WP7. This consultation has led to recommendations of cohorts with and without access to biological samples. A number of cohorts have been thus identified, also in collaboration with the EpiRadBio project. Also, possible cohorts for lifespan studies have been evaluated that do not need to start assembling necessarily new radiobiological cohorts.

Concerning the development and use of platforms for analysis some possible institutionally available platforms have been discussed ("omics", imaging and sequencing platforms). More recently, the Mapping of the European Infrastructure Landscape (MERIL) will be available as a database of European Research Infrastructures. Formally, the MERIL project ended on September 30, 2012. However, a version of the database (managed by the European Science Foundation) is currently available, and should prove to be a powerful tool for researchers engaged in radiation research and radioprotection. In the mid-long term future the development of pan-European research platforms under the ESFRI program (Euro-Bioimaging, Infrafrontier, ISBE) and ELIXIR programs merits close attention.

Presently, a direct outcome of these WP4 activities will be a workshop in Munich in April 2013 to familiarize researchers with the microbeam irradiation SNAKE facility; the establishment of a portal at CREAL as proposed by the Cross Sectional Epidemiological Task Group (see Minutes, Paris, 23 January 2013) providing information and a database (with the help of STORE) on key cohorts, dosimetry, biological samples and addresses for potential collaboration; open access to the UMB low dose irradiation facility; opening access to low dose, low-dose rate facilities in Chalk river (Canada) and IES (Japan) (see ENEA, induced brain cancer risk); and establishment of a low dose-rate facility by ISS in Rome (LIBIS).

Very importantly, all information on infrastructures is made available on the DoReMi external website with detailed information on the internal website (collaboration with WP2 task 2.3). Moreover, the integration of STORE into DoReMi may be regarded as a first step to develop long-term strategies for sustainability of these important databank resources.

Cross cutting issues

The three cross cutting issues (originally identified in the HLEG report 2009) of DoReMi are: radiation quality, tissue sensitivity and internal emitters. All of them have been and are considered in the different WPs. Microbeams and low dose and low dose rate facilities are available to facilitate experimental approaches to monitor single cell as well as tissue and whole animal effects. Systems biology approaches and modelling of health risks should also take into account radiation quality effects.

Each of these issues receives attention in the current studies of DoReMi. The sensitivity of different tissues is addressed through the range of cancer and non-cancer diseases being considered. Internal emitter studies are identified as a task in WP5, and also as a feature in the work of WP7 and in proposed pilot studies in WP6. Radiation quality is addressed in WP5 studies of neutron-induced AML, in risk modelling work (WP5, WP6) and in the context of work on neurological effects of internal and external irradiation in WP7. In the research on internal emitters the effects of radiation quality are of particular importance.

Tissue specific low dose radiation effects need to be further explored (epidemiological and mechanistic studies) taking into account the recent possibilities of tissue phenotyping (stem cells, progenitor cells), genetic and epigenetic profiling. This may lead to a better understanding of short and long term tissue responses and biological efficiencies of different types of radiations.

Studies on internal emitters (radionuclides) need better defined dosimetric approaches, clear distinction between chemical toxicity and radiotoxicity (including the effects of particle size and

nanoparticle effects), uptake and distribution analyses backed up by solid transcriptomic, proteomic and metabolomic studies. Low-dose rate effects of chronic or fractionated exposures should be considered as well as mixed exposures (different types of radiation, and/or chemicals). Such studies should give rise to a better understanding of health risks induced by internal emitters alone or in conjunction with other genotoxic agents. For this, links and possible interactions with ongoing European research projects outside of DoReMi should be taken into consideration.

Summary of key questions and sub-questions

Table 1 provides a summary of key questions and sub-questions that were already addressed in the first and second period of DoReMi (0-36 months). It also provides reference to the Tasks addressing the sub-questions related to cancer or non-cancer effects by epidemiological or mechanistic studies (Extract from Transitional Research Agenda). This review of DoReMi work programme addressing the research area was carried out in January 2013.

Table 1. Key questions and sub-questions addressing low dose risk in the DoReMi context. The numbers refer to the Tasks of the DoReMi work program addressing the sub-questions.

	Cancer (1)		**Non-cancer (2)**	
Key question	**Subquestions** ***DoReMi Tasks***		**Subquestions** ***DoReMi Tasks***	
	Epidemiology	Mechanisms	Epidemiology	Mechanisms
1. What is the dependence on energy deposition?	*5.1, 5.7*	*5.1.1*		*7.9*
2. What is the dependence on dose rate?	*4.8, 6.4*	*4.5, 4.6, 4.7, 4.8, 5.1, 6.10*	*4.8*	*4.5, 4.7, 4.8*
3. What are the tissue sensitivities?	*5.4, 5.5, 5.5.1, 5.5.2, 6.9,6;2, 6.3*	*6.9*	*7.4, 7.4.1*	*7.3, 7.5, 7.8*
4. What is the modification of risk by genetic and epigenetic factors and gender?	*6.1, 6.6, 6.9, 6.5*	*5.5.1, 6.2, 6.3, 6.4, 6.5, 6.9*	*6.1*	*7.7, 7.8, 7.9*
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?		*5.2.1, 6.8*		*7.6*

8. Is there a hereditary component in risk?				
9. What is the role of non-targeted effects in health risk?		*4.9, 5.2, 5.2.1*		*4.9*

The above list clearly indicates that the dependence of risk on age, lifestyle, mixed and other exposures and on hereditary factors have not been addressed in the DoReMi project by month 36. At present, however, consolidation and better integration of research lines thus far initiated are the main priorities of DoReMi, as well as focusing further on the development and validation of biomarkers for epidemiological studies. For the final scientific outcome of DoReMi, proof of concept for molecular epidemiological studies or systems biological approaches are among the top priorities during the second half of the project.

4. Issues to be focused on in the 3rd DoReMi period (36-54 months) and capability needs

Here below we summarize major issues identified in DoReMi periodic meetings, workshops and exploratory meetings that require special attention in the next period of DoReMi in line with future developments of MELODI within HORIZON2020. The proposed research lines are expected to decrease existing uncertainties in radiation protection, in particular at low doses and low dose rates: radiation quality factors, dose and dose-rate reduction effectiveness factor, tissue weighing factors, influences of genetic and epigenetic control, individual sensitivity responses, importance of sex, age and lifestyle, metabolic status, chronic internal and external exposures and the influence of non-targeted effects.

WP5 – Shape of dose response and tissue specificity for cancer

The focus should be on

5a Molecular epidemiological studies (cohorts of uranium miners and uranium workers, Techa river residents amongst others should be useful (as identified by the cross-sectional epidemiology task group, see also task 6.6)). For this, radiation quality, expanded dosimetry, suitable biomarkers, and studies with sufficient statistical power and the collection of biological material are essential. A 2 year concerted action may be considered to prepare future studies (ex.: childhood leukaemia)

5b Identification of biomarkers including metabolic markers and gene expression markers for radiation damage and cancers

5c Follow up of inflammatory and immune response studies, epigenetic responses and NTE in *in vivo* or 3D tissue modelsfocusing on investigation of links of NTE to disease and understanding of dose dependence relationships.

5d Concerning internal emitters, research should be promoted to distinguish chemical from radiation toxicity, involvement of redox and radical reactions and nanoparticle size effects.

5e Mechanisms of pre-neoplastic changes and cancer induction in solid cancers

5f Modelling of the involvement of damage in radiation quality effects

WP6 – Individual variability in cancer risk

The focus should be on

6a Molecular epidemiological studies (ex: uranium miners and nuclear workers, CT scan patients) should give some information on individual sensitivities if biological samples and suitable biomarkers can be made available.. Concerted actions should be set up to prepare well-focused long term studies. Genetic cohorts on AT hetorozygotes and/or BRCA1/2 carriers, paediatric CT patients should be of interest as well. Individual sensitivities may include sensitivity to cancer as well as non-cancer effects.

6b Systems biology approaches including epigenetics and mathematical modelling should allow better low dose health risk evaluations.

6c Identification of genetic and epigenetic modifiers affecting individual sensitivity and cancer risk in human populations.

WP7 – Non cancer effects

The focus should be on

7a Epidemiological pilot studies (including suitable medical cohorts) together with mechanistic studies on dose and dose rate effect relationships.

7b Studies on genetic and epigenetic factors as well as on cell communication factors involved will be essential.

7c External radiation, as well as internal emitter effects, need to be explored in suitable epidemiological cohorts (Techa river, Uranium workers and miners, Chernobyl)

WP3 – Education and training

The focus should be on

3a Strengthening of the Integrated Training and Education Network (ITEN) through dedicated meetings and Fora in the framework with other European projects.

3b Establishment of an education and training programme with short courses on specific topics in radiation research and radiation protection as well as on low dose radiation risk research.

3c Evaluation of past activities

3d Search for sustainability and funding of integrated education and training activities in Europe together with MELODI-OPERRA within HORIZON2020.

WP4 – Infrastructures

The focus should be on

4a The increase of information and guidance on existing suitable infrastructures in Europe (website).

4b Facilitating partner access to infrastructures, and the monitoring of actual use

4c Establishing links to wider ranging analysis and imaging platforms (ESFRI etc.)

4d Providing information on suitable cohorts for molecular epidemiological studies (avoiding duplication with WP5-7)

4e Identifying toxicology platforms well suited to aid internal emitter studies and facilitate partner access

4f Searching for sustainability (also beyond DoReMi)

Cross cutting issues

Although the topics highlighted above include the cross-cutting issues (radiation quality effects, tissue sensitivity and internal emitters for the forthcoming period of DoReMi, efforts on these issues should be strengthened:

a Through dedicated workshops (ex: radiation quality, radiation damage and consequences; regulation of tissue sensitivity and the involvement of stem cells, research on chemical/radiotoxicity of internal emitters and their biological consequences)

b Through increased collaborative and integrative research within DoReMi and interaction with other related European projects

The above research topics and priorities are formulated in the context of the DoReMi schedule for TRA update, Joint Research Program and Calls (see Annex 3).

5. Beyond DoReMi

The consortium will carefully consider the progress of DoReMi and also highlight the roadmap for the time beyond DoReMi. This will be the priority of the remaining project period.

The current view is that DoReMi is providing procedures and structures as well as many initial basic studies for low dose radiation health research. However, DoReMi is limited in time (up to the end of 2015) and thus, many of these procedures, structures and research lines are expected to be maintained in the future in the European Research Area. Concerning the present TRA statement, some research issues have been recognized that have to be reinforced and addressed beyond DoReMi in the future: these include high standard dosimetry, biomarker developments on the basis of full genetic and epigenetic profiling, tissue phenotyping, next generation sequencing approaches, stem cell research, detailed studies in relation to radiation induced (oxidative) damage and mitochondrial (metabolic) dysfunction, internal emitters effects, effects of intra-and intercellular signalling, immune responses and low dose, low dose rate and radiation quality effects and in particular age, lifestyle, multi(mixt)exposures related effects, hereditary (transgenerational) effects, and extended molecular epidemiological studies (retrospective and prospective). Also, these research lines will be useful complements for a systems biology approach and the evaluation of low dose radiation induced health risks. Of course, this all has to be accompanied by enhanced networking through suitable infrastructures and Europe-wide, well-focused teaching and education activities and further integration and collaboration in the European (as well as in the international) context.

6. Concluding remarks

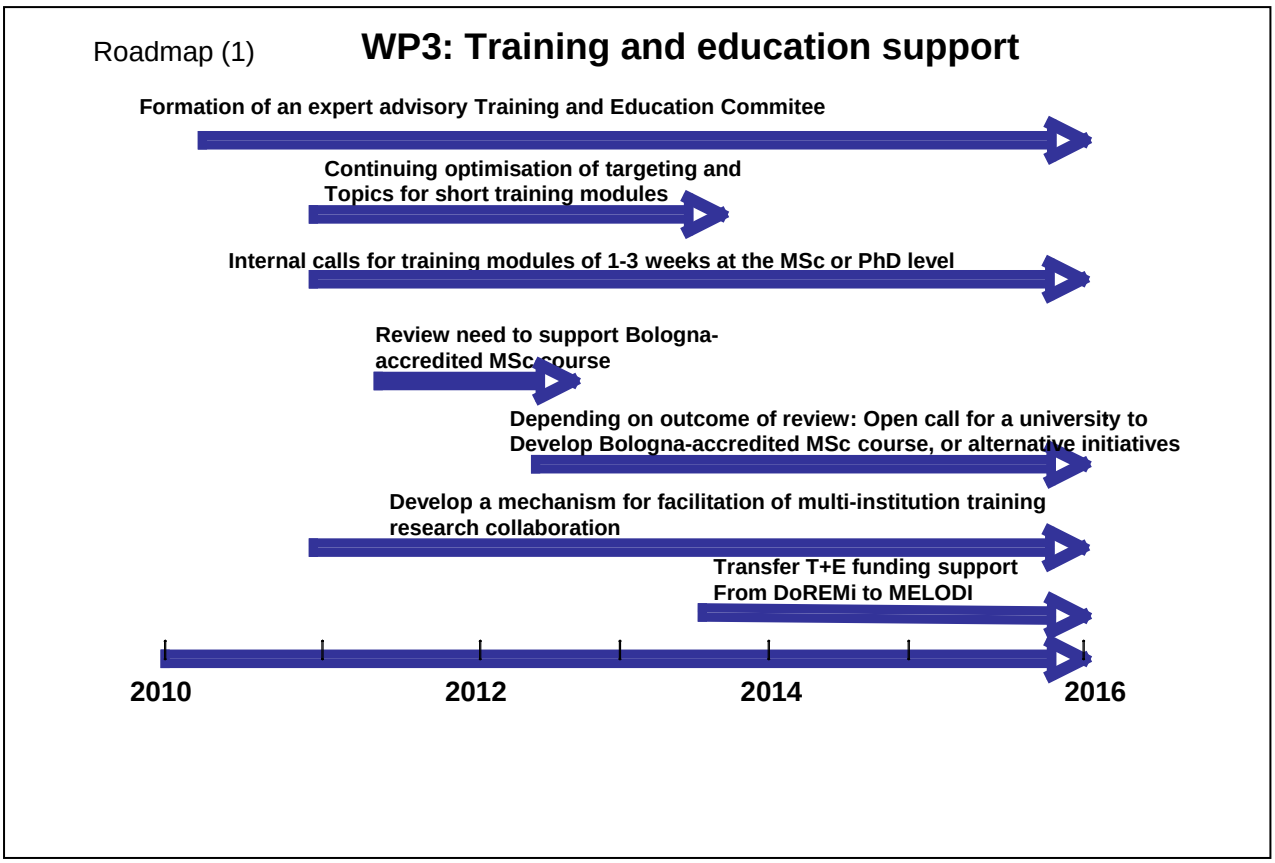
The DoReMi project has been successfully widening its research activities and increased its focus on the common goal. The DoReMi project now offers many possibilities for interactions, and the aim should be to further increase information flow (Websites, workshops etc.), collaboration and integration of DoReMi partners. Dedicated courses in Education and Training and access to suitable infrastructures promote Europe-wide networking. The output of DoReMi can be further increased by placing more emphasis on integration during the next years.

The DoReMi statement pinpoints actual priorities for the next 18 months of DoReMi following regular updating of the DoReMi TRA. It is thus an important step in the development of low dose radiation risk research in Europe and the establishment of the long-term sustainability for research on radiation and radiation protection issues by MELODI within the framework of HORIZON2020.

Annex 1: DoReMi Roadmap to integrate research and capability needs for months 37-54 (up to 2015)

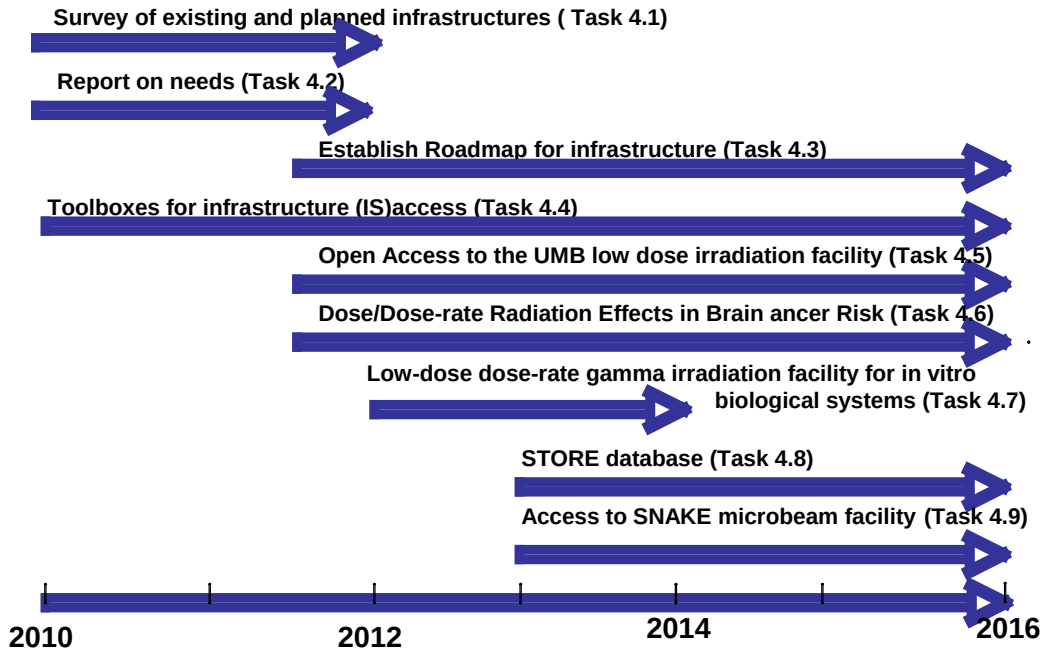
Roadmaps for the WPS 3 and 4, and the WPs 5, 6 and 7.

The following graphs constitute the updated roadmaps for DoReMi. The scheme will be regularly updated (WP2, DoReMi MB and EAB) according to forthcoming new knowledge and newly developing research lines.



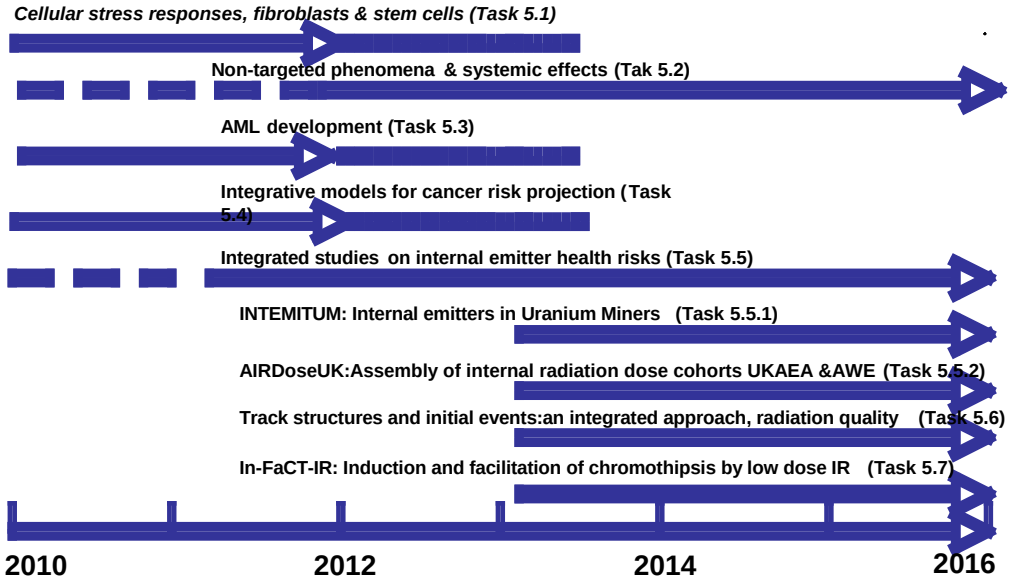
Roadmap (2)

WP4: Infrastructures (2013)



Roadmap (3) **WP5: Shape of Dose-Response Curve for cancer**

Mechanistic studies



Roadmap (4a)

WP6: TRA Individual sensitivities

Task 6.1 Review of potential biomarkers for radiation: potential use and validation through pilot studies in appropriate cohorts (based on WP4 review)

Task 6.2 Identification of genetic modifiers of indivual cancer susceptibility and their mechanisms of action - *Mouse models for genetic susceptibility to thyroid cancer*

-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

Task 6.3 Modeling individual variability

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

Roadmap (4b)

WP6: TRA Individual sensitivities (continued)

Task 6.5 Contribution of genetic and epigenetic mechanisms that influence susceptibility to radiation induced cancer

Task 6.6 Implementation of the DoReMi strategy for a large scale molecular epidemiological study to quantify genetic contribution to individual susceptibility

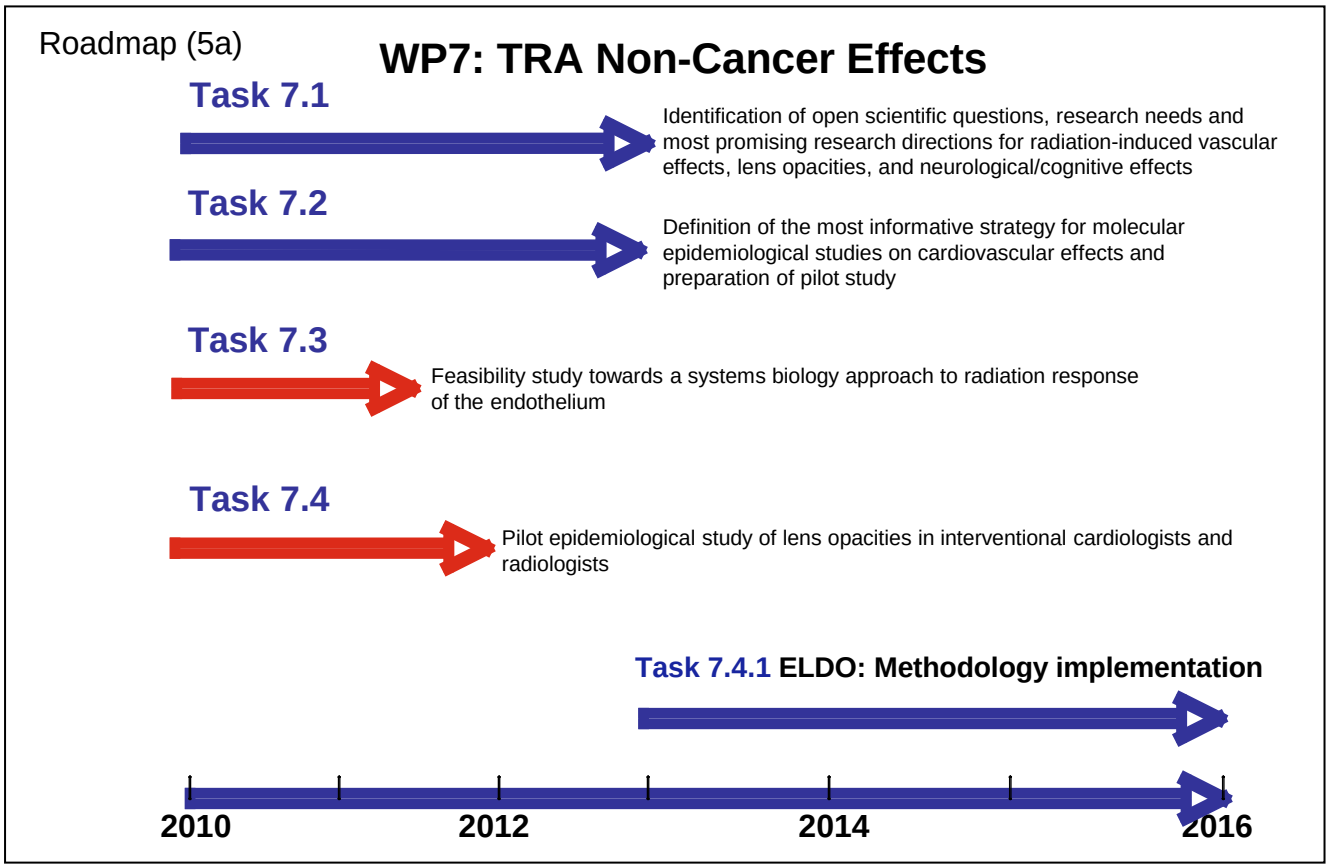
Task 6.7 Planning expansion of research portfolio through workshops

Task 6.8 Prediction individual radiation susceptibility with Raman micro-spectroscopy

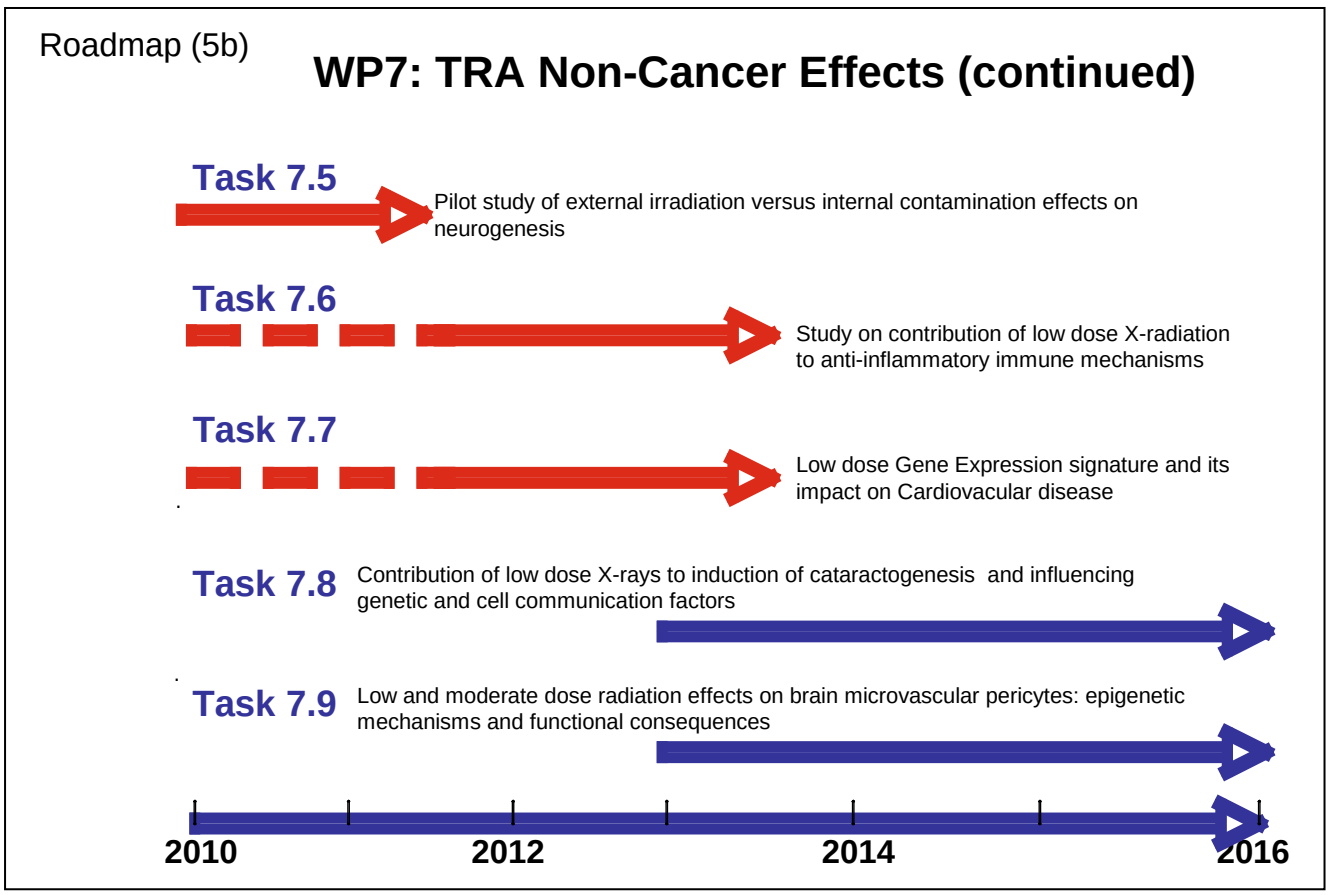
Task 6.9: Integrating radiation biomarker into epidemiology of post-Chernobyl thyroid cancer from Belarus

Task 6.10 DNA lesions in the nuclear ultrastructure of differentiated and tissue-specific stem cells after protracted low dose radiation

Roadmap (5a)



Roadmap (5b)



Annex 2: List of meetings and workshops that have been particularly relevant to the establisment of the DoReMi TRA statement

Time	Name of the meeting	Venue	Responsible organization	WP
7 July 2011	Modelling meeting	Brussels, Belgium	HMGU	WP5
2 September 2011	Task 7.3 workshop	Warsaw, Poland	SU	WP7
19-23 September, 2011	Task 7.1, Lens opacities exploratory workshop	Bombon, France	IRSN	WP7
16-18 October 2011	Systems Biology meeting (Tasks 6.5, 6.3)	Stockholm, Sweden	SU	
19-20 October 2011	Task 7.2 Workshop	Munich, Germany	BfS	WP3
2-4 November 2011	3rd International MELODI Workshop	Rome, Italy	ISS, MELODI	All
2 November 2011	DoReMi / Arch Workshop	Rome, Italy	STUK and IRSN	
2 November 2011	DoReMi-MELODI Training & Education Forum (WP3)	Rome, Italy	UNIPV	WP3
7-8 December 2011	Stem cell meeting (WP5)	Oxfordshire, UK	HPA	WP5
25-26 January 2012	DoReMi-STORE Workshop (WP4)	Rome, Italy	CEA	WP4
17-18 May 2012	INT-Thyr kick-off meeting (Task 6.9)	Barcelona, Spain	CREAL	WP6
2 September 2012	Training workshop (WP3)	Oxford, UK	UNIPV	WP3
2-5 September 2012	Systems Biology meeting	Oxford, UK	SU	
12-14 September 2012	4th International MELODI meeting	Helsinki, Finland	STUK, MELODI	All
11 September 2012	DoReMi-MELODI T&E Forum (WP3)	Helsinki, Finland	UNIPV	WP3
15 October 2012	WP2 meeting	Vietri sul Mare, Italy	IRSN	WP2

Annex 3: Schedule for TRA updating, Joint Programme of Research (JPR) and calls