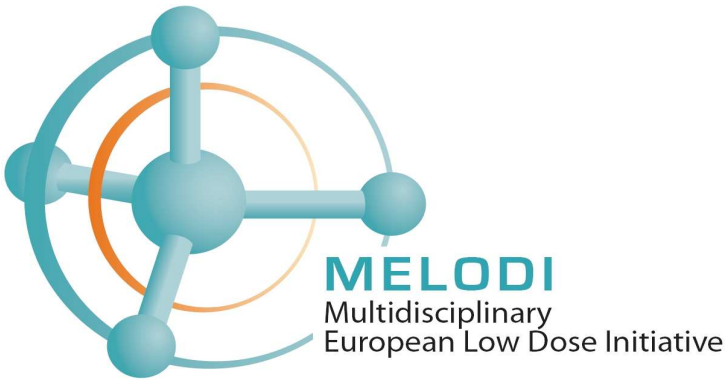

MELODI –
Multidisciplinary European Low dose Initiative

First Draft of Strategic Research Agenda (SRA)

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1. STATUS OF THE SRA

1.1 Aims

The SRA Working Group is tasked

- to develop the long-term strategic research agenda (SRA). This should serve to guide the coherent integration of national low dose R&D programmes, and to facilitate the process of preparing EURATOM calls in this field, under the responsibility of the European Commission.

- to make recommendations on suitable persons who may be invited to serve on the MELODI Scientific Advisory Committee

The overall aim is the consolidation of the European protection framework in the area of low dose exposure to ionizing radiation. This requires a forward thinking agenda to structure and establish the operational procedures for development of a **Multidisciplinary European Low Dose Initiative - MELODI platform** to ensure long term commitment (>20 y) to low dose research in Europe.

This will require development of new and original research lines in a holistic approach regarding metabolic stress, radiation induced stress and the effects of ageing, comparing radiation stress with other stressors such as other physical and chemical agents and infectious agents (bacteria, viruses etc)

Key scientific issues that should steer the SRA have been identified by HLEG, namely:
(1) shape of dose-response curve for cancer
(2) investigation of individual radiation sensitivity
(3) consideration of induced non-cancer disease

Three further cross-cutting issues that need to be considered are
(1) radiation quality
(2) tissue sensitivity
(3) internal emitters

1.2. INTRODUCTION *(background, aims, purpose of SRA: promote well-targeted low dose research in Europe)*

The presence of natural ionising radiation, or exposures to ionising radiation (IR) from human activities: nuclear weapons, mining, atomic energy production, nuclear waste, industrial and medical uses of different radiation sources, air and space flights is a matter of public concern with regard to radiation induced health risks. In spite of the fact that the health risks from high dose radiation exposures are relatively well understood and are efficiently dealt with by current radioprotection measures (ICRP) very little is known about the effects associated with low dose and low dose radiation exposures.

The current scientific consensus is that the health effects which should to be addressed are:

Cancer – including secondary cancers
Heart disease
Neurological effects
Effects on the central nervous system (CNS)
Lens opacity
Adverse effects to normal tissue from radiation therapy

After profound analysis of the situation, the High Level Expert group (HLEG) provided a detailed report (www.hleg.de) on basic scientific aspects and corresponding research needs to obtain answers to the following questions.

1.2.1 Overarching questions

- How robust is the current system of radiation protection and risk assessment?
- How can it be improved?
- What are the areas of greatest uncertainty in radiation research?
- What are the areas of greatest uncertainty in radiation protection?
- How to prioritise the questions and research needs to address these questions?

The SRA should form a link with the HLEG report, identifying a multidisciplinary strategy to address the overarching questions outlined in that report, The SRA should reflect high level thinking, in such a way that it should remain valid for several years, as a guide for the medium term MELODI strategy, providing sufficient visibility and stability for member organisations, scientific teams and stakeholders. The SRA needs to be concrete enough to serve as support for national programmes and associated calls, yet not be over-prescriptive, allowing ample initiative to R&D teams to formulate innovative proposals.

1.2.2 The early years

The answer to the questions posed by the HLEG is expected to come from multidisciplinary low dose research in Europe. To this end the HLEG recommended creation of a Network of Excellence (NoE) on Low Dose Research towards Multidisciplinary Integration (DoReMi) by an EURATOM call (Fission-2009-3.1.1 FP7 call).

DoReMi was set up in January 2010 and has 12 institutional partners (STUK, IRSN, CEA, HMGU, HPA, UNIPV, SCK-CEN, BfS, SU, CREAL and IC) coordinated by Prof. Sisko Salomaa (STUK, Finland).

The 7 Work packages are:-

WP1: Coordination and management,
WP2: Structuring MELODI,
WP3: Education and Training,
WP4: Infrastructures,
WP5: Shape of dose response for cancer,
WP6: Individual radiation sensitivity for cancer (and non cancer) and
WP7: Non-cancer effects.

1.2.3 The longer term

WP2 concerns structuring and establishing the operational tool for developing the Multidisciplinary European Low Dose Initiative, i.e. the MELODI platform to ensure long term commitment (>20 years) to low dose research in Europe. Thus, DoReMi is a transitional initiative providing EU financial support and scientific feasibility studies to facilitate and accelerate the integration process within the MELODI platform. MELODI itself is the vehicle for development of a new long term institutional European entity capable of sustainability and promotion of low dose radiation research on health risks and radioprotection.

To achieve this, a broad concerted effort is required to develop a long-term strategic research agenda (SRA) for MELODI (>20 years). The SRA should be largely based on scientific consensus integrating new research lines developed in the mid-term (6 years) transitional research agenda (TRA) of DoREMi, education and training, infrastructures and future multidisciplinary approaches on low dose and low dose rate research in both the national and international context as well focus on societal needs. In order to be effective, the SRA will require periodic updating in line with future developments arising from new scientific knowledge and technologies.

2. SCIENTIFIC VISION

2.1.The present situation *(An overview of the present scientific context; knowledge, gaps and challenges)*

The present system of health risk evaluation and radiation protection is based on current scientific knowledge and societal considerations of acceptance.
For high radiation doses where epidemiological studies are particularly significant the radiation protection system is reasonably well established. Nevertheless, uncertainties still exist and continue to need attention, such as:

- the shapes of dose response curves for different types of cancers and non-cancer diseases;
- sensitivity to *in utero* irradiation;
- variations in radiosensitivity between children and adults;
- individual radiation sensitivity and predisposition to cancers and certain non-cancer diseases;
- biological effectiveness of different types of radiation;
- sensitivity of different cell types and tissues;
- mixed radiation exposures;
- fractionated exposures;
- interactions of radiation with chemical agents;
- radiation quality effects;
- effects of radionuclides and internal contamination;
- radiation versus, or combined with, chemical toxicity;
- non-targeted effects of radiation.

The ICRP protection system uses the linear no threshold (LNT) assumption derived from high dose radiation effects extrapolated to the low dose region. It is essentially a pragmatic and cautious approach for protection purposes. At present, it does not take into account subtle differences in radiation responses of different tissues (tissue weighing factors), radiation quality and energy dependent effects (soft/hard X-rays, protons, neutrons of different energies), fractionated and low dose rate exposures or individual radiation sensitivity.
It has been widely recognized that epidemiological studies have limitations for statistical reasons for estimation of radiation risks at low doses (<100mGy) and very low doses (<10mGy). Of course, It is important to extend risk estimation down to environmental exposure levels such as mGy or nGy (see also Smith 2010, Wakeford and Tawn 2010). It is now generally accepted that, as also pointed out by the HLEG report, low dose risk estimations need to be based on an understanding of the mechanisms involved, developed from additional mechanistic studies. Indeed, at low exposure levels epidemiological studies need to be reinforced by mechanistic studies in order to increase their relevance for health risk assessments.
There are many reasons why knowledge about radiation induced insults from low doses and dose rates remains elusive. The effects of low doses are usually much smaller than those for high doses, making it much more difficult to assess risks/effects due to inherent methodological/sensitivity of detection limits. Furthermore, other parameters may interfere with or modulate the observable low

dose effects because radiation is only one of many environmental insults producing overlapping effects. There is no particular health effect that has been identified as being unique to radiation.
Ideally, as a baseline, one should have extensive knowledge on the unperturbed living system, the basic homeostatic equilibrium between metabolic activity, structure and function of cells and tissues, the “normal” physiological and proliferative state of organs and the whole human body. This is already an objective of basic science and medicine.
As a general scheme one may consider radiation-induced events at the level of cells or the whole organism as follows: Energy deposition by different types of radiation in living systems will create perturbations in the homeostatic equilibrium (metabolism) as well as reversible or irreversible damage (structural changes) which may be detectable at the molecular level by sensitive physical, chemical and biological (omics) methods. In fact, omics should make it possible to identify specific biomarkers directly linked to radiation exposure. For health risk assessments, the most important question will be which type of radiation exposure, radiation dose and dose-rate will give rise to a pathological outcome such as cancer and non-cancer diseases in the short or long term. Also at this level of investigation, it should be possible to identify specific biomarkers that can predict or are precursors of pathological developments towards defined diseases.
The scientific challenges will be to define the borderline between normal metabolism, normal physiological responses and a disease-prone perturbed metabolism being a precondition of pathology that may be induced by low dose ionising radiation.
Some types of radiation-induced damage are similar to those induced by other types of stresses (heat, solar UV, chemical pollution, endogenously). Therefore types of damage that are potential signatures of ionising radiation effects, i.e. may be attributed to observed biological (pathological) effects of ionizing radiation, need to be identified including approaches based on microdosimetric analysis of different radiation qualities. Their contributions to the detrimental health effects of radiation need to be assessed. Further, concomitant exposures to radiation and other types of stresses and/or the possible interactions/synergisms with different types of agents have to be taken into account. In some instances, comparative studies between the pathological effectiveness of certain chemical agents and ionising radiation exposure should be very informative in placing the importance of ionising radiation into context with other pollutants.
The difficulty of studying all these aspects lies in the fact that ionising radiation (or other agents) on the one hand and the biological structures and functions on the other are by themselves very complex with many parameters having to be considered. A number of these are listed:-
Ionising radiation:

- types (α, β, γ, protons, neutrons, X-rays, heavy ions);
- energy distribution and deposition;
- radiation track structure and microdosimetry;
- dose;
- dose rate;
- dose fractionation;
- external exposure;
- internal contamination exposure**.**

Biological effects on cells:

- all cell constituents;
- genetic and epigenetic background;
- hereditary effects;
- normal (oxidative) metabolism;
- energetic status;
- proliferative (differentiation) and developmental status;
- age;
- specificity of cells and tissues;
- specific cellular structures and metabolism functions;
- perturbed metabolism in diseased cells (cancer, non-cancer);
- inflammation;
- allergy;
- intra-intercellular signalling;
- normal and disease perturbed tissue (organ) physiology;
- regulatory systemic, immunological and hormonal effects;
- effects of gender;
- other confounding factors due to environmental exposures to physical agents (temperature, electro-magnetic fields), chemical and biological agents (virus, bacteria).

Advances in research along these lines should allow judgements to be made and the potential to improve the robustness of radiation protection on low dose health risks.

The SAR should thus focus on radiation specificity and biological effects indicating the onset or aggravation of pathological conditions.

2.2. Summary of the fundamental molecular interactions associated with ionising radiation

Oxidative free radicals are produced by normal oxidative metabolism in living cells/tissue. Most of these radicals are scavenged or inactivated by cellular antioxidants and anti-radical defence systems but some may initiate endogenously cellular damage. However, these antioxidant defences are limited, may be overcome by activity-mediated or environmental radiation or chemical drug-induced oxidative stress. Additionally, anti-oxidative defences appear to depend on age and life-style. This is thought to increase the oxidative burden during the course of life, being precursors of a number of non-cancer diseases such as Alzheimer's and Parkinson's, premature ageing which affects the central nervous system and arteriosclerosis, heart and onset of strokes which affect the cardiovascular system and metabolic diseases such as diabetes, as well as different types of cancers.
Ionising radiation is generally assumed to exert in living systems direct effects (about 40%) as well as indirect effects (about 60%) due to the production of oxidative free radicals if formed close to important targets. In terms of overall cellular damage to DNA, ionising radiation at low doses is adding relatively few additional oxidative lesions in relation to those formed endogenously. However, low dose ionising radiation does induce in addition to endogenous-like damage low levels of double-strand breaks, some of which are complex, and complex damage sites which are

known to be very deleterious to cells and tissues, although their identification remains to be elucidated. They are believed to constitute the genotoxic lesions initiating mutations and genomic instability and may result in cellular transformation and cancer. Not much is known on the induction of oxidative damage and other lesions to cellular proteins and membranes by ionising radiation. However, there is increasing evidence that oxidative damage induced in proteins and membranes may considerably modify cellular structures and functions including mitochondrial functions, enzymatic DNA repair and also defences against oxidative damage. From ionising radiation's interaction with living matter it can thus be inferred that direct action will induce direct and long lasting structural modifications in macromolecules (if these are not replaced or repaired). Whilst the majority of oxidative damage in DNA may be relatively well taken care of by available DNA repair systems, complex damage is difficult to repair and accompanying radiation-induced accumulation of oxidative stress in proteins and membranes impairs important general metabolic and DNA damage recognition, repair and signalling functions. In addition to these effects, oxidative free radicals have been identified as being involved in intercellular signalling between irradiated and unirradiated cells and these communication processes are perturbed by low dose radiation. The relevance of these perturbations to health effects of radiation remains to be resolved.

Interestingly, most normal metabolic cellular functions are based on partially reversible redox and free radical reactions. Perturbances of these are associated with nearly all cancers and non-cancer diseases. Thus, one of the most important future challenges of low dose research is to establish to what extent ionising radiation perturbs normal cellular metabolism at the cell, tissue and organ level as well as perturbing the equilibrium of normal systemic signalling (homeostasis) of the human body and as a consequence promotes or induces pathological conditions.

In this respect, it is interesting to note that ionising radiation of different qualities vary considerably in their ability to induce direct structural and indirect radiation effects (oxidative, free radical mediated stress), and also, by definition, the rate by which free radicals and cellular damage are produced (effects of dose rate) may condition short and long term radiation effects.

The local distribution of the free radicals produced in cells and tissues as well as the pre-existing cellular oxidative stress and the available arsenal of antiradical and antioxidant defence systems (under genetic and epigenetic control) will determine the final biological outcome. In this view, it is important that the basic metabolic, proliferative, genetic, epigenetic, immunological, hormonal and physiological status of cells and tissues need to be investigated as an important pre-determinant for low dose radiation-induced insults.

Therefore, it will be of outmost importance to launch research to define quantitatively the levels of oxidative stress in cells, tissues and organs that are part of normal homeostasis and those levels that can be achieved by low ionising radiation exposure and if they may be regarded as precursor conditions to perturb the homeostasis for the development of cancer and non-cancer diseases. Additionally, it will be important to determine relevant molecular and structural changes induced uniquely by ionising radiation directly and that are in the long term persistent and contributing to cellular, tissue and organ dysfunction. The roles of different cell types; stem cells, progenitor and germ cells will need to be defined.

2.3 Questions identified as being key issues for MELODI

These are grouped according to the three key issues specified by the HLEG and have been collated from the HLEG report and discussions at the MELODI workshop in Stuttgart, September 2009

(1) Shape of the dose-response curves for cancer

- **Mechanisms**
  - What is the dependence on track structure and microdosimetric features of the tracks spatial distribution of energy deposition events? – interplay between spectrum of damage induced and its repairability in modulating the shape of the dose response curve.
  - What is the dependence on dose rate and LET?
  - What are the **molecular biomarkers** that can be validated and used in molecular epidemiology to define pathological impact and disease? – both cancer and non-cancer
  - Are **molecular biomarkers** available or may suitable biomarkers be developed for radiation-induced carcinogenesis (molecular signatures) in animals and humans and as biological dosimetry of human exposure?
  - What is the implication of irradiation of **stem cells** in carcinogenesis?
  - Can the processes underlying radiation-induced carcinogenesis be **modelled** for different types of cancers?
  - To what extent does the sensitivity to cancer induction differ for exposures during various **developmental stages** (e.g. *in utero*, young children, adults)?
  - What is the effect of radiation quality and the sensitivity for **different tissues** for radiation-induced carcinogenesis and disease?
  - What are the mechanisms underlying the appearance of secondary cancers or out-of-field low dose radiation effects in humans?
  - Can good **animal models** be developed to analyse radiation-induced cancers other than acute myeloid leukaemia or are good animal models available?
  - What is the impact of **non targeted effects** on radiation-induced carcinogenesis? - cellular signalling at low dose and low dose rate; adaptive responses to radiation
  - What is the relationship between **oxidative stress**, DNA damage complexity, chromosomal damage, translocation, DNA damage signalling, perturbed cell cycle regulation, senescence, apoptosis and the induction of cancer (and non-cancer diseases) by radiation?
  - What is the role of **epigenetic** effects including chromatin remodelling on health effects induced by radiations of different quality?

  What is the impact of **immunological status** (systemic factors) on radiation-induced pathological responses (inflammation, cancer, non-cancer)?

Dosimetry

- How can the information on dosimetry and biokinetics of **internal emitters** be improved to understand radiation-induced short and long term effects?
- What are the most important **radionuclides** to focus on (scoping of internal emitter studies) to gain better understanding of their short term radiotoxicity and long term effects (cancer and other pathologies)?

Omics and systems biology

- How can research based on 'omics' contribute to a systems biology approach to processes underlying radiation-induced carcinogenesis and non-cancer diseases? - Involvement in homeostasis?
- How can 'omic' approaches enhance our understanding of the effects of radionuclides?

Epidemiology

- What are the cohorts that can be used for molecular epidemiological approaches to understand low dose radiation effects (cancer, non-cancer)?
- Is it possible to launch an epidemiological study on low dose induced second cancers?
- Is it possible to launch an epidemiological study on out-of-field low dose radiation effects in humans?
- Can existing biobanks (STORE, GENEPI) be used in molecular epidemiological studies?
- Can specific epidemiological studies be conducted to reveal and analyse specific radiation responsive cancer prone tissues?
- Can feasibility studies be performed on non-cancer effects (cardiovascular, lens opacities, neurological effects)?

(2) Individual radiation sensitivity

An overriding priority is for this research to include ethics considerations.

Mechanisms

- What is the evidence that individual sensitivity plays a significant role towards cancer and **non-cancer pathologies** through modulating radiation response to exposures at low dose and dose rates? - Links to cancer predisposition.
- Are there **genetic and/or epigenetic modifiers/biomarkers** available that allow determination (monitor, predict) of individual sensitivity to radiation, cancer and disease development?
- Which mammalian and non-mammalian systems should be able to validate candidate **biomarkers** related to individual radiation sensitivity?
- To what extent are **inflammatory and immunological factors** involved in individual radiation responses?
- To what extent do **non-targeted radiation responses** differ in different individuals?
- What are the factors involved in individual sensitivity and dependent on **genetic background**, age, gender and lifestyle?
- Can a multilevel approach using cells in culture, tissue cultures, non-mammalian and mammalian models help to analyse individual sensitivity?
- Can an **'omics'** approach help to elucidate individual sensitivity and be used to develop a systems biology approach?
- Can omics help to define tissue weighing factors?
- How do **stem cell and progenitor cell** biology contribute to individual radiation sensitivity and tissue responses?
- Do **genetic or epigenetic modifiers** of radiation responses affect individual radiation responses similarly at low and high LET radiation?
- Is individual radiation sensitivity dose rate dependent?

- Can risk assessments for individuals be developed on the basis of molecular indicators for cancer and disease? – leading to **genetic profiling** of individuals?
- Are mechanisms and factors governing cancer susceptibility independent of dose rate and radiation quality, or are there differences in the degree to which risk modifiers contribute to individual risk at different dose rates and radiation qualities?
- Can the magnitude of individual sensitivities be quantitatively assessed and compared?
- Can non-mammalian and animal models contribute to a better understanding of the mechanisms involved in individual sensitivity?

Epidemiology

- Are there cohorts available, or which can be set up, that allow establishment of direct links between molecular experimental studies and epidemiological studies ("molecular epidemiology") on individual sensitivity?
- Are there cohorts available, or may be set up, to allow modelling of individual sensitivity responses?
- Can populations at risk be identified and distinguished by biological markers?
- Can realistic cohorts be designed, including low dose exposures and protracted exposure scenarios (medical imaging cohorts, nuclear workers, flight crews), that allow detection of individual sensitivity by available **biomarkers**?
- Can **biomarkers, gene** markers and phenotypic traits indicate specific radiation risks in human individuals? -Ethics problems to be considered

(3) Non-cancer effects

The system of radiologial protection is mainly based on excess risk of cancer induced by ionizing radiation. The main data on stochastic effects have been derived from situations with a very short exposure at a high dose rate, like Hiroshima and Nagasaki populations. Much less information is available on effects of internal exposures or long term consequences on non-cancer effects such as cardiovascular dysfunction, neurological alterations, lens opacities, or effects on other physiological functions.

In order to tackle these important aspects there is an urgent need for multidisciplinary approaches involving cardiology, neurology, toxicology, dosimetry, radioecology, embryology, bioinformatics and biomathematics, pharmacokinetics…

Mechanisms

- What are the mechanisms involved in radiation-induced **lens opacities**?
- What are the mechanisms involved in radiation-induced **cardiovascular** effects?
- What are the mechanisms involved in radiation-induced effects on the **central nervous system** (neurogenesis) and **behavioural** changes?
- Are these mechanisms consistent with stochastic or deterministic dose responses?
- What are the mechanisms involved in radiation-induced effects on the **digestive system**?
- What are the mechanisms involved in radiation-induced effects on reproduction and **trans-generational** effects?

- What are the mechanisms involved in radiation-induced effects on the **immune** system (inflammation, immunodeficiency)?
- How can systemic effects be distinguished from organ specific effects?
- What is the impact of **non-targeted effects**?
- What is the impact of radiation quality, dose and dose rate, acute and chronic exposure?
- What are the age, gender, population and temporal effects?
- What is the possible impact of synergistic and interactive effects with other agents?

Concerning the mechanisms involved in tissue responses it has to be noted that for many years great effort has been focused on cell-level responses to radiation (eg, study of DNA repair mechanisms) which have contributed to an understanding of low dose effects and individual radiosensitivity. However, this has not greatly increased our understanding of low dose responses that may involve other processes than repair. Certainly non-targeted effects are to a large extent independent of repair processes, and tissue or system level responses such as the development of cardiovascular disease almost certainly do not require efficient repair to develop.
To better understand tissue responses, the key questions are:

- To what extent are in vitro experiments on single cell types relevant in predicting responses of more complex tissues and organs to low doses. e.g. are the biological responses uniform amongst different cell types and between tissues?
- Is there a long-term adverse tissue response at low doses in tissues other than cardiovascular/cerebrovascular tissue and lens (bone, brain etc)?
- Are the risks of impairment of system level response adequately known at low doses (e.g. immune competence, cognitive ability, reproductive capacity, osteogenic regeneration)?
- Does the known genetic predisposition to cancer risk extend to non-cancer risk of tissue level responses at low doses? If so, which biological pathways are influenced by these genetic factors?

Epidemiology

- Do **confounding factors**: diet, smoking and many other life-style factors, plus genetic and epigenetic factors, multi-stress exposures contribute to non-cancer effects?
- What are the main non-cancer diseases to be considered after low dose radiation exposure?
- Are there suitable cohorts available? (out-of-field exposures in radiation therapy, CT scans, nuclear medicine patients, interventional cardiologists, dentists, staff preparing radiopharmaceuticals (PET imaging), workers exposed to alpha emitters (Mayak), uranium miners and others (fluorspar), aircrews)

2.4.Research Priorities

The research priorities derived from the above listed key questions are presented in the following order: I) radiation quality related issues and shapes of dose response curves, II) biological mechanisms, III) epidemiological issues. This includes research on the interaction of low dose ionizing radiation with macromolecules and living matter, the biological consequences at the cellular and tissue level as well as human health risks.

2.4.1. Radiation quality related issues

Research on

- ionizing radiation energy deposition,
- track structure,
- definition of the “dose” (Monte Carlo),
- dose rate,
- dose fractionation in relation to well-identified and characterized damage to biologically important macromolecules,
- main cellular targets (aspects of antiradical protection, protective mechanisms in cells and tissues (reversibility, persistence, reparability, long term perturbation) in relation to tissue weighing factors,
- biological effectiveness on divers biological endpoints.

Extensive research is needed aimed at understanding the impact of radiation quality on those aspects of cell responses which could be relevant in risk estimates for both cancer induction and non-cancer diseases. They should include oxidative damage and stress, cell signalling modulation in the microenvironment and the relative roles of “targeted” and “non targeted” effects.

Studies to be prioritized:

- *Track structure methods still need further improvements, particularly for ions of great importance and also for understanding neutron effects.*
- *The role of the different characteristics of initial damage and repair pathways with respect to different radiation qualities, still need to be investigated particularly clustered/complex damage in conjunction with microdosimetric approaches and nature of the chromatin.*
- *The biological significance of complex chromosome aberrations preferentially induced by high-LET radiation should be evaluated.*

Some criteria to be applied:

- Integrated studies with common theoretical and experimental approaches should preferably be aiming to understand the mechanisms related to low dose and low dose-rate effects. (The important issues of internal dosimetry, microdosimetry and retrospective dosimetry have to be covered in association with other EU programs such as EURADOS).
- In vitro and non-low dose studies are recommended provided they are part of a clear strategy towards a better understanding of in vivo low dose effects.
- Research on microbeam-induced radation effects with ions or soft X-rays) should be encouraged.

2.4.2. Biological mechanistic issues

- **Research on "omics" (transcriptomics, proteomics, metabolomics…).** This involves essentially identification of pathways responding to or affected by specific types of radiation or exposure conditions (dose rate) and discrimination of the effects from normal homeostasis or background noise. This may allow useful comparisons between radiation-induced stress (radical, ROS) responses to that induced by other stressors (chemicals, infectious agents, nanoparticules…). Specific effects of different types of radiation on well identified components of biological pathways (oxidative metabolism, cellular signalling, oxidative metabolism, death pathways, DNA repair pathways, ..) should give rise to the development of **biomarkers that are specific for exposure.** These may include markers for specific types of damage (clustered damage etc.).The link between the disruption of specific pathways and radiation-induced pathological conditions (cancer and non-cancer) may give rise to biomarkers for specific pathologies and to the definition of corresponding molecular signatures that can be then further developed and validated in animal models or in specific human diseases. The stability and persistence (short or long term) of these specific **biomarkers for radiation exposure and disease will be an important issue of research.**
- **Research on systems biology**
  The information collected on the multiple pathways may then become part of An overall **systems biology approach** which will allow modelling of biological dose responses (cancer, non-cancer).
  Two types of systems biology approaches should be considered (1) an approach to describe the overall set of pathways and interactions of components ('networks') wihin a single cell. This approach should allow understanding and predicting of the cellular responses to stress such as low dose radiation in relation to that encountered by other agents. (2) an approach to understand the inter cellular communication between cells within a tissue and communication between different tissues in the whole body.
- **Stem cell research**
  Research on radiation quality effects on normal and mutated (including precancerous and cancerous) **stem cells** should define their sensitivity and their developmental capacity with respect to their role in radiation-induced carcinogenesis and disease.
- Research on **pathological effects** induced by ionizing radiation of different radiation qualities using a systems biology approach will give rise to extensive modelling (modelling of important biological and pathological mechanisms, link between energy deposition and both cancer and non-cancer pathologies). The models will then be validated on specific animal models (AML?) and some well designed human retrospective and prospective cohorts.
- Research on **individual radiation sensitivity** to cancer and non-cancer diseases should be promoted. It should cover the following items: sensitivity specific developmental stages, children versus adults, sensitivity of different cell types (stem cells and progenitor cells) in different types of tissues), redox profiles (oxidative stress) in different radiation sensitive and resistant individuals, genetic (SNPs, sequencing..) and epigenetic profiles, the DNA repair capacity, capacity to undergo radiation-induced death, the

immunological, hormonal, inflammatory, general health status of radiation sensitive and resistant individuals, latencies for different pathologies.

- Research on **intra- and intercellular signalling** after low dose radiation appears to be important in order to define localised radiation effects linked to the cellular microenvironment and more systemic effects (involving the release of cytokines, specific mediators and clastogenic factors) linked to inflammation and disease. The possibility that these bystander effects may give rise to long term and trans-generational effects including genomic instability needs to be studied as well.
- Research on **radiation-induced oxidative stress** involves many inter-related responses. Different radiation qualities and dose rates are likely to be linked to specific types and ratios between different types of oxidative damage (simple and complex (clustered) damage). Oxidative stress is linked to
  - signalling of cellular damage,
  - perturbations of normal cellular metabolism, mitochondrial dysfunction and normal cell differentiation
    development and cell cycle progression,
  - induction of pathological diseases (cancer, non cancers), apoptosis, senescence, genetic and epigenetic (changes in chromatin structure) effects including possible radiation-induced epigenetic reprogramming of germinal cells, inflammatory, hormonal, immunological changes (systemic factors) in relation to the onset of pathological effects.

  Oxidative stress thus plays an important pivotal role for inducing alterations of normal homeostasis that may lead to the development of cancer and non-cancer diseases.

  - Research on **internal emitters** following internal contamination with radionuclides needs to be promoted. It is clear that the local uptake and distribution (biokinetics) radiation quality of the emitters and dose-rate effects are of greatest importance. However, also confounding factors such as chemical toxicity, specific damage to cellular and tissue components using toxicological and nanotechnological approaches should be considered. It would be most profitable and relevant to focus studies on: tritium and actinides in the nuclear industry; mining industries that cause radium and thorium exposures; diagnostic, and possibly therapeutic, applications of radiopharmaceutical in nuclear medicine
    Individual whole body and/or organ dosimetry is often difficult with internally deposited radionuclides but is highly important for any dose-response research. Nuclear medicine applications are possibly a rich source of experimental study because planned, monitored and controlled delivery of radiopharmaceuticals gives scope for precise dosimetry follow-up.

2.4.3.. Epidemiological issues

Research on suitable human epidemiological cohorts remains a very high priority of research in forthcoming years. Epidemiological studies are considered to be essential hallmarks for the evaluation of radiation health risk taking into account the effects of factors that may modify risk of diseases, including age, gender and factors in the general environment and genetic, epigenetic factors and non-targeted radiation-effects. Not only promising research on existing retrospective epidemiological cohorts should be continued, but also research on new prospective cohorts should

be initiated on cancer and non-cancer diseases. Epidemiology should be combined with molecular / biomarker assays on the study subjects .

- Until specific biomarkers for exposures and disease are validated appropriate biobanking of materials has to be considered. It might be possible to use some existing biobanks such as STORE, GENEPI.
- Cohorts have to be backed up with good dosimetry encouraging retrospective dosimetry for existing ongoing studies (eg. cytogenetics, EPR etc.) and also for newly initiated studies.
- Proper medical surveillance of the cohorts is essential. Low dose exposures from medical radiology and radiation therapy, including nuclear medicine, can be the most productive cohorts because exposure is taking place in a controlled environment with good dosimetry and controlled discrimination of exposure fields.
- Cohorts such as children exposed to CT scans, occupationally exposed individuals such as interventional cardiologists, flight crews, radiation therapy patients with significant out-of-field exposures (conformational radiotherapy) should be considered and, of course, studied not only for cancer incidence but also the non-cancer conditions of concern.
- Links should be sought with ongoing epidemiological studies such as ALPHA-RISK (i.e. health risks from domestic alpha exposure), CHILD-THYR (i .e. risk of thyroid cancer following early life exposure to 131I), GENE-RAD-RISK (i.e. radiation exposures at early age and impact of genotype on breast cancer risk), ARCH (i.e. long term research on health consequences of radiation from the Chernobyl accident) and CHILD-MEDRAD. and CHILD-MED-RAD (i.e. health risk follow up prospective study of trans-national cohorts of patients with substantial paediatric diagnostic exposures).
- The promoted suitable epidemiological studies should be associated with (accompanied by) mathematical modelling taking into account mechanistic aspects in order to support low dose health risk evaluations..
- Overriding **ethical issues** should be sorted out and settled by consensual interaction with the national ethical commitees involved.
- Combined epidemiological and animal model studies may be of use in identifying risk variants. Inclusion of various functional assays for radiation sensitivity in epidemiological studies will increase statistical power for identifying risk factors in later genome wide association studies. Moreover, additional functional cohorts could come from human longevity studies (cancer susceptibility and radiation response), cancer susceptible individual and radiation therapy patients with aberrant responses.

2.5. Justification and expected outcomes

2.5.1.. Shapes of dose response curves and radiation quality effects.

2.5.1.1. Basic aspects

The basic scheme involves the relationship between radiation energy deposition and biological effects. So far, most information has been collected for low-LET photon radiation. Thus, not much information is available on the role of radiation quality in radiation protection issues although both low and high LET components are present

in many environmental, occupational and medical exposures.The qualitative and quantitative differences between low and high-LET ionizing radiation rely on the spatial (and temporal) energy deposition properties of the radiations at the nanometer, micrometer and higher scales. The quantity “absorbed dose” (dose) for low dose high-LET exposures is of scarce meaning. In this condition a low number of cells are irradiated with a significant dose associated with single radiation tracks. In this case, the interaction of irradiated with non-irradiated cells is crucial to understand risk of cancer in an organ vs the effects in a cell. For instance, with a typical dose of 10 mGy deposited by 100 keV/μm α-particles less than 5% of cell nuclei are traversed by a track each of the hit cells absorbs a dose of the order of 200 mGy in a very short time, independently of the fluence rate.. The energy deposition within the hit nucleus represents a very high “local” dose along the α-particle track. The very short timescale relative to energy deposition of a high LET particle traversal (of the order of picoseconds) may affect the radiobiological effectiveness.

2.5.1.2. General knowledge gaps.

Radiation weighting factors, w_R, as used by ICRP have been specified for stochastic effects as “factors by which the mean absorbed dose in any tissue or organ is multiplied to account for the detriment caused by a specific type of radiation relative to photon radiation (ICRP, 2007). The concept of average organ absorbed dose may be inappropriate when energy deposition is highly inhomogeneous. Thus, at low average organ dose high-LET irradiation may result in a significant level of cell damage. It can be questioned whether the health effects of low doses of various radiation qualities can be evaluated by the w_R approach and whether the currently adopted w_R values are reasonable estimates for radiation protection purposes. This problem holds in particular for neutrons, since estimation of risks associated with them is only indirect, relying on scaled estimates of risk from low-LET radiation (ICRP Publication 99, 2005). The shapes of the dose effects curves after low- and high-LET irradiation can be very different, and the results obtained for the former cannot be extrapolated to the latter just on the basis of rescaling factors. Also, the influence of dose rate is expected to be different.
This clearly emphasizes that specific strategies are needed for the assessment of the risk of low-dose, high-LET radiation. Furthermore, studies on the dependence of biological effects on radiation quality can be extraordinarily useful tools to test mechanisms underlying these effects.
The observation that inflammatory response is a predisposition to malignancy and may be a risk factor for the development of many clinical conditions lends support to the hypothesis that radiation injury may predispose to a range of health consequences wider than was previously thought. Understanding whether indirectly affected cells can contribute to the effects of irradiation at low doses in a radiation quality-dependent fashion can have important implications.

2.5.1.3.. Identification of knowledge gaps and prioritization.

To improve our 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 main biological “targets”. Critical questions are to what extent quality effects are responsible for radiation-induced (oxidative) stress and conditions its possible reversibility, how radiation quality affects the initial damage (DNA and non-DNA), and its time evolution (considering both faithful repair and mis-repair processes), intra- and intercellular signalling, and non-DNA-targeted effects. A deeper understanding is needed on the relevance of complex and clustered DNA damage induced by a single

radiation track in chromosome aberration, mutation induction and carcinogenesis and also on the possible role of dose-rate and that of mixed radiation fields (including possible synergistic and adaptive phenomena).

2.5.1.4. Future Research lines

The mechanisms that govern the possible different shapes of dose- (fluence-) effect curves at low dose still need further investigation. Especially, radiation-quality specific studies are needed to explore processes possibly leading to biological effects relevant to cancer and non-cancer risks. An "omics" and system biology approach for these radiation effects is advisable, coordinated with epidemiological studies. Experimental and modelling approaches should be combined.

Important research issues involving radiation quality effects are:

- Studies on initial damage characteristics (related to time and space evolution of track structure) and its time evolution (including DNA damage repair and misrepair processes), their conversion into chromosome and other endpoints relevant for low dose cancer and non cancer induction.
- Studies on the radiation quality dependence of epigenetic phenomena and occurrence of genomic instability.
- Studies on the radiation quality dependence of oxidative damage and stress (generation of reactive oxygen species), cell signalling and microenvironment (cell-to-cell communication).
- Studies on mixed fields effects (possible additive or synergistic phenomena and adaptive responses).
- Studies on the role of dose/fluence rates, and the extent to which this varies with different radiation types.

2.5.1.5. Expected outcomes

The above mentioned studies should provide a better perspective of the relationship between low dose exposures for cancers (which currently steers present radiation safety regulations) and the more recently appreciated non-cancer disease and the mechanisms by which they can be radiation-induced.

2.5.2. Individual radiation sensitivity

2.5.2.1. Basic aspects

This research largely responds to public concerns on how to protect every individual and how to define the individual's health risks after low dose radiation exposure. Obviously, further knowledge on individual radiation sensitivity would help to better evaluate personal risks from accidental or therapeutic low dose exposures. In radiation therapy, better knowledge on this topic should help to further limit the risk of radiation out-of-field and other side effects. The development of reliable biomarkers for exposure and predisposition for disease (cancer and non-cancer) is an essential pre-requisite. Such biomarkers are not yet close to deployment. It is likely that in the current framework of DoReMi such biomarkers will be developed. At present, it will be necessary to store material from on-going research cohorts. However, at the present state it is not clear what to store because we do not know what markers will emerge. Furthermore, there are formidable ethics restrictions placed on this type of research in Europe and of course logistical limitations on what may be collected from human subjects. For the time being, it seems appropriate to store retrievable DNA (frozen or possibly fixed blood cells) and

samples from blood serum or even skin biopsies. The importance of setting up prospective study cohorts of persons exposed to low radiation doses is paramount.
Because of the necessity for ethics approval it seems best to concentrate first on available medical cohorts from diagnostic radiology such as children undergoing CT scans and nuclear medicine or radiation therapy. Moreover, it will be important that a substantial proportion of the cohort is available for recall in the event that an eventual individual sensitivity biomarker requires some other, as yet unknown, assay that can not be performed with the banked material.
Of course, a critical factor is proper dosimetry. Whatever the effect measured, it has to be related to dose and/or more subtle parameters such as track structure (including micro and nanodosimetry approaches). For in vitro experiments on cells, tissues and whole animals good dosimetry has a long tradition. However, problems arise with A-bomb survivors, Chernobyl cohorts and also some prospective study cohorts such a national surveys of radiation workers where standard badge type monitoring is, at best, approximate. Thus, prospective studies from medical radiology or radiation therapy appear to be more promising because the systems are already in place for doses and fields to be well specified.
Using such cohorts, knowledge on genes and genetic polymorphisms (DNA repair, cell cycle checkpoint genes, oncogenes, genes of DNA and general metabolism, hormonal and immune responses etc.) as well as epigenomic imprints should be sought in order to define their role in individual low dose radiation responses. This knowledge then can be used to define sensitive subpopulations in the cohorts and the effects of confounding factors such as age, sex, gender, lifestyle, physiological and reproductive status,and concomitant exposures to other physical, chemical or infectious agents.
Some endpoints have shown promise in the field of markers for individual radiosensitivity e.g. G2 sensitivity, dicentric chromosomes or micronuclei and may need further study. However, to date, all assays have fallen short of being reliable individual predictors. For example, when applied to groups of normal or over-responding radiotherapy patients a bi-phasic profile can be seen but there is a considerable overlap. Applying some newer assays for markers of radiation exposure (γH2AX, 53BP1) and specific DNA repair activities (RAD50, MRE11) have shown greater promise for indicating intrinsic individual radiation sensitivity and repair capacity and this work should be encouraged. Some tests (e.g. MRE11) may even be predictive for long term cancer risks in human. These newer cytological and molecular assays have to be applied on a large scale for validation. It is possible that an integrated analysis based on a constellation of results from several markers will emerge as the most reliable way to specify an individual's sensitivity.
In-bred laboratory animal models cannot represent the intrinsic variability of a human population. However, they can be useful for validation purposes. Specific endpoints can be examined and specific modifiers can then be further explored using suitable animal models (e.g. for osteosarcomagenesis (RB1), mammary tumours (Aps) and medullablastoma (ptch). Radiation quality and dose-rate effects should be considered as well.

2.5.2.2. Expected outcomes

From molecular and initial human studies over the timescale of 3-5 years there is a reasonable likelihood that some suitable biomarkers for radiation exposure and pathological conditions (cancer) will become available. Probably, several biomarkers and indicators will have to be used in suitable cohorts in combination to assess individual sensitivity.
However, it should be realised that cohorts and other human studies require ethics approval. Experience has shown that obtaining approval in different European countries is very time consuming and introduces considerable delays to getting the actual research

started. It would be a considerable advantage if the MELODI platform would explore ways that facilitate ethics approval throughout Europe overcoming national boundaries for such studies.

2.5.3.Non cancer effects

Non-cancer effects at low doses cannot be readily explained by the mutational theory (DNA paradigm) underlying the extrapolation of cancer risk from high to low doses (LNT). It has been traditionally assumed that the non-cancer effects and diseases show a threshold at doses that are well above the levels of exposure typically encountered in the public environment, at work or from medical diagnostics. However, some epidemiological evidence as well as various tissue responses and non-targeted effects recently observed at low doses call for new experimental (mechanistic) and epidemiological studies that address the extrapolation issue.

2.5.3.1. Present state of science in this area of research

Tissue responses

Acute responses to high-dose radiation exposure (therapeutic and accidental) have well-documented consequences. There are both qualitative and quantitative differences in the reaction of different cell and tissue types which can be most conveniently summarized by ranking organ radiosensitivity to unit dose. Chronic effects of high dose exposure also show tissue-specific differences, but these are primarily related to radiation fibrosis, malignant growth, or as yet mechanistically unexplained tissue-level damage to the eye lens and the vasculature. Until very recently no great attention has been paid to tissue differences in the response to low dose exposures in the range typically experienced by most people. The majority of the radiobiological studies on low dose responses have focused on readily accessible and easily cultured monotypic in vitro cell models (peripheral blood lymphocytes, fibroblasts) to the exclusion of more complex tissue-level models. There is a plethora of phenomenological studies reporting acute tissue-level responses to low doses. These studies focus primarily on non-targeted effects such as the adaptive response, abscopal effects and bystander effects, but consistently lack a plausible explanation of the underlying biological mechanisms. Consequently, little information is available on the constancy of acute low dose damage recognition, signalling and response mechanisms across tissues, and on the long-term development of radiation effects in different tissues at low doses.

Cardiovascular diseases

It has been generally accepted that high dose (several Gy) radiation exposure to the heart or other parts of the circulatory system result in long-term increases in circulatory disease risks. Over the past 10-15 years evidence has been emerging from the long term follow-up of atomic bomb survivors and other populations that relatively low dose acute exposures (< 2 Gy) are also associated with increased circulatory disease risks. Although the estimated relative risks are smaller than for cancer, it is clear that radiation-associated circulatory disease deaths will account for a substantial fraction of the total radiation impact on mortality in the atomic bomb survivors. However, those epidemiological data do not, and probably cannot, provide definitive evidence of increased circulatory disease risks following low dose (say 0.005 to 0.5 Gy) exposures. Despite this uncertainty, these findings have increased interest in efforts to identify mechanisms for long-term radiation effects on the circulatory system and prompted the re-examination of circulatory disease risks in other populations.

As far as the potential mechanisms of the radiation induced cardiovascular diseases are concerned, there are several hypotheses (inflammatory, micro vascular, mutation induced, and others). An inflammatory mechanism that is more consistent with deterministic effects is currently more plausible.

Cognitive functions

Dose response relations for radiation effects on cognitive functions show thresholds around 100 mGy for exposures of the foetus between weeks 8 and 15 but the current judgement is that induction of IQ deficits at low doses is of no practical significance (ICRP Publication 103). The mechanistic understanding of the effects of radiation on the foetus is coupled to the developmental stage of the brain during the critical weeks 8-15 when the cell proliferation and migration is maximal, while the later stages seem less critical. Therefore considerable interest was generated when a study on the effect of low doses of ionizing radiation in infancy on cognitive function in adulthood was published in 2004. The conclusion was that low doses of ionizing radiation to the brain in infancy influence cognitive abilities in adulthood. This discovery of a second time window (at infancy) for radiation induced adverse effects on the cognitive functions opens new aspects for much needed investigation

Lens opacities

At high doses (0.5-2 Gy), ionizing radiation causes lens opacities in humans that may manifest as cataracts, and other changes that hamper vision. Several recent epidemiological studies have indicated that the prior assumption of a relatively high threshold dose may not be justified. Indications of lens opacities have been reported in US interventional radiologists, Icelandic pilots exposed to cosmic radiation, people exposed to Chernobyl fallout, and after exposure to X-rays. Studies on A-bomb survivors suggest that there is either no threshold or the threshold is much lower than was previously assumed.

2.5.3.2. Other biological and physiological effects

Recent animal experiments have demonstrated that chronic exposure by ingestion of low doses of radionuclides may induce effects on unsuspected biological targets, such as the central nervous system, liver and major organism metabolisms. Chronic uranium exposure at low doses led to molecular and cellular effects on metabolisms of xenobiotics, vitamin D, cholesterol and iron. Behavioural and cognitive effects were also reported after chronic uranium exposure at low doses, in addition to the well-known nephrotoxic effect of uranium. In human populations, uranium has been shown to affect bone metabolism. There is also some evidence that chronic contamination by cesium-137 could affect cardiovascular functions.

Generally speaking, it is likely that the underlying mechanisms involve as starting points (initial events) radical formation and radical (oxidative stress) induced lesions very similar to those implicated in cancer. However, subsequent stages involving different tissues, metabolic, hormonal, immunological, inflammatory and tissue micro-environmental responses) are likely to be rather specific and different from those identified for cancer. It will be important to attract new disciplines into the field of radiation research. In the case of non-cancer diseases, parmacotoxicologists, cardiologists, neurologists, toxicologists, ophthalmologists have to be involved. Similar to research on radiation induced cancers, confounding factors such as smoking, diet, lifestyle, gender, age, genetic background etc. have to be considered.

Suitable cohorts may be constructed from radiation diagnosis and radiation therapy patients as well as from interventional cardiologists, dentists, flight crews etc .
***Non cancer endpoints have thus to be included in prospective studies in addition to the cancer surveillance*.**

2.5.3.3. Expected outcomes
We expect to obtain relevant information on the mechanisms involved in non-cancer effects of low dose radiation exposures. In particular, a better understanding of the mechanisms will guide us to answer the important question on the existence or not of thresholds for non-cancer effects, i.e. whether the effects are of stochastic or deterministic nature.

3. NEXT STEPS

3.1. Evolution of research areas to be exploited

It is clear from the above questions relating to key issues that the research cannot be adequately undertaken by only extending already existing fields in radiation research such as radiation physics, radiation chemistry, radiation biology, radiation therapy and diagnostics, radiotoxicology etc. New lines of research have to be developed based on recent achievements arising from areas outside of radiation research to broaden thinking with a view to a new dynamism. For example, there have been in recent years many discoveries on specific metabolic functions and pathways, homeostasis, signalling mechanisms, stem cell biology, cellular stress, proliferation, genetics, epigenetics, systems biology, toxicology, genotoxicology, physiology, pathology, immunology, inflammatory research, hormone research, research on cell death (apoptosis, mitotic catastrophy, autophagy), the central nervous system, recognition and behavioural effects, molecular markers for imaging, effects of nanoparticles (nanotechnology), heredity, transgenerational transmittance, diseases (medical treatments and diagnosis of cancer and non-cancers, …).

3.1.1. Approaches to be considered

Classical
- Cytogenetic (Multi-FISH, chromosome painting) radiation chemistry, biochemistry, radiation sources, microirradiation, genetics

Emerging
- Transcriptomics, Proteomics, Metabolomics, Epigenomics, transcriptomics
- Systems Biology (Identification of molecular pathways)
- development of exposure and disease specific biomarkers
- inactivation of specific genes (miRNA, epigenomic silencing…)

New techniques:
- Molecular Imaging
- new radiation devices: microirradiation, synchroton, heavy ions, conformational radiation therapeutic devices, radiation pharmacology, immunoradiology
- QT-PCR
- Nanostring nCounter
- High throughput sequencing

- Reproduction - hereditary transmission
- 2 and 3D electrophoresis
- mass spectrometry electrospray, HPLC, chromatography,
- nanotechnology
- genetic an epigenetic imprinting,
- Molecular imaging
- MRI
- computer assisted tomography,

Epidemiology

Classical and molecular Epidemiology

- whole Populations
- retrospective and prospective cohorts
- mathematical modelling
- Reliable medical assessment and follow-up of suitable cohorts (short and long term pathologies)
- Genetic and transgenerational studies in mice and humans

Annex 1 gives a fuller list of the research fields to be considered and important topics that should be applied to the appropriate above approaches.

3.1.2. Infrastructures

For low dose and low dose rate research the lack of suitable infrastructures is at present a limiting factor. A strategy for the upgrading of the infrastructures should be thus given a high priority.

- Most important are suitable cohorts that allow at the same time molecular and medical follow up. Some cohorts of industrial and nuclear workers, medically exposed groups, residential radon exposures may be potentially informative. Additional cohorts of prospective nature should be generated such as patients with substantial paediatric exposures and some collaborative international studies (such as Mayak workers, Techa river cohort, Chernobyl children..) may be useful. The informativeness of these cohorts should be increased by conducting a regular survey on the information collected and documented including dosimetric issues, data storage conditions, availability of biological samples… Furthermore, mechanisms have to be set-up to ensure their continued availability for research, including data base management and periodic updates of follow-up. Harmonisation of the collected data and of the methods of collecting them has to be strengthened and the possibility of accompanying these studies by molecular (and mechanistic) studies to improve the statistical power and the overall informativeness of the studies by mathematical modelling.
- Also, suitable tissue banking is needed to be able to store and process different biological samples.
- Suitable sources with associated laboratory facilities able to deliver low and low dose rate radiation to cells, tissues and whole animals (both external beam irradiators and internal radionuclides) are to be identified and /or developed already during DoReMi and then made available in the MELODI context..

3.1.3.Education and training

In recent years, many European member states have lost key competences and are no longer capable of independently retaining their current research activities in radiation sciences, with implications for effectively fulfilling operational and policy needs and obligations. Thus, specific programmes aiming at knowledge management across generations have to be designed in order to achieve sustainable continuity and development. Important aspects to be considered are:
(1) the underlying scientific programmes have to address questions that are attractive to both young scientists and faculties of universities as well as to the management of research organisations.
(2) the attractiveness of the field has to be increased by a multiple approach implemented from Summer schools to master degrees, PhD and post-doctoral European research training programmes.
(3) In the long term, such programmes cannot be successful unless they do provide job opportunities to young scientists.
(4) In the present situation, sustainability of such programmes can only be achieved by a long-term commitment of funding bodies.
The MELODI platform does effectively respond to these needs and aims at establishing an integrated approach to education and training of research and teaching at Universities and non-university research organisations. Existing elements of education and training activities in this domain such as the European MSc course should be strengthened, making it compliant with the Bologna Process which creates the European Higher Education Area (EHEA) and is based on the cooperation between ministries, higher education institutions, students and staff from 46 countries, with the participation of international organisations. At present, only a few universities in Europe will have the resources to offer a full educational program at the basic as well as the advanced level of subjects such as radiation biology and radiation physics. Thus, an integrated approach is needed.
In line with this, the following steps are to be implemented:

- Audit of radiation courses in Europe (undertaken by DoReMi) to establish a European course (and/or summer school) in radiation biology and radiation protection with conventions with European universities and institutions
- Identification of stakeholders able to support long term sustainability.
- Proposition of EU calls directed to education and training that promote new ways of setting up new multidisciplinary interactive courses that are Bologna compliant and based on solid conventions with leading universities and research organisations and that allow inclusion of most recent research developments in the field of low dose radiation research and the evaluation of radiation health risks.

3.2. Maintaining the SRA

It is essential that the SRA is periodically revised in order to take account of new developments, achievements of research from DoReMi, feedback from the consultation processes listed above and the progressive unrolling of the SRA targets. Revision should include a statement of achievements in terms of scientific ground covered, the establishment of multidisciplinary and multinational teams and the development of infrastructures.
MELODI should organise on a permanent basis a team tasked with this review process and the team should make input, initially yearly, to the MELODI workshops.

The Scientific Advisory Committee should review and approve successive revisions of the SRA and pass them to the Governing Board for formal endorsement. At this point it may be circulated to all stakeholders and organisations as a support to the continued integration of national R&D programmes and to the formulation of R&D calls.
Revision should be made at least every 3 or 4 years and, if necessary, the MELODI Governing Board may wish to initiate more frequent intermediate revision in the light of any important developments. The timing and frequency of the revision needs to be well adapted to the main stream of budgetary procedures, including the Euratom call process.

3.3. ROADMAP

Knowing that the discussions on this first draft of the MELODI SRA will be further substantiated in the forthcoming 2nd MELODI Workshop October 18-20, 2010 in Paris the SRA Working Group considers it premature to outline a ROADMAP for MELODI that would be more detailed and thus even more meaningful than the Roadmap presented by HLEG in January 2009. Part of the projected low dose program is realized by the DoReMi TRA covering the next 6 years and involves important scientific feasibility studies and starting with putting into place important aspects of essential infrastructures and new approaches to education and training. From the above SRA it is clear that intrinsically, most prioritized research items will have to follow a more or less preset time scale. In this view, it is evident that the search for suitable biomarkers for defined radiation exposures (internal or external), predictions for the initiation of pathological pathways and for final pathological outcomes will come first in the research on radiation biology networking. Some of these biomarkers are expected to stimulate molecular epidemiological studies and the establishment of suitable prospective or retrospective cohorts (i.e.. prospective cohort of CT scans in children, induction of secondary cancers in out-of field radiotherapeutic sites). This research work will be accompanied by fundamental and mechanistic studies on the specific low dose and low dose-rate radiation effects together with their relationship to perturbation of cellular and tissue homeostasis and the induction of cancers and non cancers. This fully integrated research will highly rely on the input from non radiobiological research disciplines such as toxicology, immunology, inflammatory research, physiology, pathology, genetics, epigenetics, cardiology, neurology, ophthalmology etc. (see SRA). It is expected that in the long term a systems biology approach together with well defined epidemiological studies will allow mathematical modelling and the evaluation of low dose health risks.
Taking into account feedback from the MELODI GB, the outcomes of the 2nd MELODI workshop and the input of the MELODI SAC, the scientific community and the stakeholders the MELODI Roadmap should then (end 2010) give the forseeable timing of the different research lines as well as possible financial sustainability program.

3.4.Major considerations

- MELODI needs to promote multidisciplinary integrated low dose research in Europe

- Positive efforts are required to bring in ‘new blood’. These comprise specialists with skills in research areas that previously have not been associated with ionising radiation
- Sustainability of infrastructures, education and training
- Ongoing interaction and communication with stakeholders and the public is required.

3.5. Consultation

A working group of experts constituted by MELODI will list important domains of low dose research, prioritize scientific questions relevant for low dose radiation risk research and assess the corresponding research needs in the light of present EU funded research and other international programmes. In order to promote a high degree of multidisciplinary integration covering as wide range as possible of scientific areas a large consultation is foreseen of the general scientific community through specific MELODI (and also DoReMi) workshops and expert group meetings. E-mail contacts, the DoReMi and MELODI Web sites, contacts to the members of the MELODI advisory Board and to experts in complementary fields (not yet necessarily involved in radiation research) should be explored. In fact, DoReMi and MELODi workshops open to a large scientific community will be held to attract new scientific competences, new players and provide a driving force in the field. Additionally, links to other relevant European research projects will be sought. If necessary, specific working groups will be created to develop strategies to deal with very specific research items and issues (for example, new technological and ethics problems).
For the selection of actual research needs as well as topics for future scientific calls a hierarchy will be established based on priorities and consideration of presently funded projects to pre-defined criteria including relevance, feasibility, sustainability, expected outcomes etc.
A regular survey and mapping of national scientific research (as well as education and training activities) launched by MELODI will be required to identify original and novel research lines relevant to low dose research but as yet not realised. Further, the availability and sustainability of suitable infrastructures, education and training as well as modes of interaction and communication with stakeholders and the public will need to be developed.

Thus, it is recommended that there should be

- Fully interdisciplinary working groups held to develop, refresh and update based on on-going research and re-appraise the research areas and priorities
- Discussion forums set up to attract fundamental scientists
  (from radiation physics, biophysics, radiation chemistry, toxicology, imaging, physiology, immunology, cancer research, DNA repair, genetics, oxidative stress, epigenetics, molecular signalling, developmental research, nanotechnology, inflammatory research, ‘omics’, protein research, miRNAs, systems biology, medicine).
- Started a Series of MELODI sponsored mixed forums-conferences-seminars-colloquia on e.g.
  - molecular intra- versus extracellular signalling/ immunological responses
  - cellular damage/ epigenetics
  - nanotechnology/toxicology/internal emitters
  - ‘omics’ and systems biology

- stem cell research/ cancer/non cancer
- Infrastructures, radiation facilities, omic centres, animal research
- Training, degree courses, regulators, researchers etc

3.6. Establishment of the Scientific Advisory Committee (SAC)

The SRA working group was tasked with suggesting names of potential SAC Members and a list (not shown here) was delivered to the MELODI Governing Board. It comprises 22 names, including 7 persons located outside the EU. The list was chosen to include experts with well-founded reputations. It embraces a wide range of disciplines covering both the existing branches of radiation biomedical sciences and the new areas that this SRA document identifies as being important for attracting into the MELODI programme.

The next step is for the Board to discuss and finalize the composition of the first SAC. The President of MELODI will then formally issue invitations and, if accepted, appoint the members who are not representing a specific institution or country, but are serving MELODI as individual experts.

4. EXECUTIVE SUMMARY

The SRA Working Group was tasked to develop a long-term strategic research agenda to guide the coherent integration of national low dose R&D programmes, and to facilitate the process of preparing EURATOM calls in this field. The SRA builds on the initial considerations of the HLEG that formulated overarching questions concerning specified key issues. The SRA supplements a transitional research agenda (TRA) composed within the DoReMi network of excellence that considered shorter term research needs and priorities over the time scale of the first 5years. The SRA attempts to take this forward to structure and establish the operational procedures for development of a long term commitment (>20y) to low dose research in Europe.

The SRA thus attempts to look beyond the TRA and to define the broader concepts and directions that low dose research should achieve taking account of the needs of national and international stakeholders and, very importantly, the public perceptions and anxieties concerning low dose irradiation.

As a general scheme one may consider radiation-induced events at the level of cells or the whole organism as follows: Energy deposition by different types of radiation in living systems will create perturbations in homeostatic equilibrium (metabolism) as well as reversible or irreversible damage (structural changes) which may be detectable at the molecular level by sensitive physical, chemical and biological methods. It should be possible to identify specific biomarkers directly linked to radiation exposure. Additionally there is a high priority for research aimed at being able to define individual radiosensitivity and for this reliable markers are essential. For health risk assessments, the most important question will be which type of radiation exposure, radiation dose and dose-rate will give rise to a pathological

outcome such as cancer and non-cancer diseases in the short or long term. Also, at this level of investigation, it should be possible to identify specific biomarkers that can predict or are precursors of pathological developments towards defined diseases. The overall scientific challenges will be to define the borderline between normal metabolism, normal physiological responses and a disease-prone perturbed metabolism being a precondition of pathology that may be induced by low dose ionising radiation.

Priorities that need to be addressed concern fundamental mechanistic research ranging from radiation track structure and the deposition of energy in biologically important molecules; the resultant homeostatic perturbations and the steps in the cellular and tissue metabolic pathways that eventually lead to disease pathologies.
In fact, the main priorities are here the step-wise elucidation of the mechanisms of radiation-induced (oxidative) stress responses and their impact on radiation-induced cancers and non cancer diseases. To achieve this a holistic approach is proposed staring with radiation-specific effects, radiation-induced molecular, biological and pathological effects involving a systems biology approach as well as molecular epidemiology and mathematical modelling in order to come up with more solid low-dose health risk assessments. The pathologies considered are outlined in the report where the need is stressed for the MELODI platform to involve a constellation of classical and emerging technologies in a highly multidisciplinary approach. Elucidating the shapes of low-dose response relationships and resolving the question of thresholds is paramount to resolving questions of risk for both populations and individuals. Much is known about radiation-induced cancer in humans and animal models but this needs to be pursued particularly at low doses. More recently, the scientific community has realised that low radiation–induced health effects range well beyond cancer. The priority non-cancer areas that need to be brought into focus are cardiovascular, neurological and ophthalmic. The SRA notes that this will require input from disciplines, clinicians and scientists where there has been little or no prior involvement in radiation research.

This SRA represents a point early on in the MELODI programme, indeed prior to research outcomes from the DoReMi network. The programme will evolve; some lines of enquiry will emerge showing great promise whilst it will become apparent that others are less likely to yield answers to the key issues. Thus, it is essential to keep the SRA under review and periodic reassessment and revision. Revision is necessary to take account not only of specific research achievements but also the feedback from a wide ranging consultation with the scientific community and in particular from the MELODI workshops and the Scientific Advisory Committee.

5. REFERENCES

ICRP: International Commission on Radiological Protection 2007. The 2007 recommendations of the International Commission on Radiological Protection. ICRP Publication 103. Ann. ICRP 37(2-4)1-332.

ICRP: International Commission on Radiological Protection 1991. The 1990 recommendations of the International Commission on Radiological Protection. ICRP Publication 60. Ann. ICRP 21(1-3)1-201.

HLEG: www.hleg.de

MELODI : www.**melodi**-online.eu/

Smith GM. What is a low dose? Response to "Reply to 'The RBE of low-LET radiations' " Reply to the Response to "Reply to 'The RBE of low-LET radiations' " Comment on 'Updated estimates of the proportion of childhood leukaemia incidence in Great Britain that may be caused by natural background ionising radiation' Reply to "Comment on 'Updated estimates of the proportion of childhood leukaemia incidence in Great Britain that may be caused by natural background ionising radiation' ". J Radiol Prot. 2010 Mar;30(1):93-101;

Wakeford R., Tawn E.J. The meaning of low dose and low dose rate. J. Radiol. Prot. 30(2010)1-3.