Introduction to MELODI activities and the Strategic Research Agenda (SRA)

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Introduction

Human exposure to low ionising radiation from natural, industrial and medical sources is quite common, and there are concerns about the associated short and/or long term health effects.

Actual Radiation Protection Standards in Europe are based upon scientific knowledge (UNSCEAR) and recommendations of the International Commission on Radiological Protection (ICRP).

- Radioprotection for high doses is well established. However, with respect to low doses a number of uncertainties and open questions exist.

HLEG High Level Expert Group

- The report of the HLEG in 2009 pointed out that a **better understanding as well as the acquisition of new scientific knowledge is needed** to optimise radiation protection measures for workers, the public and the environment in order to **improve the protection of the public, radiation workers and medical patients from adverse radiation health effects.**

According to HLEG the **key questions** to be answered were the following:

- 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 research priorities?

HLEG also proposed an operational strategy for getting answers to these questions involving the setting-up of R&T in Europe on a long term basis, **through a dedicated organisation.**

Birth of MELODI and DoReMi

On these grounds a platform and a network of research have been created:

1. the **European platform MELODI « Multidisciplinary European Low Dose Initiative »** *consisting of major national bodies with research programmes and long term commitment to low dose risk research in Europe and designed to combine and pilot efforts on low dose ionising radiation research in Europe.*
2. (as part of the 7th Framework Programme of Euratom) the **Network of Excellence (NoE) DoReMi « Low Dose Research towards Multidisciplinary Integration »**, as *an operational tool for adressing/resolving HLEG key policy questions and developing the **MELODI** platform.*

MELODI

Multidisciplinary European Low Dose Initiative

Open RTD platform guiding priorities
in low dose research in Europe (long term 2010-2030)
www.melodi-online.eu

DoReMi

Low Dose Research towards Multidisciplinary integration

Network of Excellence 2010-2016 (short term)
www.doremi-noe.net

Structure of MELODI

- MELODI has been created to consolidate the European radiation framework in response to scientific, public and regulatory concern about low dose ionizing radiation health risks.
- Since January 2010 the MELODI platform has been an association according to the French Law 1901 with 22 members from prominent institutions which are in charge of radiation research and protection in Europe.
- **MELODI is a European research platform,**
  open to all interested scientific and regulatory organizations and stakeholders.

4th International MELODI Workshop 2012
Helsinki, Finland

MELODI Multidisciplinary European Low Dose Initiative

1.	• **BfS** Federal Office for Radiation Protection, Germany
2.	• **CEA** Atomic Energy and Alternative Energies Commission, France
3.	• **HMGU** Research Center for Environmental Health, Germany
4.	• **HPA** Health Protection Agency, United Kingdom
5.	• **IRSN** Institute for Radiological Protection and Nuclear Safety, France
6.	• **ISS** Direttore, Dipartimento Tecnologie e Salute Director, Technology & Health Department Istituto Superiore di Sanità, Italy
7.	• **ITN** Instituto Tecnologico e Nuclear, Portugal
8.	• **National Institute for Nuclear**, Chemical and Biological Protection, Czech Republic
9.	• **RIVM** National Institute for Public Health and the Environment, Netherlands
10.	• **SCK.CEN** Belgian Nuclear Research Centre, Belgium
11.	• **Stockholm University** Centre for Radiation Protection Research, Sweden
12.	• **STUK** Radiaton and Nuclear Safety Authority, Finland
13.	• **TEXNIO** Universitat Rovira I Virgili, Spain
14.	• **KVSF** Kompetenzverbund Strahlenforschung, Germany
15.	• **Universidad Madrid** Universidad Autónoma de Madrid, Spain

15 founding members of MELODI and recent members:

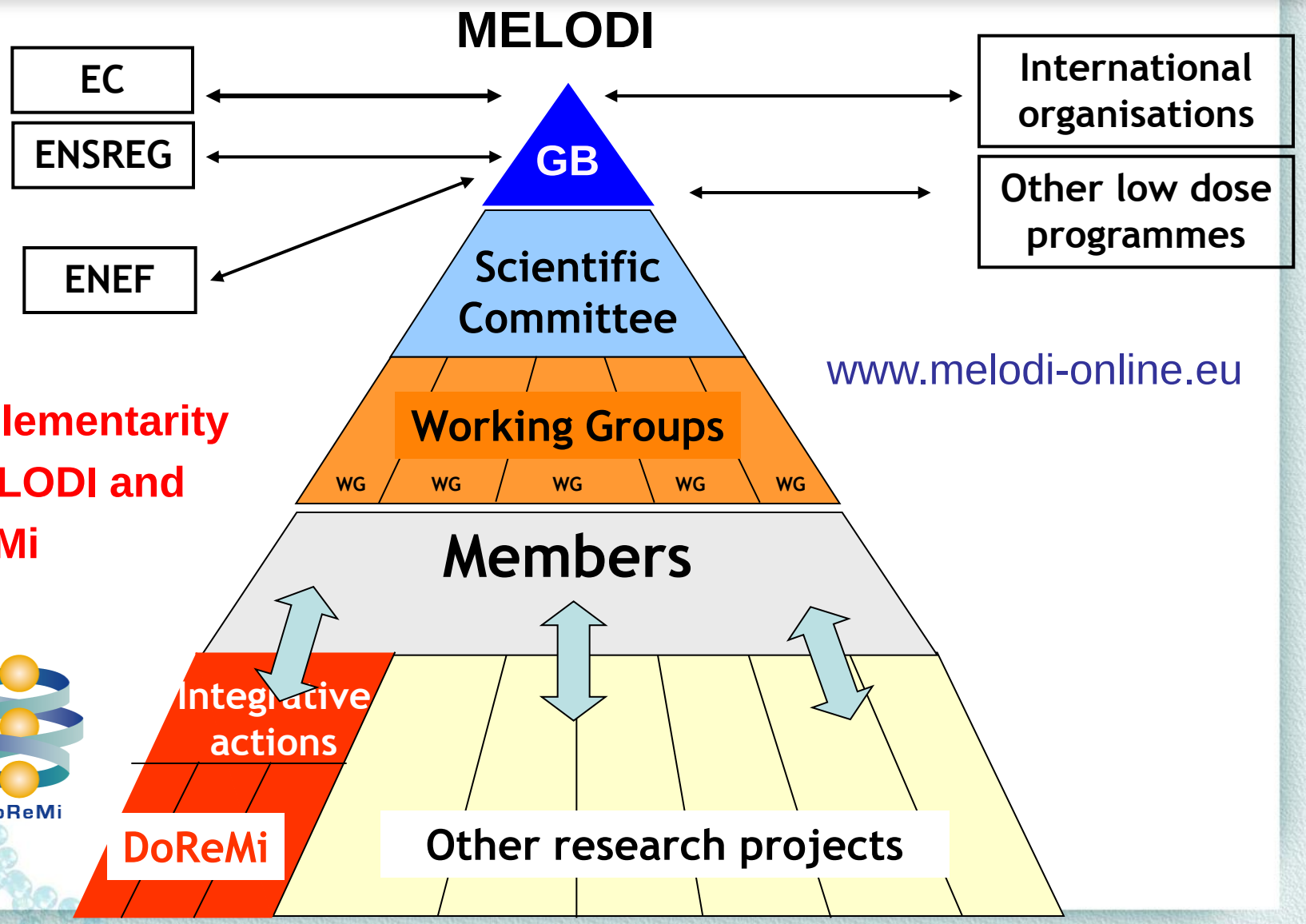
CREAL, Spain
DUTH, Greece
NCRRP, Bulgaria
NINCBP, Czech Republic
ENEA, Italie
IRA, Suisse
NRIRR, Hungary
SSM, Sweden
and
Dr.Wolfgang Weiss (BfS)
as honory member

MELODI
Multidisciplinary
European Low Dose Initiative

Structure of MELODI

MELODI consists of

- a '**General Assembly**' (GA), a '**Governing Board**' (GB) and a '**Bureau**' that runs the Association's affairs.
- The actual **President** is **Jacques REPUSSARD (IRSN, France**).
- A **Scientific Committee** (SC) of 9 renowned scientists in relevant key disciplines.
- **Ad-hoc working groups** which are non permanent structures dedicated to the coordination and elaboration of MELODI positions on specific issues.
- **The European network of excellence DoReMi (WP2**) which is involved in **structuring MELODI**, the establishment and updating of the MELODI **Strategic Research Agenda (SRA)** and in dissemination and long term sustainability issues.



www.melodi-online.eu

Complementarity of MELODI and DoReMi

DoReMi

Mission of MELODI

- **MELODI is willing to play a key role in coordinating present and future low dose risk research in Europe**

- **Organisations taking part in MELODI share the common mission of developing and updating a joint research agenda in low dose risk and radiation protection.**

MELODI Objectives (1)

- **To foster scientific cooperation and coordination of present and future low dose risk research in Europe,** in other words to set up the continuous operational coordination of R&T policies in Europe.

- To identify **priorities for radiation research** at low doses and low dose rates and to establish a **long term Strategic Research Agenda (SRA)** and associated « Roadmap »**.**

- To promote **multidisciplinary, highly coordinated research and the** development of integrated and long term sustainable research on health risks associated with low dose ionising radiation exposures.

- To help ensure the sustainability of **infrastructures, education and teaching, and dissemination and knowledge management** (see **MELODI website: www.melodi-online.eu**).

MELODI Objectives (2)

- To encourage **joint research initiatives between MELODI members**.
- To foster **consolidated European-based views on key radiation protection issues and policies.**
- To ensure a **Europe-wide dialogue with public authorities, stakeholders and international partners such as IAEA, WHO, DOE, Japan…….**

MELODI: Programs and activities

Programs

- Integration of R&D
- Program for training and education
- Program for infrastructure
- Workshops

Activities

- **Updating the SRA**
- Development and promotion of **sustainable R&D programs** (at the European level and at the national level)
- Develoment of **sustainable Promotion of Education & Training and Infrastructures** (at the European level)
- **Interaction with international Organisations**
- Setting up **internal calls**
- **MELODI Awards**
- **Dissemination of knowledge**

MELODI: Activities and results

Activities

- **Updating the SRA**
- Development and promotion of **sustainable R&D programs** at European level and at the national level
- Develoment of **sustainable Programs for Education & Training and Infrastructures** at the European level
- **Interaction with international Organisations**
- Setting up **internal calls**
- **MELODI Awards**
- **Dissemination of knowledge**

Expected results

- **Integration with common goals**
- **Optimization of radiation protection in Europe**
- **Advice and service to the European Commission**
- **Active part in HORIZON 2020**
- **Access to Education & Training and to infrastructures in Europe**
- **Joint actions with international Organisations**
- **Strengthening of R&D by internal calls**
- **Knowledge management**

The SRA: a cornerstone of MELODI activities

Scientific and organisational challenges

Scientific challenges

- How can uncertainties in low dose risk estimation be reduced?
- What are the levels and types of low radiation exposures disrupting cellular and tissular homeostasis leading to pathological effects?
- What are the mechanisms involved?
- What is the health risk from low doses?

Organisation challenges

- Identify interested actors
- Promote integration and coordination around a common goal
- Attract and ensure funding from EU and national sources
- Ensure long term sustainability

The SRA: A Way to Reduce Uncertainties in Radiation protection

*With regard to the health effects of **low dose radiation** exposure, more knowledge is needed on the :*

- shapes of dose response curves for different types of **cancers** and **non-cancer effects**;
- sensitivity variations as a function of age with possible differences between *in utero* irradiation, infants and older children and between young and old adults.
- **individual radiation sensitivity and predisposition** to cancers and certain non- cancer effects;
- biological effectiveness of different types of radiation; W_R
- radiosensitivity of different cell types and tissues; weighting factors W_T
- mixed radiation exposures;
- dose rate effect, including chronic and fractionated exposures;
- interactions of radiation with chemical agents;
- effects of radionuclides and internal contamination;
- role of non-targeted effects of radiation.

Main focus of the SRA

- *induction of cancers*
- *non-cancer effects,*
- *radiosensitivity of individuals and tissues,*
- *effects of radiation quality,*
- *effects of internal contamination*,
- *mixed exposures*

Why is the MELODI program so ambitious?

- Radiation protection measures are largely based on epidemiological studies. However, these have limitations for statistical reasons for the estimation of radiation risks at low doses (<100mGy) and very low doses (<10mGy). It is now generally accepted that low dose health risk estimates need to be based on a better understanding of the mechanisms involved.

- This implies that we should know more about « normal » life processes.

  → The more we know about normal life processes, the greater chance we have to identify radiation induced anomalies.

Difficulties to overcome are:

- Dosimetry for radiation of different qualities.
- Effects of low doses are usually much smaller than those of high doses, making it much more difficult to assess risks/effects due to the inherent challenges of working close to the limits of detection.
- Depending on the dose level and condition of radiation, low doses may simply have a modulating effect on normal metabolism which, however, may result in persistent perturbation and damage when combined with other stresses.
- Many other parameters (specific tissue reactions) 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 stringent specificity of ionizing radiation, i.e. no particular health effect has been identified as being unique to radiation.

The three level approach of the MELODI SRA

The SRA proposes a combination of approaches:

1) **Fundamental and molecular research**: dissection of altered metabolic pathways as a function of low dose →'omics', biomarkers, systems biology
2) **Epidemiological research**: suitable (*retro- and prospective*) cohorts :→ precise definition of doses and pathologies with the help of suitable biomarkers
3) **Mathematical modeling** of altered metablism and pathways in relation to persistent pathological changes. →Evaluation of radiation health risks.

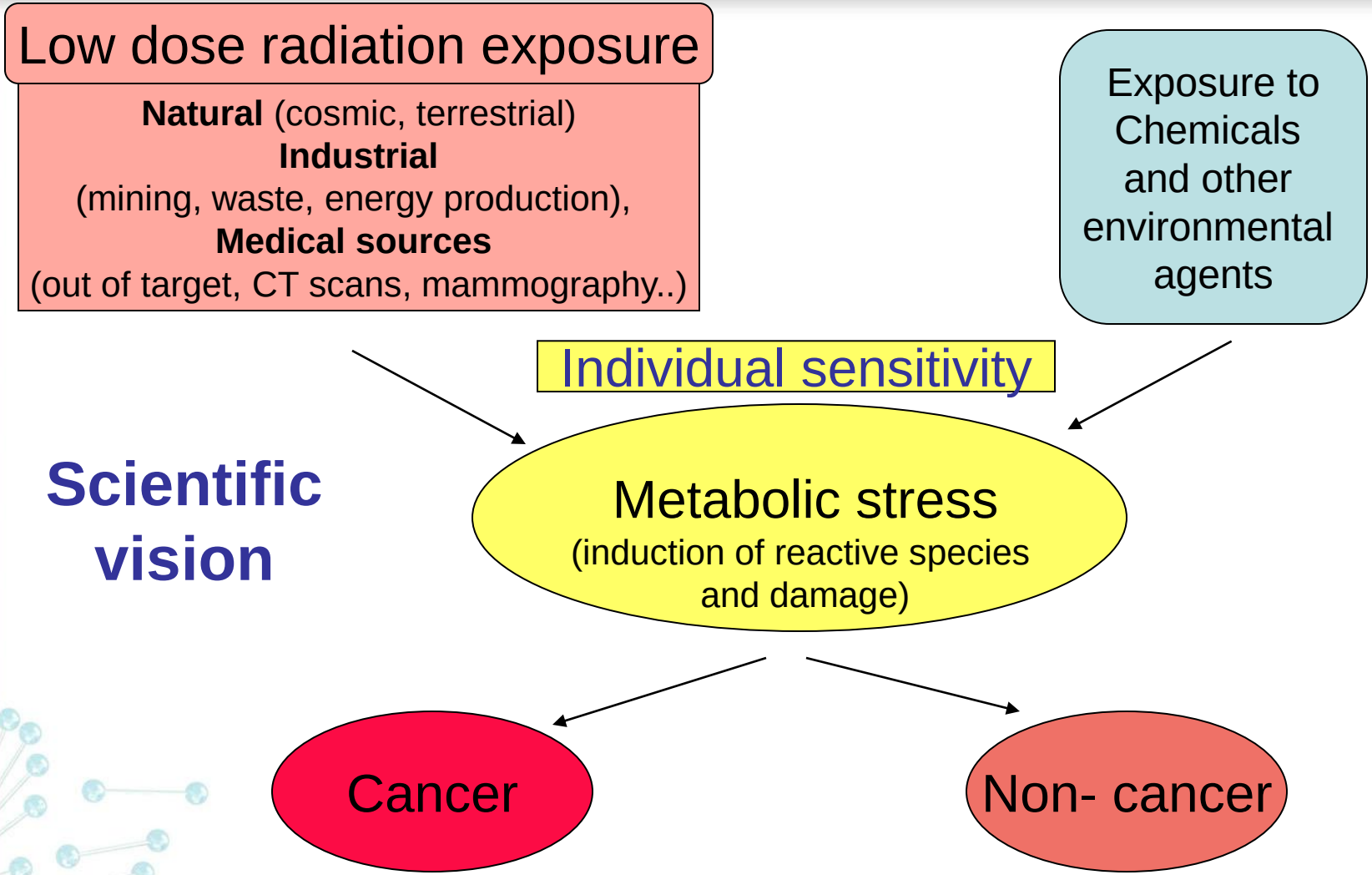
Pre-requisites:

A. Better definitions in mechanistic studies of:

- **dosimetric matters**
- **biological endpoints and health effects**: molecular analyses (e.g. 'omics' etc.) and their producibility as well as classical endpoints (survival, mutation…)

B. Better definitions in epidemiological studies of:

- **dosimetric matters**
- the **pathologies examined together with confounding factors** (gender, age, lifestyle…): use of molecular biomarkers for specific pathological conditions (cancer, non cancer), physiological states (hormonal state, level of antioxidant, DNA repair, immunological defences, metabolic deficiencies etc.)
- **additional exposures** (or stresses) other than radiation (including metabolic or chemical stress), whenever possible, with the help of suitable molecular biomarkers


Low dose radiation exposure
Natural (cosmic, terrestrial)
Industrial
(mining, waste, energy production),
Medical sources
(out of target, CT scans, mammography..)
Exposure to Chemicals and other environmental agents
Individual sensitivity
Scientific vision
Metabolic stress
(induction of reactive species and damage)
Cancer
Non- cancer

Research priorities

1. Dose response relationship for cancer (1)

- Epidemiological studies on suitable cohorts (uranium miners, nuclear workers, CT scan patients…) (*ex.: recent cohort study on leukaemia in children with CT scans M.S. Pearce 2012),* preferably with access to relevant biomaterial for joint molecular studies.→ importance of setting up dedicated data- and biobanking infrastructures

- Research on relevant pathways in low dose radiation induced cancers and identification of biomarkers ('Omics', genetic and epigenetic profiling, next generation sequencing..)

Research priorities

1. Dose response relationship for cancer (2)

Studies on

- The **spectrum of low dose radiation damage** in relation to cellular, tissue responses and cancer induction

  (IR is quite unique in inducing complex damage to DNA that is mostly lethal but may also have a mutagenic component, see P. O'Neill. This also poses the question on the repairability and persistence of IR induced lesions)

- The **mechanisms of cancer induction**, role of mutations, non targeted effects, gene silencing, stem cells and cell differentiation
- The extent to which **sensitivity to cancer induction** may develop during life (ex.:prospective cohorts of young children exposed to dental cone beam, CT scans..).
- The role of **individual sensitivity** in cancer induction (→ search for suitable biomarkers of individual susceptibility)

Research priorities

1. Dose response relationship for cancer (3)

Studies on

- **Animals** to complement specific mechanistic studies on low dose/low dose rate radiation induced cancers (including those from internal contamination)

  (Studies with transplantable tumors are useful to specify the role of tissue micro-environment and non-targeted responses. The induction of cancer prone genomic instability may be investigated by 'omics' and epigenetic profiling)

- **Mathematical modeling** should help to link exposure and mechanistic data to pathological outcomes and to estimate actual low dose health risks.

Research priorities

2. Non-cancer effects (1)

- **Combined epidemiological and fundamental mechanistic studies** are needed to determine the dose-effect relationships for the induction of **cardiovascular, lens opacities and neurological (cognitive) impairments**. (Here, the question of the presence or absence of thresholds is important). *For this, suitable cohorts (some retrospective, but most prospective) with sound dosimetry and medical control should be identified and set up.*
- For these pathologies, **age and developmental specific effects** should be determined (including the involvement of tissues, metabolic, hormonal, immunological, inflammatory responses).
- Research on **cardiovascular effects** should include low (<100 mGy) and medium doses (> 100 mGy). *Of particular interest here is the interaction between elevated cholesterol and radiation-induced arterosclerosis and clarification whether the mean heart dose or the dose distribution to main arteries are the most relevant parameters (F.A. Stewart, Rome)*

Research priorities
2. Non-cancer effects (2)

- Combined epidemiological and mechanistic studies on dose relationship for **lens opacities** after acute and chronic exposures. *Cohorts may include interventional cardiologists, airplane pilots, children living in contaminated areas (Taiwan, Chenobyl..) and nuclear clean up workers.*

- Research on **neurological disorders** induced by low dose and low dose rate radiation. *Studies should focus on premature babies and infants exposed to diagnostic radiology with follow-up as cognitive impairment may occur in adulthood.*

- **Animal studies** on acute and chronic low dose non cancer effects are important complements. *In particular, lifespan and low dose-rate studies, and studies during the perinatal period should be performed.*

Research priorities

3. Individual radiation sensitivity (1)

Clinical evidence from diagnostic and therapeutic uses of ionising radiation shows that it is important to identify radiation sensitive individuals before exposure and to understand the mechanisms involved.

Priorities in this area of research are:

- Set up of suitable (dosimetrically and medically well-definedl) **cohorts together with concomitant molecular studies**.
- Define the **sensitivity** of different cell types, genetic and epigenetic profiles, capacity for DNA repair and apoptosis, immunological, hormonal, inflammatory, and general health status in radiation-sensitive versus radiation-resistant individuals and latencies for pathologies (cancer, non-cancer effects).

Research priorities

3. Individual radiation sensitivity (2)

•Determine in well-defined cohorts (with knowledge on genes and genetic polymorphisms and epigenomic imprints) the role of these in individual low dose radiation responses in order to **define sensitive sub-populations**, confounding factors (age, gender, lifestyle, physiological and reproductive status), effects of mixed exposures to other agents and the amount of radiation sensitive tissue (ex.: glandular versus adipose).

(For justification and optimization of medical use, the identification and use of user-friedly biomarkers for dose and risk will be important. Moreover, inclusion of functional assays for sensitivity in epidemiological studies would help to identify risk factors in genome wide association studies. Also, human longevity studies (cancer susceptibility and radiation sensitivity) on patients with aberrant responses are of interest.)

•**Combined epidemiological and animal model studies** *should be useful in identifying risk variants and for validation purposes (see RB1 for osteosarcoma risk, Aps for mammary tumours, ptch for medulloblastoma or thyroid rRET-PTC cancers). Radiation-quality and dose-rate effects should be analysed as well.*

Research priorities

4. Hereditary and transgenerational effects

Although hereditary radiation effects have not yet been observed in humans, their possible occurrence should be considered. It is likely from lower animal studies that they exist and may be seen at very long term (several generations later) (P. Smeesters, Rome, as postulated earlier by Bernard Dutrillaux, CEA, France) and Sankaranarayan (Leiden, Rome).

- **Trans-generational effects should be explored including expanded simple tandem repeats (ESTR) (tandem mutations in mitochondria) and changes in epigenetic profiles in connection with radiation-induced human (and animal) diseases in offspring. Epigenetic profiling is likely to provide relevant molecular biomarkers (miRNA…).**

- **In view of possible transmissible genomic instability, the transmission of persistent oxidative stress and the bystander mediated induction of transmissible genomic instability should be analysed**.

The Way Forward (1)

Contributions of DoReMi:

- Important scientific aspects of this SRA have already been launched in the **DoReMi project** (see **scientific work** packages 5, 6 and 7), and the results obtained will be considered during the updating of the SRA by the Scientific Committee of MELODI.

- Also, the establishment of suitable **Infrastructures** such as cohorts, radiation sources, data-and biobanking and high throughput analyses platforms as well as sound **Education & Training activities by MELODI** are prepared by the work of **DoReMi Workpackages 4 and 3**, respectively.

The Way Forward (2)

Infrastructures

- **Cohorts**: Cohorts have been identified (also by **DoReMi WP4**) that may allow proper dosimetry, molecular and medical follow-up. *Ways to store relevant data and biomaterials have to be specified.* ***STORE and BBMRI infrastructures are already examples that MELODI could exploit.*** *MELODI should consider creation of a Europe-wide infrastructure to facilitate ethics approval.*

- **Irradiation Facilities:** Suitable radiation sources such as microbeams, devices for alpha, beta, gamma, x-ray, neutron, proton exposure as well as facilities for low dose rate exposures have been recensed (by **DoReMi WP4**). MELODI is going to help in providing access.

The Way Forward (3)

Infrastructures

- **Databases and Biobanks:** Bio- and databanking appear to be important for accompanying classical and molecular epidemiology. Obviously, banking is needed to collect and keep relevant biological samples, also from animal studies. Important links to existing facilities have been supported by national or EU funds (see **STORE** project) through DoReMi and their exploitation pursued. Very importantly, and this will be a matter of **discussion of breakout session group A on Thursday, the number of interested future users should be clearly identified**. **MELODI** will take over the challenge of **ensuring free access and long term maintenance** with the help of the EU and the European partners.
- **Analysis Platforms:** Analysis platforms for high throughput 'omics do exist in Europe. Access is usually possible via collaborative projects or direct individual contracting. MELODI will seek support for such activities as well as for next generation sequencing in the framework of defined low dose research projects.

The Way Forward (4)

Education and Training (1)

To develop and keep expertise and to ensure current and future research activities and maintenance and dissemination of knowledge an integrated approach to education and training of research and teaching at universities and non-university research organisations has to be established in Europe.

- Existing elements of E&T activities in this domain (ex: **European MSc course**) should be strengthened, making it compliant with the **Bologna Process** which creates the European Higher Education Area (EHEA) based on the cooperation of actors from 46 countries with the participation of international organisations.
- Radiation courses in Europe have been recensed by **DoReMi WP3** and a **European course in radiation biology and radiation protection** set up with conventions with European universities and institutions.

The Way Forward (6)

Education and Training (2)

- Stakeholders have to be identified who are willing to provide long term sustainability of such courses.

- EU calls directed to E&T have to be launched to promote setting-up new multidisciplinary interactive courses. *These should be Bologna compliant and based on solid conventions with universities and research organisations. They should include most recent research developments in the field of low dose radiation research and the evaluation of radiation health risks.*

The Way Forward (7)

Dissemination and knowledge management

Communication with the general scientific community, the public and the stakeholders is an important part of MELODI activities.

→ ***WEBSITES:***

The available **MELODI (**http://www.melodi-online.eu/ **and DoReMi (**http://www.doremi-noe.net**) websites** are important instruments to launch scientific exchange, discussion and comments to ensure regular, as much as possible, consensual updating of the **MELODI SRA** (and the **DoReMi TRA**). It is a living document for establishing guidelines for future low dose risk research in Europe.

Also, in DoReMi (WP2) a useful website is available with direct links to the MELODI website. It helps in keeping abreast of operational development and activities (calls and projects) in low dose research at the European level. It also includes the DoReMi Scientific Information Center and knowledge management.

In 2016, a possible fusion of the two websites could be envisaged.

MELODI Way forward (8): summary

1. **SRA**: continous priority setting in the field of radiation research (guidance and interaction with other related European initiatives)
2. **Promotion of Education and Training**: maintenance of expertise and new recruitment
3. Ensuring the **maintenance of key infrastructures for R&D** in Europe
4. **Dissemination and knowledge management**
5. Increase involvement of **representation of national authorities and universities and research instituts in RP research**
6. Adapt Statuts of the MELODI association to its role now in active radiation research in Europe with a proper funding mechanism (in Horizon 2020).
7. Increase coordination and interaction with scientific, industrial and medical actors and the public in particular with stakeholders, also on the international level.

Conclusions

MELODI provides a **unique opportunity for the integration and coordination on low dose radiation health risk research and radioprotection in Europe** and the efficient use of European resources.

MELODI is aiming to **assemble all actors** interested in these areas of research **around common goals**: setting-up an, as much as possible, **consensual strategic research agenda (SRA) that can guide future research** and provide a **roadmap** focusing on the key questions to be answered, in a reasonable time scale, in order to improve low dose risk evaluation and radiation protection.

Since it is a long term activity, **assuring long term sustainability of MELODI activities** is essential. It is a joint effort that has to count on the combination of all possible available resources, in particular those from the EU, European institutions and organisations and stakeholders.

MELODI is also **promoting continous Interaction and cooperation** on these issues **at the international level** wherever possible.

Thank you for your kind attention!