MELODI Statement

(15 April 2013)

on a

Short- to medium-term research agenda (I) for R&D projects to improve the scientific basis for radiation protection in Europe and (II) on the building of an integrated research platform for the promotion and administration of research in radiation protection in Europe in the wider context of the Horizon 2020 initiative of the European Commission

MELODI is the European Platform dedicated to low dose radiation risk research. In April 2009 five partners (BfS, CEA, IRSN, ISS and STUK) previously involved in the High Level Expert Group (HLEG) signed a Letter of Intent, in which they jointly marked their intention to progressively integrate their R&T programmes in low dose radiation risk research with similar R&T programmes funded by the European commission. MELODI has thus constituted a platform for radiation protection research in EUROPE to promote the idea of joint programming and integrated funding for R&T. A key point of the evolving platform is the openness of MELODI to all national R&T organisations and regulatory bodies as well as stakeholders in Europe interested, willing and capable to sustainably engage in such an integration process. Based on this intention and under guidance of the initial signatories MELODI was founded in 2010 as a registered association with 15 members.
The purpose of MELODI is:

- to develop a strategic research agenda (SRA) and to propose R&T priorities for Europe in its field of competence
- to seek the views of stakeholders on the priorities for research, keep them informed on progress made, and to contribute to the dissemination of knowledge.
- to interface with international partners like WHO and IAEA.
- to organize open MELODI scientific workshops.

Up to now, the MELODI workshops have been the driving force for MELODI to review the state of knowledge on low dose radiation effects at the international level, with the focus on identifying open questions and uncertainties relevant to radiation protection. The workshops are used to develop and continuously refine the SRA for low dose research in Europe and roadmaps for the key research fields, to scope the research area and to prioritise topics of immediate and medium term action for each of the key research fields. As an immediate output of the workshops MELODI summarizes in yearly statements what has been achieved and in which direction the field of low dose research should evolve. The recommendations of the MELODI statements were used and integrated in the launch of EU-calls for research proposals on prioritised topics.
Up to the end of 2012, MELODI reached a total of 22 members and organised 4 open workshops, developed a SRA and updated it on a yearly basis and published yearly statements on research priorities in the field of low dose radiation research.

The following statement of the MELODI governing board provides information on research priorities, which are currently being refined into an extended Strategic Research Agenda of MELODI, elaborated on the basis of the concepts developed by HLEG, of the transitional research agenda of the Network of Excellence DoReMi and of the proceedings of the annual workshops (1st MELODI workshop, 28-29 September 2009, Stuttgart; 2nd MELODI workshop, 18-20 October 2010, Paris; 3rd MELODI workshop, 2-3 November 2011 Rome; 4th MELODI workshop, 11-14 September 2012, Helsinki). This executive statement of the MELODI governing board updates and consolidates the MELODI statement from October 2011.

The research calls by EURATOM for R&T projects have been led by the policy goals to improve radiation protection standards in Europe, and to prioritise and focus European research efforts to achieve maximal impact on scientific knowledge and avoid duplication of research, with a view to consolidate the current scientific basis for the system of radiation protection, as recommended by ICRP and defined in the Basic Safety Standards. These goals are fully supported by MELODI.

With the Horizon 2020 initiative, the European Commission will disband the traditional framework programmes, and will introduce new management modes for research and training within EURATOM. While the administrative processes will be reorganised, radiation protection will remain a key EURATOM objective. Joint and/or coordinated research activities, in particular in the fields of effects and risks from low doses from industrial, medical or environmental exposures, of radioecology and of radiological and nuclear emergency preparedness will be further supported by EURATOM to provide a pan-European basis for a robust, equitable and socially acceptable system of radiation protection.

In this regard, MELODI together with ALLIANCE, EURADOS and NERIS will act as a focal point to promote research in the field of radiation protection in Europe and its member states. It is in the interest of the scientific community to ensure cost-efficiency in managing future research and training programmes and to foster high-performance research in radiation protection in Europe. This implies the promotion of interdisciplinary collaboration by attracting scientists from other disciplines and research areas to the field of radiation protection and the development of innovative mechanisms for 'joint programming' within the wider field of radiation protection and between national and European research and training programmes.

MELODI will prepare, in close collaboration with ALLIANCE, NERIS, EURADOS and others the implementation of the radiation protection part of the EURATOM research and training programme. To achieve this goal, a new umbrella organisation will have to be set up, with appropriate governance structures, statutes and procedures. In order to achieve this goal, MELODI itself is also strengthening its governance structures, statutes and procedures. The ongoing development of the Strategic Research Agenda (SRA) in the field of low dose research in parallel with similar activities in radioecology and nuclear emergency preparedness, the implementation of structures and procedures for priority settings and the establishment of a strong, cost –efficient management structure will lay the foundation for future research and training programmes in radiation protection in Europe.

The Fukushima nuclear accident has highlighted again the necessity to consolidate the scientific knowledge on radiation risk at low doses in a way that emergency response measures, especially for the general public in directly affected regions and beyond, can be based on the best scientific evidence that conveys to the public the validity of measures taken in order to simultaneously protect public health and the environment, and ensure the economic and societal continuity in the country.

MELODI recommends the introduction of research projects specifically addressing the long lasting situations in Fukushima and Chernobyl where Europe could join national and international efforts to develop suitable cohorts for the purpose of long term research. This could be of interest for cancer and non-cancer somatic effects as well as for other health effects, in particular of impaired cognitive function. Considerations of the quality and reliability of radiation dosimetry will be critical in determining the feasibility of such studies and their statistical power to provide insights into the health impact of radiation exposure in such situations. Apart from demonstrating the solidarity with the people affected by Fukushima and Chernobyl, this could be a further incentive for European R&D teams to join efforts with teams from affected countries.

European R&D activities in this research area have to be backed up by complementary organisational dispositions ensuring maintenance and development of competences by adequate education & training activities and access to suitable infrastructures, i.e. irradiation facilities, epidemiological cohorts, data- and biobanks and analysis platforms.

The present radiation protection system is mainly based on scientific knowledge from epidemiological studies, which have played an important role in assessing the magnitude of radiation risk in the dose range down to about 100 mSv, although more recently studies indicating risk at lower doses and dose rates are becoming available. Low dose radiation risk may involve natural radiation exposures as well as industrial and medical exposures (including therapeutic out of field exposures as well as diagnostic exposures).

Conjoint epidemiological and mechanistic studies are proposed to further improve evaluation of radiation risks and overall radiation protection. Epidemiological studies continue to contribute to low dose risk research and particularly assessments of risks from low dose rate chronic exposures,

risks from internal emitters and non-cancer risks. However, further refinement of low dose risk estimates will necessitate the close association of epidemiological with experimental mechanistic studies. For example, by using suitable molecular and cellular biomarkers, the value of future epidemiological studies (molecular epidemiology) for radiation risk research is expected to be maximised for prognosis in accidental situations as well as in diagnosis in medical exposures. To achieve maximal value, validated and reliable biomarkers are required for exposure, for effects on the cellular and tissue level, individual radiation sensitivity and, most importantly, for different consecutive stages in the development (in-situ stages) of radiation-associated diseases. Any research should include a realistic assessment of the associated uncertainties.

Experimental evidence suggests that both effects in target cells and effects and responses in the tissue environment (microenvironment) contribute to radiation-induced disease. The relative importance of these effects for different radiation qualities, at different dose levels and exposure conditions (acute, chronic, fractionated) in relation to different diseases is currently not sufficiently understood. Experimental work can best contribute by seeking dose levels where disease-associated effects are or are not observed, either in target cells, in the tissue environment or in the interacting system of both (tissue, organ or organism). Recent findings indicate that radiation effects do not only include potent genetic but also epigenetic and immunological control mechanisms that may be of importance for cell and tissue specific effects, individual radiation sensitivity and trans-generational responses. The role of tissue and cancer specific stem cells in radiation responses needs to be clarified as well. Careful analysis of cellular and tissue level regulation pathways should allow the application of systems biology approaches for risk evaluation purposes.

The experimental and epidemiological studies require a commitment to collect and to sustainably archive biological materials and data and to assure their actual utilization.

Mathematical and computational modelling of experimental data will allow a better understanding of the radiation track and energy transfer as well as the mechanisms of radiation effects (1) at the genomic level (including genome-wide analysis studies (GWAS), transcriptome, spliceosome and epigenome, (2) at other intracellular targets such as the mitochondria, (3) at the level of target cells and (4) at the tissue environment. In this context, MELODI recommends enhanced development of omics-based analysis capabilities (including microarrays and next-generation sequencing) in a scope of future multidisciplinary research projects. The combination of modelling efforts and animal, cellular and epidemiological data applying systems biology approaches will provide further insights into biological effectiveness of radiation quality.

According to MELODI, priorities for forthcoming and long-term future research should take into account the need to investigate effects of ionising radiation of different qualities, i.e. high-LET radiation on radiation-induced cancer and non-cancer diseases as well as on individual variation of radiation risks. All efforts should include a careful dosimetric approach. The long-term priorities include the following areas:

(1) for direct effects on radiation-induced diseases

- Identification, establishment and continued follow-up of suitable cohorts of radiation exposed populations for epidemiological studies related to cancer and non-cancer effects. A re-assessment of dose (uncertainties) is highly recommended
- Identification of the synergistic effect of combined exposure with environmental pollutants, to better match the real situation of an exposed population.
- Identification, development and validation of biomarkers for radiation exposure, effects and disease.
- Continuing development of suitable whole animal as well as human cellular models (including somatic stem cells) for radiation carcinogenesis and non-cancer diseases which bear clear relationships to human diseases.
- Examination of the impact of low dose and low dose rate radiation effects on pathways/processes contributing to human pathologies. This involves the understanding of the relationship between early and late effects, targeted and non-targeted effects as well as the role of delayed genetic instability.
- Identification of the nature and number of target cells at risk for specific radiation related diseases in humans.

- Clarification of the contribution of radiation effects in target cells as well as radiation effects and responses in the tissue environment and interaction between both target cell and tissue environment at different dose levels to the development of radiation-associated diseases.
- Examination of the impact of low dose and low dose rate radiation effects on pathways/processes contributing to non-cancer disease such as cardio- and cerebro-vascular disease, cataract and impaired cognitive function.
- Better understanding of the risks of internal emitters following internal contamination with radionuclides, paying attention to the type of decay, particle size (if applicable), the intake pathways, chemical speciation of the radioelement (and its daughters) in the tissue or body fluids and the biodistribution. Comparison of the theoretical impact using biological effectiveness data with the experimental data.

(2) for individual and general health and radiation protection issues

- Understanding the impact of inter-individual variation of radiation risks in relation to cancer and non-cancer diseases, and how this might impact on dose response relationships in populations.
- Examination of the impact of low dose and low dose rate radiation effects on immune function.
- Understanding the effect of age-at-exposure on radiation risk, from unborn child to adult ageing stage.
- Examination of the effect of cell death in carcinogenesis during chronic irradiation in tissue level.
- Understanding of the dependence of radiation risk on gender
- Analysis of the role of trans-generational effects and heritable radiation effects

As an ongoing process, MELODI develops and periodically updates the long-term SRA and makes use of the yearly MELODI executive statements to recommend short- to medium-term priorities. These remain in principle unchanged to the statement 2011. In the years to come priority should be given to:

- Quantification of the role of ionising radiation in the development of non cancer disease such as cardio- and cerebro-vascular disease, eye lens opacities and impaired cognitive function after low dose (< 500 mSv) irradiation.
- Development of suitable biomarkers for exposure, cellular and tissue effects as well as for in situ stages of diseases. The biomarkers should be usable for molecular epidemiological studies.
- Clarification of the role of effects in target cells and in the tissue environment (including stem cells and cells of the immune system) in a dose range with clear focus on low doses and low dose rates. This may include *in vivo* detection systems as well as suitable *in vitro* systems.
- Identification and analysis of suitable epidemiological cohorts if available with archived biomaterial to improve low dose radiation risk assessment by reducing uncertainties especially for the age- and gender-dependency of radiation risk. Uncertainties due to the exposure assessment should be clearly announced. Suitable data and biomaterial banks should be established with a clear focus on the possibilities to share data, material and knowledge within the scientific and wider radioprotection community.
- Development of guidelines for short, medium and long-term exposure and health risk monitoring in case of a major nuclear accident in Europe. This is to ensure the public that all possible scientific efforts are undertaken to record, document and analyse exposed populations in the scientifically best available way to generate in a comprehensive manner information about health consequences from possible accidents in the future.