



# 5th International MELODI Workshop 2013, Brussels, Belgium

Multidisciplinary European Low Dose Initiative

## MELODI 4th SRA

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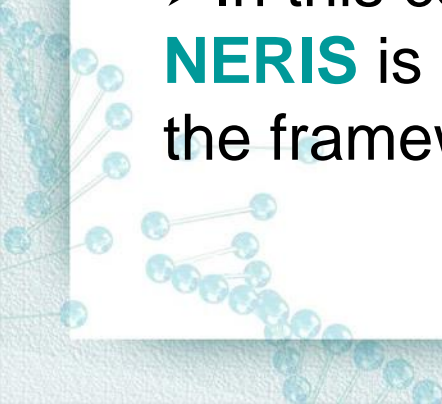
MELODI WS 8-10 October 2013, Brussels, Belgium

12h30-13h00 Bedford Hotel



The **MELODI Association** 'Multidisciplinary European Low Dose Initiative' founded in 2010 aims at consolidating European research initiatives on low dose ionizing radiation health risks and radioprotection.

- The main goal is to prioritize the scientific basis for long term coordination of R&T policies and research and to improve radiation protection standards in Europe.
- In this context, **MELODI** together with **ALLIANCE** and **NERIS** is promoting the European project **OPERRA** in the framework of **HORIZON2020**.



## The harmonic pathway to the OPERRA



## **What we need when we want to go to the OPERRA: MELODI and the Strategic Research Agenda (SRA)**

Due to recent evolutions in European policies and recent research developments it is urgent to take up scientific discussions on the **MELODI SRA** and to reformulate **MELODI SRA priorities**:

**MELODI** is promoting research lines on low dose health risk research and radiation protection that complement the research efforts on environmental radiation effects (**ALLIANCE**) and radiation emergency issues (**NERIS**) within the **OPERRA** project in the context of **HORIZON 2020**.

**The MELODI Strategic Research Agenda (SRA) defines:**

- **priorities (and time schedules) for low dose radiation research and radiation protection as well as**
- **sustainable infrastructures and education and training activities.**

## **MELODI SRA(1)**

- **The scientific issues that steer the MELODI SRA are those previously identified by the High Level and Expert Group (HLEG) in 2009.**
  - **The MELODI SRA focuses on the key questions for radiation protection which cannot be solved by a single group or country.**
  - **The SRA is a living document that is updated each year according to the MELODI WS, recent research developments, comments from the scientific community and societal needs. It gives important priorities for low dose risk research and radiation protection.**
- **This MELODI WS is dedicated to further SRA updating!**

## Main SRA goals: the reduction of uncertainties in radiation protection at low dose radiation

- **Shapes of dose response relationships** 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; **Radiation weighting factors  $W_R$**
- **Radiosensitivity of different cell types and tissues**; **Tissue weighting factors  $W_T$**
- **Mixed radiation exposures**;
- **Dose rate effects**, including chronic and fractionated exposures;
- **Interactions** of radiation with chemical agents;
- Effects of radionuclides and **internal contamination**;
- Role of **non-targeted effects** of radiation.

## Challenges of low dose risk research

- Proper dosimetry at low doses or dose rates.
- Working at the limits of detection of low dose effects makes the assessment of risks and effects difficult.
- For statistical reasons, epidemiological studies are not very reliable at low doses and dose rates and have to be backed up by mechanistic studies.
- Low doses and dose rates may simply modulate normal metabolism. This, however, may result in persistent perturbation and damage when combined with other stresses.
- There is no stringent specificity of ionizing radiation, and no particular health effect can be uniquely attributed to radiation.
- Observable low dose effects may be interfered with by many other confounding factors and specific tissue reactions since radiation is only one of many environmental insults.

## **Priorities of the SRA and the derived MELODI statements**

**The SRA contained a long list of priorities (see presentation at the 3rd MELODI WS in Helsinki last year. A short MELODI statement was derived from it that included as long term priorities :**

- Quantification of the role of IR in non cancer diseases
- Development of biomarkers (exposure, effects, disease) that are useful for epidemiological studies
- Role of target cells (including stem cells and cells of the immune system)
- Improvement of low dose risk assessment: reduction of uncertainties (age, gender, exposures), and data and biomaterial sharing (suitable infrastructures)
- Set up of guidelines for short, medium and long term exposure and health risks monitoring in case of major nuclear accidents



## Why now 10 highest priorities had to be selected from the original SRA 'shopping list' ?

It was decided during the **OPERRA Kick-Off meeting** (18 June 2013 in Paris) that:

- At the end of 2013 **MELODI** should launch a call for projects on the effects of low doses in the framework of the new project **OPERRA**.
- For this, a call text has to be provided by an independent confidential body of experts and published at mid-December by **MELODI**. These experts are chosen by the **EU** and **HERCA**, and they are totally independent of **MELODI** and **OPERRA**.

## Way towards the 10 highest priorities for low-dose risk research (2)

- To prepare the call before the end of 2013, **MELODI Board members** were invited to send before the end of July 2013 critical comments and suggestions (to Jean-René Jourdain and Dietrich Averbeck (WP2 of DoReMi) to allow **updating of the 3rd version of the MELODI SRA** (from March 2013).
- Responses were received from SU, SUJCHBO, HMGU, BfS, CEA, ISS, IRSN, etc.
- From the latest version of the SRA, a **MELODI statement** listing the 10 highest priorities was prepared (editors JRJ and DA) and sent for comments to the members of the MELODI Bureau (IRSN, BfS, SCK-CEN, ISS).

## Way towards the 10 highest priorities for low-dose risk research (3)

• After approval, this list was sent by the **MELODI chairman Jacques Repussard** to all MELODI Board members. To get a statistical overview on preferences among the highest priorities each member was asked to select 3 most relevant priorities up to the 4th of October 2013 to allow presentation of the most pertinent issues (in preparation of the 4th final version of the SRA at this MELODI WS (5th MELODI WS in Brussels 8 October 2013) and to stimulate further discussion and refinement of priorities by the MELODI WS audience.

• The SRA (+ statement) and the list of emerging priorities will be evaluated by the **Scientific Committee of MELODI** before asking for final approval by the **MELODI Governing Board** who will send the list of finalized priorities (only 3 outstanding ones) to the **EU** to be transmitted to an **independent group of nominated experts** .

## **MELODI: 10 priorities were first selected from the SRA**

- A. Impact of radiation quality (radiation weighting factors  $w_R$ )
- B. Impact of tissue sensitivity (tissue weighting factors  $w_T$ )
- C. Impact of individual radiation sensitivity
- D. Exposures to internal emitters
- E. Mixed exposures (radiations/chemicals)
- F. Impact on pathways/processes contributing to carcinogenesis
- G. Impact on pathways/processes contributing to non-cancer effects
- H. Hereditary and trans-generational effects
- I. Epidemiological studies
- J. Modeling studies

## **MELODI statement on the 10 highest priorities for low dose risk research (*Draft-24 September 2013*)**

- Scientifically, it is widely recognized now that epidemiological studies alone are unable to access low-dose health risks associated with ionizing radiation and need to be backed up by mechanistic studies. Thus, multidisciplinary efforts of fundamental (mechanistic) as well epidemiological research on medical, industrial or environmental exposed human cohorts with proper access to and use of suitable infrastructures (radiation facilities, analysis & imaging platforms, animal facilities) are essential for a better evaluation of low-dose health risks.
- The 10 MELODI highest research priorities focus on research activities for a better understanding of underlying mechanisms (priorities A.1-A.7), a better health risk evaluation at low-dose exposure (priorities B1-B2) and consider also the needs related to infrastructures, cohorts and E&T issues (priority C).

## **The 10 highest priorities for low dose risk research**

***(MELODI statement Draft-24 September 2013) (1)***

### **A. Mechanistic studies**

**A.1.** Characterization of spatial and temporal energy deposition events (track structure and dose rate) and their role in in low-dose radiation responses (among others, examination of radiation damage and biological effectiveness (RBE) values of different types of radiation).

**A.2.** Analysis of mechanisms involved in low dose radiation through use and development of suitable cellular models (2D, 3D, including somatic cells, stem cells, and organo-typic tissue models) as well as animal models.

**A.3.** Identification of specific metabolic pathways and tissue biomarkers (e.g., epigenetic profiles) related to radiation specific tissue responses.

## The 10 highest priorities for low dose risk research (2)

### **(Mechanistic studies continued):**

**A 4.** Role of genetic background, immunological status, age, gender and lifestyle on radiation-induced effects, as well as identification of other factors influencing individual radiosensitivity.

**A.5.** Relationships between radio- and chemical toxicity and their respective influence on radiation-induced effects resulting from incorporation (internal contamination) of radionuclides.

**A.6.** Examination of the mechanisms and effects of mixed (radiation/chemical) and multi-exposure (radiation/radiation) on cells, tissues, animal models and humans.

**A.7.** Examination of possible regenerative processes allowing the promotion of medical countermeasures for the treatment of adverse radiological effects (including the effects resulting from the use of radiation in medical applications).

## **The 10 highest priorities for low dose risk research (3)**

### **B. Health risk evaluation studies**

**B.1.** Identification, development and validation of biomarkers for radiation-induced health (cancer and non-cancer) effects through sound (molecular, i.e. using most recent methods such as omics, genetic and epigenetic profiling, new generation sequencing and systems biology) epidemiological studies in children and/or adults in conjunction with most suitable and promising retrospective (Techa River, Mayak, Chernobyl, Fukushima, Uranium miners, nuclear workers, secondary cancer patients with radiation therapy in childhood) and prospective (CT scan patients, medical diagnosis patients, new treatment modality RT patients) cohorts with access to biological samples and sound dosimetry.

**B.2.** Development of mathematical and molecular modeling studies based on findings of mechanistic and epidemiological studies dedicated to low-dose health (cancer and non-cancer) risk evaluation.



## **The 10 highest priorities for low-dose risk research (4)**

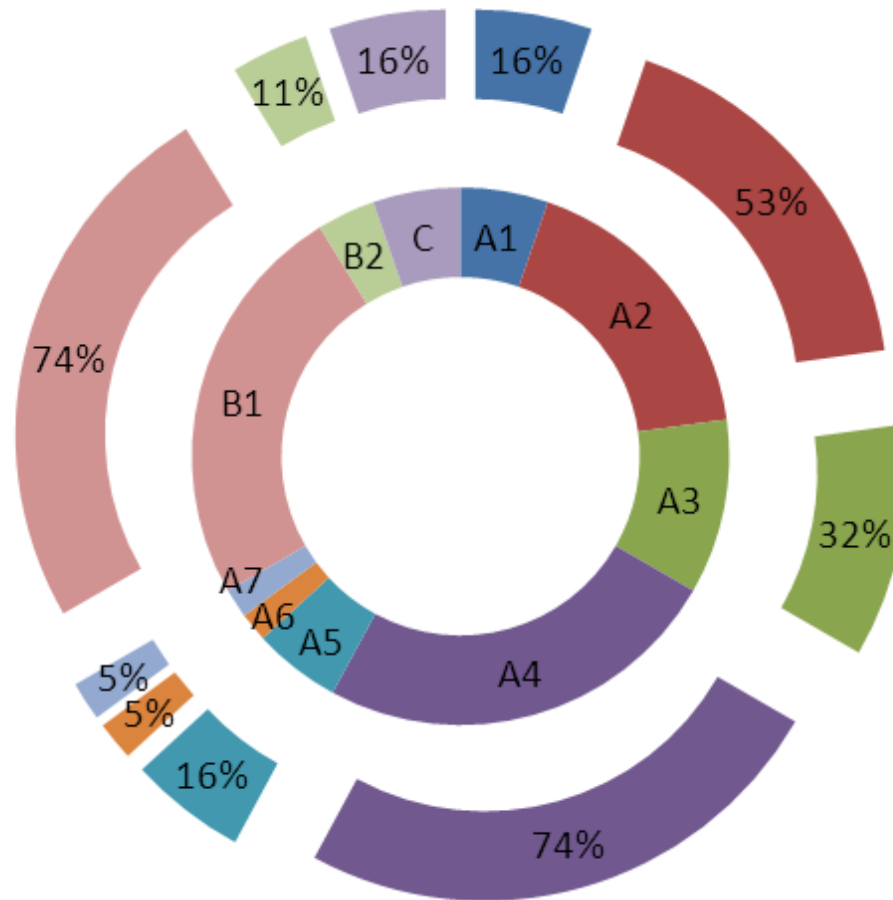
### **C. Other activities contributing to low-dose risk research**

**C.1.** Development and facilitation of access to infrastructures dedicated to low-dose risk research.

**C.2.** Consolidation of major cohorts suitable for molecular epidemiological studies.

**C.3.** Maintaining a high level of education and training for radiation protection.

- As of 7 October 2013, 19 members among 22 voted (86%)



- Priority list: A4 (74%), B1 (74%), A2 (58%) – Fourth is A3 (32%)

## **Tentative Priority List (from MELODI member votes only)**

**A. 4.** Role of genetic background, immunological status, age, gender and lifestyle on radiation-induced effects, as well as identification of other factors influencing individual radiosensitivity .

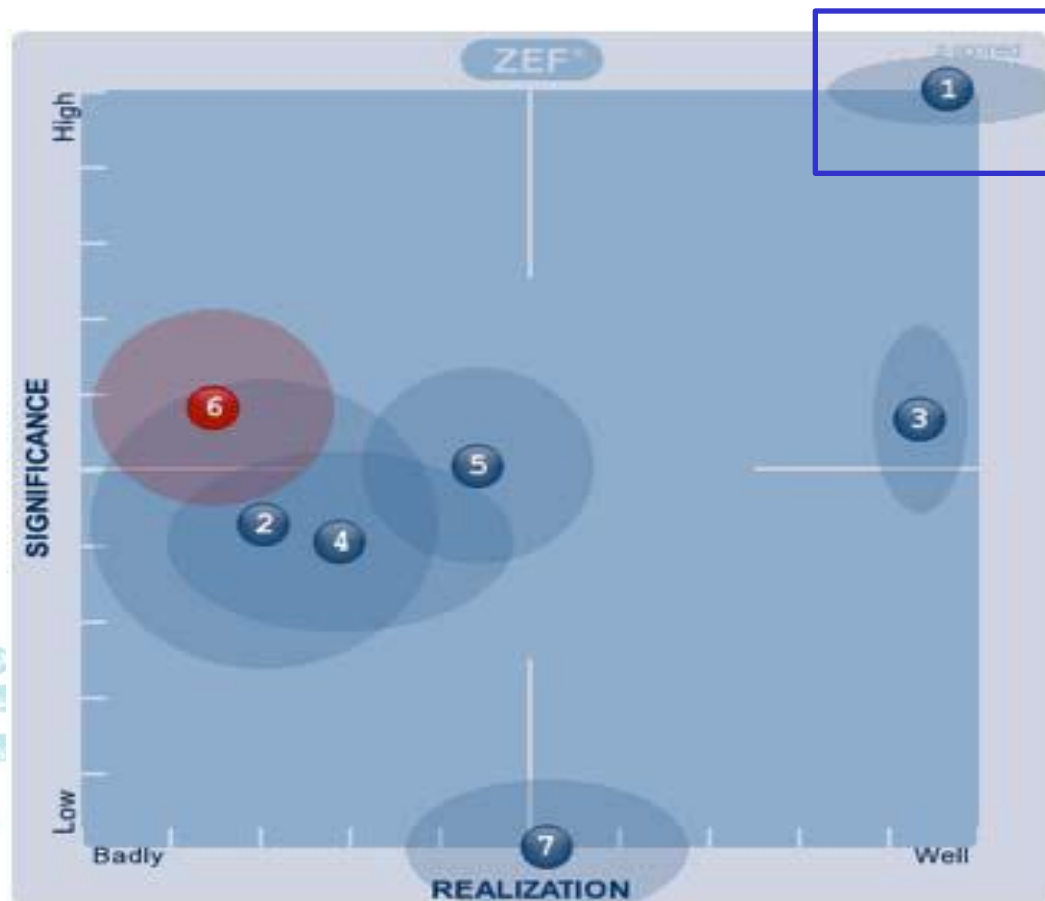
**B.1.** Identification, development and validation of biomarkers for radiation-induced health (cancer and non-cancer) effects through sound (molecular, i.e. using most recent methods such as omics, genetic and epigenetic profiling, new generation sequencing and systems biology) epidemiological studies in children and/or adults in conjunction with most suitable and promising retrospective (Techa River, Mayak, Chernobyl, Fukushima, Uranium miners, nuclear workers, secondary cancer patients with radiation therapy in childhood) and prospective (CT scan patients, medical diagnosis patients, new treatment modality RT patients) cohorts with access to biological samples and sound dosimetry.

**A.2.** Analysis of mechanisms involved in low dose radiation through use and development of suitable cellular models (2D, 3D, including somatic cells, stem cells, and organo-typic tissue models) as well as animal models.

## **Refining the tentative priority list (deadline: end of October 2013)**

- Each participant in the **MELODI workshop** is now invited to give its opinion (see box collecting your vote)
- Use more sophisticated tool such as ZEF evaluation engine: the responders will place each priority into a 2D field; at the same time, the responders will evaluate the ***feasibility*** of the priority in question as well as the ***relevance for radiation protection***
- Additional information on the dimensions may be added in order to help the evaluators: scientific relevance and potential impact for RP and the feasibility of research (availability of technologies, timeliness, cost, etc.)

## Refining the tentative priority list (deadline: end of October 2013)



A small ellipsis around the answer point indicates a similarity between answers, while a big ellipsis indicates a pronounced deviation. Also take into account the shape of the ellipsis: the deviation can be greater in one direction rather than the other



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### The way forward for MELODI SRA updating

- In the future an SRA working group of MELODI will be constituted that is in charge to prepare a newly updated SRA following the discussions and scientific exchanges during this 5th MELODI workshop.
- For this your suggestions and comments will be most welcome.



**Thank you very much for your  
attention!**

([www.melodi-online.eu](http://www.melodi-online.eu))

- (<http://www.melodi-online.eu/sra.html>)

➤ **Your input to the SRA is most welcome !**



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