DoReMi - Low Dose Research towards Multidisciplinary Integration

Publishable Summary

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1. A summary description of project context and objectives

The aim of the DoReMi consortium is to promote the sustainable integration of low dose risk research in Europe. This will facilitate efforts to resolve the key policy questions identified by the 'High Level Expert Group (HLEG) on Low Dose Risk Research' (www.hleg.de). These are the shape/s of cancer dose-risk relationship/s, variation in risk between individuals, differences in tissue sensitivities for cancer, effects of radiation quality, risks from internal exposures and the risks of non-cancer effects. The research activities of DoReMi focus on the research areas identified by the HLEG as being the most promising in terms of resolving the stated key policy questions. DoReMi provides an operational tool to continue the development of the MELODI platform (Multidisciplinary European Low Dose Risk Research Initiative) that represents the major national bodies and research programmes with a long term commitment to low dose risk research in Europe. The Joint Programme of Activities (JPA) of DoReMi includes: (i) a Joint Programme of Research (JPR) covering the research priorities (key questions) outlined above and including the sharing and updating of existing infrastructures; (ii) a Joint Programme of Integration (JPI) to promote sustainable integration between the key players in Europe; and (iii) a Joint Programme for the Spreading of Excellence (JPSE), covering in particular knowledge management, training & mobility and the communication of significant DoReMi findings to stakeholders and policymakers. The Joint Programme of Research addresses three main topics: the shape of dose response curve for cancer, effects of individual susceptibilities and the risks of non-cancer effects. Radiation quality, internal exposures and tissue sensitivities are addressed as cross cutting themes within these main research areas. The research activities take a multi-disciplinary approach, including interfacing with the broader (i.e. non-radiation) biological, toxicological and epidemiological research communities. A substantial proportion of the activities of DoReMi are dedicated to the joint programme of research as DoReMi will take the lead towards sustainable integration of low dose risk research in Europe. In the longer term this will aid the resolution of the key policy questions in radiation protection.

Strategic planning of DoReMi activities is carried out in close collaboration with MELODI. The long term Strategic Research Agenda (SRA) for European low dose radiation risk research has been developed by MELODI. DoReMi has formulated research priorities in a Transitional Research Agenda (TRA) that focuses on objectives that are feasible to achieve within the 6 year lifetime of the project and that are in areas where stimulus is needed in order to proceed with the longer term strategic objectives of the SRA.

2. A description of the work performed since the beginning of the project and the main results achieved so far

Since the beginning of the DoReMi Network of Excellence in January 2010, there has been rapid progress in the establishment of a European research platform to focus on questions of low dose risk. DoReMi continues the initial work of HLEG by contributing to the development of the long-term SRA of MELODI, and by establishing the more detailed shorter-term DoReMi TRA. Engaging the broader scientific community via exploratory workshops has proven to be an efficient way in developing the research agendas. The research agendas provided by MELODI and DoReMi have helped to identify priorities for low dose risk research not only by the organisations involved but also in national, European and global contexts. The planned enhancement of the DoReMi network through the inclusion of partners with new expertises was initiated through the first competitive call. This was launched in September 2010 and resulted in 10 new organisations joining the network from the beginning of July 2011. This very successful activity has enhanced the competence of the consortium in several key areas, by integrating research experts in biomarker identification, immunological/inflammatory pathways, and the effects of chronic low dose exposures.

DoReMi has implemented research programs addressing the three key research areas: shape of dose-response curve for cancer, individual radiation sensitivity for cancer and non-cancer effects. The research activities are all performed at appropriately low doses. DoReMi defines these low doses as those of 100 mGy or less. Low dose rates are defined as 0.1 Gy/h or less for low LET radiations. For high-LET radiations, dose

and dose-rates of interest are lower, e.g. for alpha radiation by an order of magnitude. Low dose studies are complemented by higher dose/dose-rate studies to inform judgements on extrapolation from moderate and high doses/dose-rates to low doses/dose-rates. All RTD activities address the cross-cutting issues of radiation quality, tissue sensitivity and internal emitters. During the first 18 months, several workshops were convened to develop strategies that focus on the most promising lines of research for the three areas. Experimental programs have been launched in all three areas, including a number of feasibility studies preparing the field for large international collaborative efforts. The RTD approaches have been closely coordinated through discussions on needs for research infrastructures and analytical platforms, as well as targeted stimulation of training and education of next-generation researchers at the European level.

The DoReMi research program on the shape of the dose-response for radiation carcinogenesis has two overarching aims: (i) to improve knowledge of the underlying processes and dose dependency of cancers induced by low doses/dose rates in humans and (ii) to improve low dose/dose-rate risk projection models through improved integration of these biological processes. A work plan centered on five inter-related tasks has been established and has been extended through the external call and ad hoc funding opportunities. Over the first eighteen months our studies on cellular stress at low dose rate effects, on mechanisms of leukaemogenesis and on modelling of cancer risk have progressed well. Priorities in the areas of non-targeted, systemic effects and on internal emitter risk have been identified during the workshops. Following the external call work on the effects of low doses on inflammatory responses in vitro and in vivo has been added and additional work on gene expression responses across a wide dose range has been incorporated. Further workshops are planned to establish consensus priorities for future integrated studies relevant to low dose/dose rate radiation cancer risk. In particular workshops on mathematical modeling approaches and stem cell radiobiology are anticipated in the next reporting period. The work planned undertaken to date will strengthen the evidence on which low dose radiation cancer risk estimation is based. Such improved evidence may be expected to improve wider public confidence in the assessment of radiation risk and so reduce concerns on beneficial uses of radiation while maintaining rigorous and credible protection standards.

The DoReMi research program on individual sensitivity aims to determine the contribution of individual variations in sensitivity on the risk of developing cancer following exposure to low doses/dose rates. The influences of inter-individual differences are addressed at three levels, using population studies, animal models and in vitro models. A workshop was convened to identify potential biomarkers of radiation exposure for use in future molecular epidemiological studies of radiation-induced cancer in exposed cohorts. At this meeting the cornerstone was laid for a consensus report on the identification and validation of candidate biomarkers. A new partner with expertise in the biophysical analysis of individual plasma samples has been recruited through the external call. Using Raman spectroscopy it will now be possible to search for metabolite biomarkers defining individual responses to radiation exposure. The contentious issue of epigenetic markers and biological processes in radiation-induced cancer was also examined in a DoReMi workshop. The main conclusion was that epigenetic processes must now be recognised as a key mechanism mediating the interaction between the environment (radiation) and the individual. The meeting recommended that a research strategy addressing these epigenetic processes be adopted into the next TRA. Experimental studies to define the contribution of both highly penetrant and weakly penetrant genetic differences to modifying individual sensitivity have been initiated. We have begun a large scale study on the genetic components that determine sensitivity to radio-iodine induced thyroid cancer, as well as starting a range of complementary in vitro studies on the biological effects of thyroid cell irradiation. The complex issue of low dose rate effects on individual sensitivity was the subject of the external call. Two new partners with considerable expertise in the study of low dose rate carcinogenesis have joined DoReMi. The next workshop will consider the implications of systems biology as a tool for the effective conceptualisation of the effects of individual variations in the radiation response over multiple scales (cell, tissue and organism).

The DoReMi research program on non-cancer effects was launched. Although the acute damaging effects of high dose exposures on the endothelial cell system (loss of cell-cell integrity, failure of fluid barrier maintenance, cell death without replacement, new phenotype chronic activation) are well recognised, there is no evidence for the development of acute and/or chronic radiation pathology at low doses. However,

epidemiological studies of radiation exposure and cardiovascular morbidity indicate that damage to the vasculature may indeed be a late effect of low dose irradiation. In situations of internal contamination, there is almost no information on effects on physiological systems. Thus, it remains an open question if there is a correlation between the accumulation of low doses from internally incorporated radioactive material and the development of vascular impairment. This is an important question of relevance to the radiation protection system. The full interpretation of epidemiological data for the purposes of radiation protection at low doses is hindered by the almost complete lack of knowledge on the mechanisms of radiation effects that contribute to radiogenic diseases other than cancer. The overarching strategic objective of DoReMi is to implement a long-term, integrated approach involving several disciplines, namely, epidemiology, radiobiology and toxicology, for the purpose of risk evaluation for radiation-induced non-cancer effects. An exploratory workshop addressing the low-dose-radiation-induced vascular effects concluded that, below 0.5 Gy, there remains uncertainty about possible vascular effects in epidemiological studies. Therefore there is a need for more epidemiological and clinical studies that specifically address these lower doses. Effects of total body and local irradiation on the vasculature need to be investigated. Differences between mouse strains were in particular observed for cardiovascular effects, and genetic factors should be taken into account in the development of future studies. Also, because vascular effects have a long latency, lifespan studies are essential. A remarkable observation from both the CARDIORISK and NOTE projects is the co-existence of pro- and anti-inflammatory responses at low doses. This is a topic that requires further research, in particular the possible role of radiation-induced changes in inflammation in the etiology of cardiovascular diseases. Prospects for molecular epidemiology in the study of vascular radiation damage were discussed in another “think tank” meeting. The preparation of a future workshop to address the risks and biology of low-dose-radiation-induced lens opacities was initiated. In the experimental part of this program a feasibility study for adopting a systems biology approach to define the radiation response of the endothelium is underway. Cell culture under protracted irradiation at low dose rates (1.4 or 4.1 mGy/h) has been performed at the Stockholm University (SU). Several DoReMi partners have made contributions to this investigation using a wide range of endpoints.

A pilot epidemiological study of lens opacities among a cohort of interventional radiologists and cardiologists is progressing. Preliminary results from one country indicate that interventional radiologists have a significantly higher risk of developing posterior subcapsular lens opacities. This association was not , however, seen among the physicians in another participating country. A pilot study of the effects of external irradiation versus internal contamination on neurogenesis was initiated. During the first reporting period, a common protocol of experimental procedures was developed and validated that will allow work on the same samples using standard methodologies. Neuronal cultures at various points of neuron maturation were irradiated. Preliminary results indicate that there are effects on the neuronal cytoskeleton, on neurite length and branching. These are shown to depend on the time of irradiation and the neuronal maturation stage. It was also confirmed that the branching number of neurons decreases following low dose exposure, which means that the ability to establish a neuronal network may be modified by low dose irradiation.

The availability of suitable infrastructures for performing low dose risk research is specifically addressed by DoReMi. Without access to the appropriate infrastructure, research effort will be restricted. Experimental radiation research is wholly dependent on the availability of appropriate radiation sources that are reliable, capable of delivering a range of radiations, are robust and accurate. Low dose research also needs access to well defined epidemiological cohorts, reliable databases and biobanks and as well the appropriate platforms for analysis. During the first 18 month period DoReMi has evaluated reports from members on available facilities and has begun to identify the needs of the consortium and the wider research community. We identified existing facilities at DoReMi partners’ institutions via a web survey. The need for access to a facility offering low dose rate exposure of animals was identified. Consequently, two new partners possessing low dose rate irradiation facilities, one in Norway and one in Japan, were recruited to the consortium via a competitive call. For smaller scale experiments, an additional low dose rate facility in Stockholm is available. Two other needs in terms of irradiation facilities were also identified: 1) a facility for internal contamination (subject to future clarification on the optimal use of existing facilities) and 2) facilities for exposures with different radiation quality such as microbeams and heavy ions. The cross-evaluation of research vs. infrastructure needs will be performed during next period.

A survey and workshop was also organised to identify radiation exposed cohorts that are suitable for inclusion in future molecular epidemiological studies. Information on sixty studies on cohorts of persons exposed to low dose radiation were obtained, 26 of which were related to occupational exposure, 10 to environmental exposure and a further 24 to medical exposure. However, the biosamples needed for molecular studies had only been collected in 16 cohorts. The actual availability and usefulness of these samples for future radiobiological studies will be evaluated during next period. Activities to assess infrastructure needs will continue. The next workshop and web survey planned will consider requirements for the speedy implementation of the research roadmaps. All databases collected from the DoReMi surveys will be made available in an electronic form and the long-term archiving using the STORE databases will be explored.

Training and education are fundamental activities for the functioning and purpose of DoReMi. The specific objectives for the first 18-month period of the project have been to determine current needs for training and education activities within the community, to assess availability at institutions offering appropriate training, and to explore processes for networking and sponsorship of courses. A Training and Education Committee (TEC) was set up with membership from DoReMi partners to provide input and help with setting policy and priorities. All initiatives were discussed at meetings of the TEC. Course sponsorship was piloted by opening an internal call for 2-week courses to be hosted by partner institutions, on topics identified by HLEG, MELODI and DoReMi as being mission critical. Six courses were funded in the first 6 months of 2011, and they were judged to have been very successful, both in terms of personal gain, and in attracting students and graduate researchers from a wide range of backgrounds. This call will be repeated each year, with the benefit of experience gained from participant feedback. Information about future courses will be provided via the DoReMi and MELODI websites. In order to ensure the optimal European involvement in the training and education network the planning has been evolved compared to the original proposal. The most promising approach appears to be to be run the network training activities on a cooperative voluntary basis through an extended Training and Education Committee that will include interested experts from outside the DoReMi consortium. Plans are underway to operate through regular networking workshops, possibly held in conjunction with the annual MELODI International Workshop. DoReMi funding is available for travel of experts to such meetings. An exploratory DoReMi/MELODI training and education meeting is planned in conjunction with the 2011 MELODI Workshop in Rome.

Dissemination of information on ongoing low dose risk research to the general public, the scientific community, policy makers and stakeholders is an important part of DoReMi networking activity. The DoReMi website (http://www.doremi-noe.net/) is operational: The publicly accessible part of the site contains general information on scientific aspects of low dose radiation research as well as aspects of training and education activities and of infrastructures. The website is seen as an important tool for internal and external communication. Through the website we will promote interdisciplinary interaction and increase European integration of research as well as facilitate the spreading of knowledge and enhancing our visibility outside of DoReMi. Key documents such as the DoReMi TRA, as well as the links to the MELODI website, other platforms and EURATOM RTD activities can be found on the website. Input from the wider scientific community is actively encouraged via the website to allow efficient development of new research strategies within DoReMi and MELODI.

3. The expected final results and their potential impact and use (including the socio-economic impact and the wider societal implications of the project so far)

Although much is known about the quantitative effects of exposure to ionising radiation, considerable uncertainties and divergent views remain about the health effects at low doses. In 2009, the European High Level and Expert Group (HLEG) identified a series of key policy questions to be addressed by a strategic European research agenda. This resulted in the establishment of the MELODI European Research Platform, Multidisciplinary European Low Dose Research Initiative) to sustain the impetus and continue evolution of the research programme via the SRA. DoReMi will act as an operational tool for the sustained development

of the MELODI platform during the next years, creating sustainable integration of European research on low dose risk and providing answers to key policy questions. The DoReMi joint programme for research focuses on the areas identified by the HLEG and MELODI as being the most promising in terms of addressing and resolving the key policy questions. By addressing the scientific basis underlying the system of radiation protection DoReMi is contributing directly to strengthening the credibility of scientific evidence relevant to the development of radiation protection policy. Ultimately DoReMi can be expected to contribute more widely to radiation protection through engagement with International Commission on Radiological Protection and other national and international bodies.

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DoReMi List of beneficiaries:
(Note that the beneficiaries 13-22 joined the project on 1 July 2011 onwards, from the beginning of the 2nd reporting period.)

Beneficiary no.	Beneficiary name	Beneficiary short name	Country	Date enter project	Date exit project
1 (Coordinator)	Radiation and Nuclear Safety Authority	STUK	Finland	1	72
2	Institut de Radioprotection et de Sûreté Nucléaire	IRSN	France	1	72
3	Helmholz Zentrum München	HMGU	Germany	1	72
4	Commissariat à l'Energie Atomique	CEA	France	1	72
5	Health Protection Agency	HPA	UK	1	72
6	University of Pavia	UNIPV	Italy	1	72
7	Istituto Superiore di Sanitá	ISS	Italy	1	72
8	Belgian Nuclear Research Centre	SCK-CEN	Belgium	1	72
9	Bundesamt für Strahlenschutz	BfS	Germany	1	72
10	University of Stockholm	SU	Sweden	1	72
11	Centre for Research in Environmental Epidemiology	CREAL	Spain	1	72
12	Institut Curie	IC	France	1	72
13	Universitaetsklinikum Erlangen	UKER	Germany	19	72
14	Johann Wolfgang Goethe-Universitaet, Frankfurt am Main	GUF	Germany	19	72
15	Universitaet Rostock	UROS	Germany	19	72
16	Norwegian University of Life Sciences	UMB	Norway	19	72
17	Norwegian Radiation Protection Authority	NRPA	Norway	19	72
18	Nasjonalt Folkehelseinstitutt	NIPH	Norway	19	72
19	Agenzia Nazionale per le Nuove Tecnologie, l'Energia e lo Sviluppo Economico Sostenibile	ENEA	Italy	19	72
20	Institute for Environmental Sciences	IES	Japan	19	72
21	Dublin Institute of Technology	DIT	Ireland	19	72
22	Erasmus Universitair Medisch Centrum Rotterdam	Erasmus MC	Netherlands	19	72

DoReMi WP structure and WP leaders