

MELODI

Strategic Research Agenda

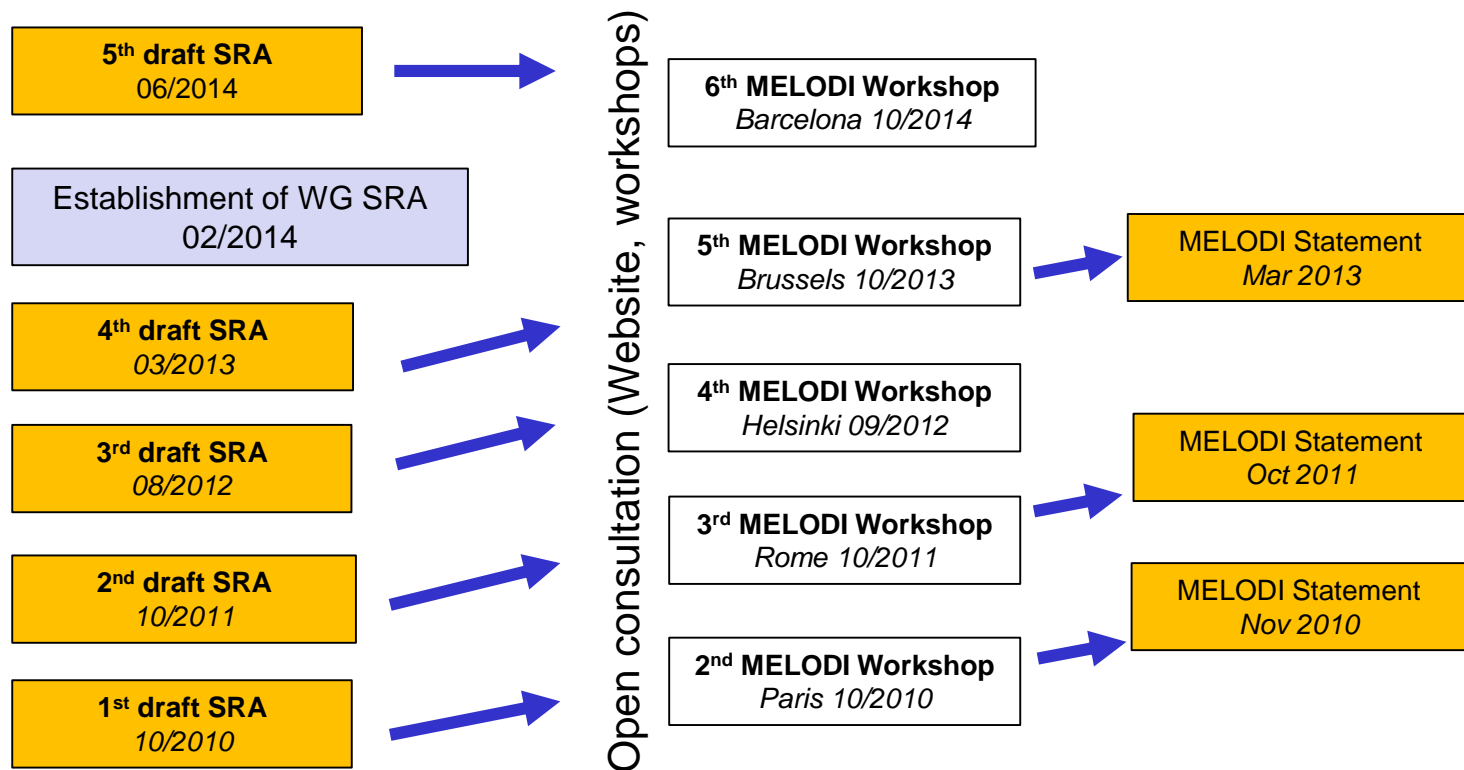
Jean-René Jourdain (IRSN, France)
On behalf of Michaela Kreuzer (BfS, Germany)

09 June 2015, Aix-en-Provence
STAR Final Dissemination Event

Background

- A major activity of MELODI is the establishment and updating of a long term **Strategic Research Agenda** (SRA) for research on low dose risk for radiation protection in Europe (>20 years)
- The SRA is intended to **guide the priorities** for national and European research programmes, and the preparation of competitive calls at the European level
- MELODI WG SRA annually updates the SRA, prepares a statement on the top priorities (prior to calls) and a long-term roadmap

History of the MELODI SRA



In addition, two lists of top priorities for low-dose risk research have been prepared for the OPERRA calls (October 2013 & 2014)

MELODI WGs Nomination Process

Aim:

To appoint 10 WG members per WG (SRA, E&T, Infrastructures)

Applicants:

- 21 SRA (12 biologists, 2 epidemiologists, 2 dosimetrists, 5 others)
- 9 Education and Training
- 6 Infrastructures

Criteria:

- No double nominations in the three different WG's
- Multi-disciplinarity of competences relevant for the task
- Representation of different countries and organisations

MELODI Working Group SRA

- **Michaela Kreuzer (Chair)**, *BfS, Germany*
- **Friedo Zölzer (Vice-Chair)**, *Czech Republic*
- **Katja Kojo**, *STUK, Finland*
- **Peter Jacob**, *HMGU, Germany*
- **Simon Bouffler**, *PHE, UK*
- **Simona Pazzaglia**, *ENEA, Italy*
- **Elisabeth Cardis**, *CREAL, Spain*
- **Mats Harms-Ringdahl**, *SU, Sweden*
- **Imre Balashazy**, *MTA-EK, Hungary*
- **Jean-Rene Jourdain**, *IRSN, France*

- **Kevin Prise**, *UK*
- **Dietrich Averbeck**, *IRSN, France*



Strategic Research Agenda of the Multidisciplinary European Low Dose Initiative (MELODI)

M. Kreuzer, D. [Averbeck](#), I. [Balashazy](#), S. [Bouffler](#), E. [Cardis](#),
P. Jacob, J.R. [Jourdain](#), M. [Harms-Ringdahl](#), K. [Kojo](#), S. [Pazzaglia](#),
K. [Prise](#), F. [Zoelzer](#)
A. [Ottolenghi](#), L. [Sabatier](#)

Status : [13 June 2014](#)

Shape of the SRA report

Document should be

- concise
- clearly structured
- readable, also for non high-level experts
- not longer than about 20 pages
- include summary of WG Education and Training and WG Infrastructures
- Include synergistic topics with other radiation research platforms



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Structure of SRA report

1. Executive Summary
2. Background
3. Strategic Research Agenda
4. Synergistic topics of MELODI with other platforms
5. Education and Training
6. Infrastructures
7. Research Priorities
8. References

Total: 23 pages

MELODI SRA frames a holistic strategy
with **3 Key questions** + 3 research paths
(from the cell to the whole organism)

- Dose/dose rate dependance of cancer risk?
- Threshold exposures for protection from health risks other than cancer?
- Reliable methods for identifying individual radiation sensitivity, and addressing related ethical issues?

MELODI SRA frames a holistic strategy

3 Key questions; 3 research paths

(from the cell to the whole organism)

- Radiobiology research to improve understanding of mechanisms contributing to radiation risk
- Epidemiology research to integrate biological indicators into radiation risk evaluation
- Radiation protection research to better understand the specificities of internal or inhomogeneous exposures, and of different radiation qualities

Three key research questions

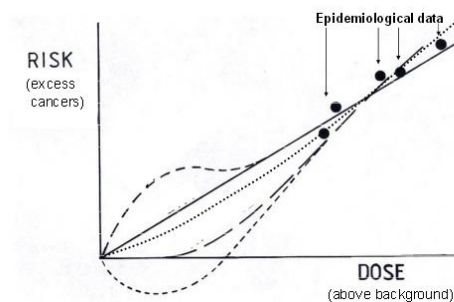
- **Dose and dose rate dependence of cancer risk**
 - Basic Mechanisms
 - Health risk evaluation
 - Impact of radiation exposure characteristics

- **Non-cancer effects**
 - Basic Mechanisms
 - Health risk evaluation
 - Impact of radiation exposure characteristics

- **Individual radiation sensitivity**
 - Basic Mechanisms
 - Health risk evaluation
 - Impact of radiation exposure characteristics

Key question 1: Dose and dose rate dependence of cancer risk

- Epidemiological studies provide evidence of dose-related increases in cancer risk at doses of about 50-100 mSv and above
- Major uncertainties concerns
 - (i) magnitude of all cancer risk following protracted exposures of the order of **100 mSv or less**
 - (ii) organ specific risks following acute or protracted exposures of a **few hundred millisievert**, particularly for inhomogeneous dose distributions



Basic Mechanisms

Priority research areas are:

This area requires the use of well validated animal and human cellular/tissue models to determine

- The nature of the target cells for radiation carcinogenesis
- The contribution of DNA damage / mutational processes
- The contribution of (epi)genetic modifications
- The influence of cell micro-environmental, stem cell, non-targeted and systemic processes
- The extent to which any of the above are different at high dose/dose-rate by comparison with low dose/dose rate

Dose and dose rate dependence of cancer risk

Health risk evaluation

Priority research areas are:

- To determine the shape of the dose-response relationship in humans for different cancer sites based on key informative cohorts
- To identify and validate biomarkers of exposure and cancer effects
- To collect tumour tissue for molecular characterization of tumours and the study of dose-response in relation to each tumour type
- To investigate pre-stages of cancer in tissue or blood
- To evaluate cancer risks through systems biological analyses and models of carcinogenesis based on integration of epi and mechanistic studies

Priority research areas are:

- Epidemiological studies of internal emitters, incorporating detailed dosimetric assessment and evaluation of uncertainties, and - where feasible and possible - biological samples
- Experimental studies *in vivo* or *in vitro* to test exposure scenarios where dose modulation plays a role, (e.g. localized vs. uniform, acute vs. protracted) to inform biomarker development and risk quantification
- Epidemiological or mechanistic studies on cancer risk including exposures to different radiation qualities

Key question 2: Non-cancer effects

- It has been traditionally assumed that health effects other than cancer show **a threshold** at doses that are well above the levels of exposures typically encountered in the public environment, at work or from medical diagnostic uses
- Recent results from epidemiological and experimental studies indicate increased risks from vascular diseases, cataracts and cognitive effects not only at doses above 5 Gy, but also at a range of doses from 5 to 0.5 Gy and, possibly **even at lower doses (<0.5 Gy)**

Basic Mechanisms

Knowledge on the underlying biological mechanisms in the moderate and low dose range is very sparse and assumed to be different from high dose exposure

Priority research areas are:

- Development of *in vitro* models and animal models for radiation-associated vascular diseases, cataract and other non-cancer outcomes to clarify which regulatory pathways are involved
- Application of a full range of analytical methods including 'omics' technologies and consideration of the target cells and surrounding micro-environment

Results from available epidemiological studies are not always consistent, bias and confounding cannot be excluded.

Priority research areas are:

- To determine the shape of the dose-rate or dose response relationship in humans at low or moderate doses based on key informative cohorts
- To identify, develop and validate biomarkers for exposure, early and late effects
- To investigate early stages in the progression of non-cancer effects in tissue or disease related endpoints in biological samples from cohort members
- To evaluate non-cancer risk by integrating mechanistic and epidemiological data through mathematical modelling

Key question 3: Individual radiation sensitivity

- Differences in radiation risk may relate to gender, attained age, age at exposure, state of health, genetic or epigenetic make-up, lifestyle or other exposures.
- Such differences, if significant, raise the ethical and policy question as to whether some individuals or groups are inadequately protected by the present system and regulations
- We need better knowledge on the extent of the variations in sensitivity in the population, both
 - *in the sizes of variations*
 - *and also in the proportions of the population that are affected*

Basic mechanisms

Priority research areas are:

- To develop a systems model of the acute and long-term responses to low doses of radiation so that differences in the response pathways can be detected and used to predict differences in outcome at an individual and population level
- To identify biomarkers of susceptibility to radiation associated disease that can be applied in molecular epidemiological studies
- To investigate mechanisms by which these factors may affect radiation risk

Priority research areas are:

- To validate candidate biomarkers of individual sensitivity identified from mechanistic studies in cohorts of exposed and non-exposed that have developed cancer or non-cancer diseases
- To improve key cohorts and conduct studies to determine factors involved in individual sensitivity to radiation-induced diseases
- To quantify the variation in risk between different populations groups and the impact of different factors

Education and Training

- Maintenance of the range of expertise essential for effective research on low dose radiation risk
- Knowledge management across generations to achieve sustainability

Priorities in this area:

- Support for students and young scientists (e.g. post-graduate scholarship)
- Promotion of E&T for dissemination (workshops, courses, etc.)
- Coordination and collaboration of E&T providers

Infrastructures

- To ensure the availability and access to research infrastructures
- To promote the use of mature infrastructures
- To avoid unnecessary duplications
- Development of new infrastructures, if necessary
- To harmonize practices amongst multiple facilities
- Sustainability of rare, but necessary facilities

- Infrastructures include
 - Exposure facilities (external, internal exposure)
 - Cohorts and biobanks
 - Data bases and tissue archives (e.g. STORE)
 - Analytical platforms („Omics“, „Biodosimetry“)

MELODI vs. ALLIANCE Opinions

- According to the 2014 OPERRA e-survey, MELODI and ALLIANCE share the same views on 4 of the top 5 research priorities:
 - Development of monitoring strategies, processes and tools
 - Development of health surveillance procedures
 - Biological indicators of radiation exposure, effects, health risk and disease susceptibility to inform emergency management and epidemiological studies
 - Biomarkers of exposure and effects in living organisms

MELODI vs. ALLIANCE Opinions

- Four of the top 5 ALLIANCE research priorities have been selected for the second OPERRA call (December 2014):
 - Development of monitoring strategies, processes and tools
 - Development of health surveillance procedures
 - Biological indicators of radiation exposure, effects, health risk and disease susceptibility to inform emergency management and epidemiological studies
 - Spatial and temporal environmental modelling and human dose assessment after a nuclear accident

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