MELODI Strategic Research Agenda

MELODI SRA Working Group

Dietrich AVERBECK *(IRSN/CEA, DoReMi WP2)*
David LLOYD *(HPA, UK)*
Peter O'NEILL *(University of Oxford, UK)*

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Aula Pocchiari, Istituto Superiore di Sanità,
Viale Regina Elena 299, 00161 Rome, Italy

Outline of the talk

1 Introduction
2 Goals of MELODI
3 SRA introduction: situation, goals, purpose
4 Methodology used
5 Scientific vision
6 Proposed Research priorities
7 Recommendations on organisatorial and practical issues
8 Infrastructures (cohorts, radiation facilities, data-and biobanking)
9 Maintenance of the SRA
10 Major considerations, Consultations, Establishment of MELODI Scientific Committee, Research areas, Final chapters
11 Conclusions

Why are we pre-occupied by low dose radiation effects?

- Most human beings are exposed to low doses only (cosmic rays, terrestrial background radiation, diagnostic , environmental exposures including radioactive waste and contaminations from nuclear accidents (Chernobyl, Fukushima).

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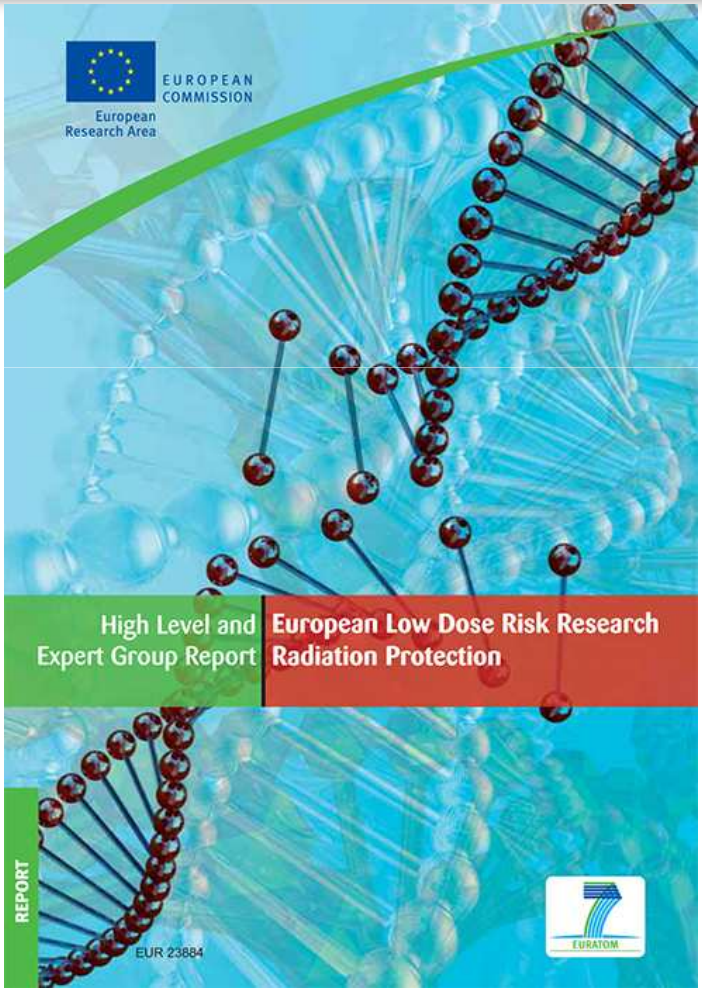
3rd International MELODI Workshop, Rome

HLEG Report 2009



High Level Expert Group

See Cordis for EC Report
EUR 23884

www.melodi-online.eu

Birth of MELODI

Following the work of the **High Level Expert Group (HLEG) the Multidisciplinary Low Dose Initiative MELODI** has been created with focus on:

- **ionising radiation research on low dose health risks** with final contribution to the improvement of radiation protection.
- In addition, the European NoE **DoReMi** has been created to help paving the way for MELODI with project design and scientific studies.

- Important features: they are opening up the radiation field to the general scientific community.

MELODI

Multidisciplinary European Low Dose Initiative

Open RTD platform guiding priorities in low dose research in Europe (long term)

www.melodi-online.eu

DoReMi

Low Dose Research towards Multidisciplinary integration

Network of Excellence 2010-2015 (short term)

www.doremi-noe.net

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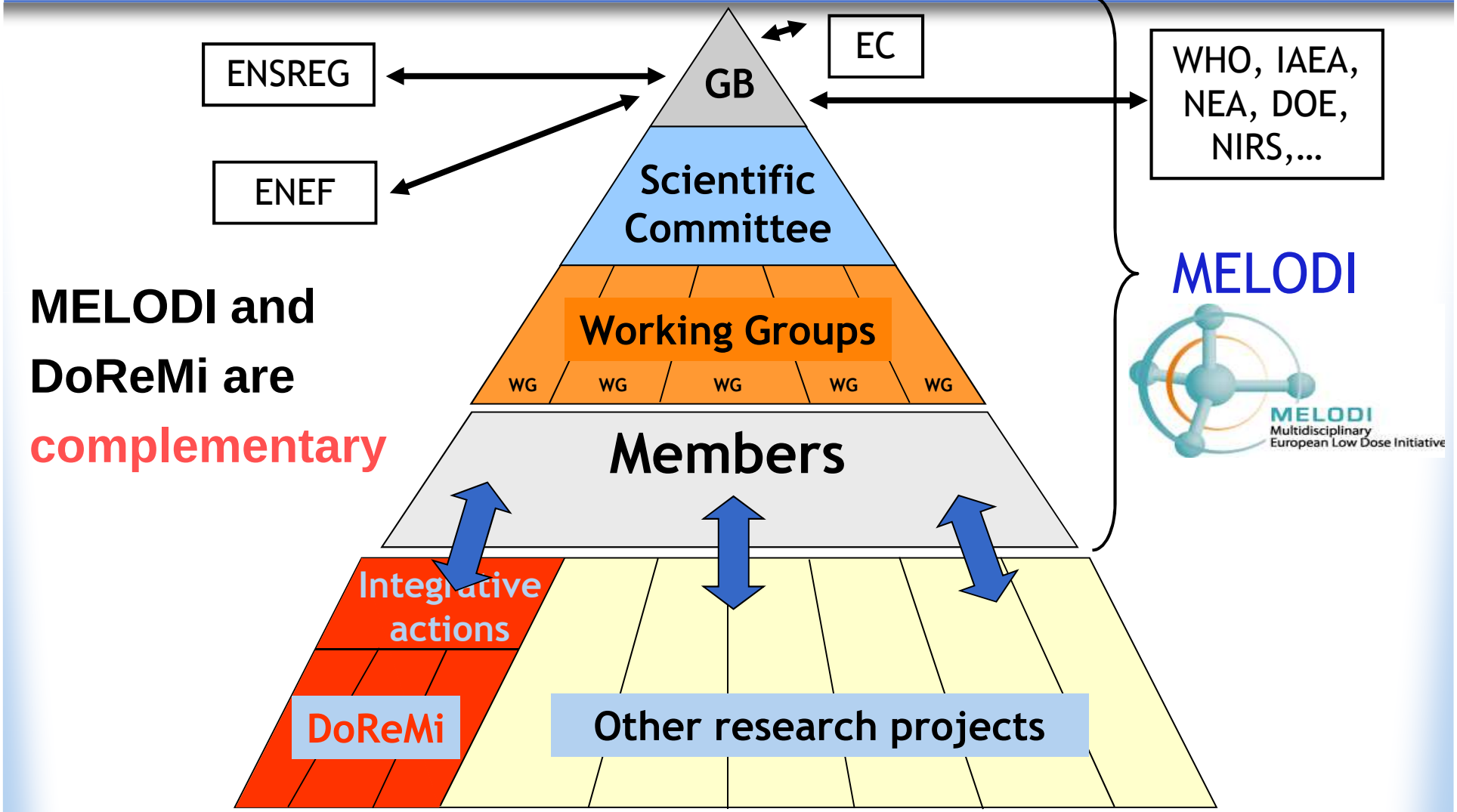

MELODI and DoReMi are complementary

Recent developments

- The **European NoE DoReMi** (co-ordinated by Prof. Sisko Salomaa (STUK, Finland) was set up in January 2010, initially with 12 institutional partners (BfS, CEA, CREAL, STUK, IRSN, ISS, SCK-CEN, SU, HPA, HGMU, UNIPV and IC) and attracted 10 additional partners (UKER, GUF, UROS, UMB, NRPA, NIPH, ENEA, IES, DIT, Erasmus) thanks to a DoReMi external call in 2011.
- The **MELODI platform** is a well-structured association with 15 institutional founding members (in 2010) and has attracted additional associated members in 2011.

The MELODI goals (1)

The overall goals of the MELODI platform are:

- **Consolidation of European initiatives on researching and better understanding of the health effects of exposure to low dose ionising radiation.**
- **Stimulation of low dose risk research in Europe through an open and integrative Strategic Research Agenda (SRA) approach.**

MELODI Goals (2)

- **To create a forum for a dialogue between scientists, EU institutions, stakeholders and the public.**
- **To interface with international partners (WHO, IAEA, USA (DOE), Japan (NIRS),…**

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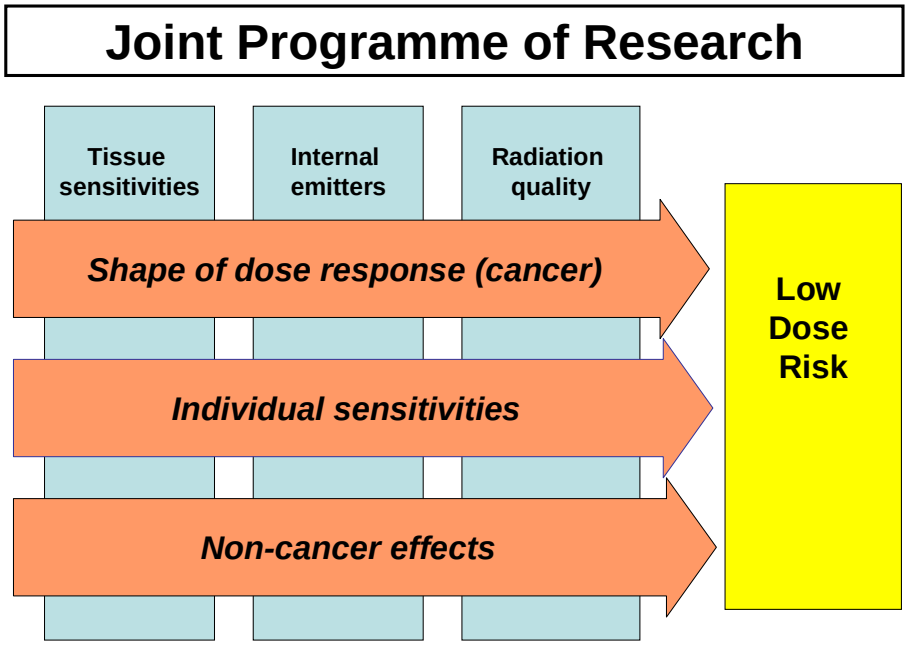
Major implications of MELODI: promotion of

- **coordination of Multidisciplinary integrative low dose research in Europe**
- **attraction of new scientific competences and scientists from complementary disciplines**
- **sustainability of infrastructures, education and training**
- **interaction and communication with stakeholders and the public. (see also the MELODI Website** (www.melodi-online.eu))

Scientific aims of DoReMi and MELODI are overlapping

- address the main scientific questions and cross-cutting issues set by HLEG
- prepare and update **the short term DoReMi Transitional Research Agenda (TRA) (6 years)**
- contribute to and establish a long-term **Strategic Research Agenda (SRA) of MELODI (>20 years)**



Present situation

We are lucky: considerable and somewhat surprizing scientific progress has been made in recent years due to the development of highly sensitive molecular approaches and new technologies.

Research at radiation doses in the low dose range (<100 mGy) has become experimentally accessible (see for example: EU projects Risc-Rad/ NOTE):

- Cells react very sensitively to very slight environmental changes
- Cells react differently at low and high radiation doses and thus the biological consequences are expected to be different.

Goals of the MELODI SRA

In order to achieve the scientific goals, **MELODI** needs a long-term **Strategic Research Agenda (SRA)** as an operational framework

1. **to guide the coherent integration of national low dose R&D programmes, and**
2. **to provide a useful basis towards the considerations of the EU when designing EURATOM calls in this field.**

Purpose of the SRA

To achieve these goals:

A Strategic research agenda is proposed with a scientific vision able

- to confederate and to take advantage of most recent research developments
- to promote and drive a common, as much as possible consensual, multidisciplinary initiative (**MELODI**) in order
- to get a better understanding of the mechanisms underlying low dose radiation effects,
- to most effectively **reduce existing uncertainties** and to provide clear answers to the **key questions in low dose research** in order
- to contribute to an improved **estimation of low dose radiation health risks.**

SRA Methodology (1)

The present SRA is based on:

- Consultation of scientific experts in the field of low dose radiation research and outside.
- Suggestions and comments received from the scientific community.
- Scientific issues formulated by the HLEG (2009)
- Transitional Strategic Agenda (TRA) of DoReMi (short term)
- Proceedings of previous MELODI workshops (Stuttgart 2009, Paris 2010).

SRA Methodology (2)

Steps towards the SRA

The present (2nd) Draft of the SRA has been worked on by considering the following steps:

1. Identification of relevant scientific questions
2. Identification of corresponding research projects
3. Proposal of priorities according to criteria and consensual comments from the general research community (including the MELODI workshops, the DoReMi (TRA) and contributions from MELODI members).
4. Some thoughts on a possible Roadmap
5. Design of a mechanism for the yearly updating of the SRA

Starting points (1)

Overarching questions
(as identified by the HLEG)

- 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 and radiation protection?

➢ How best to prioritise these questions and to identify research needs to address these questions?

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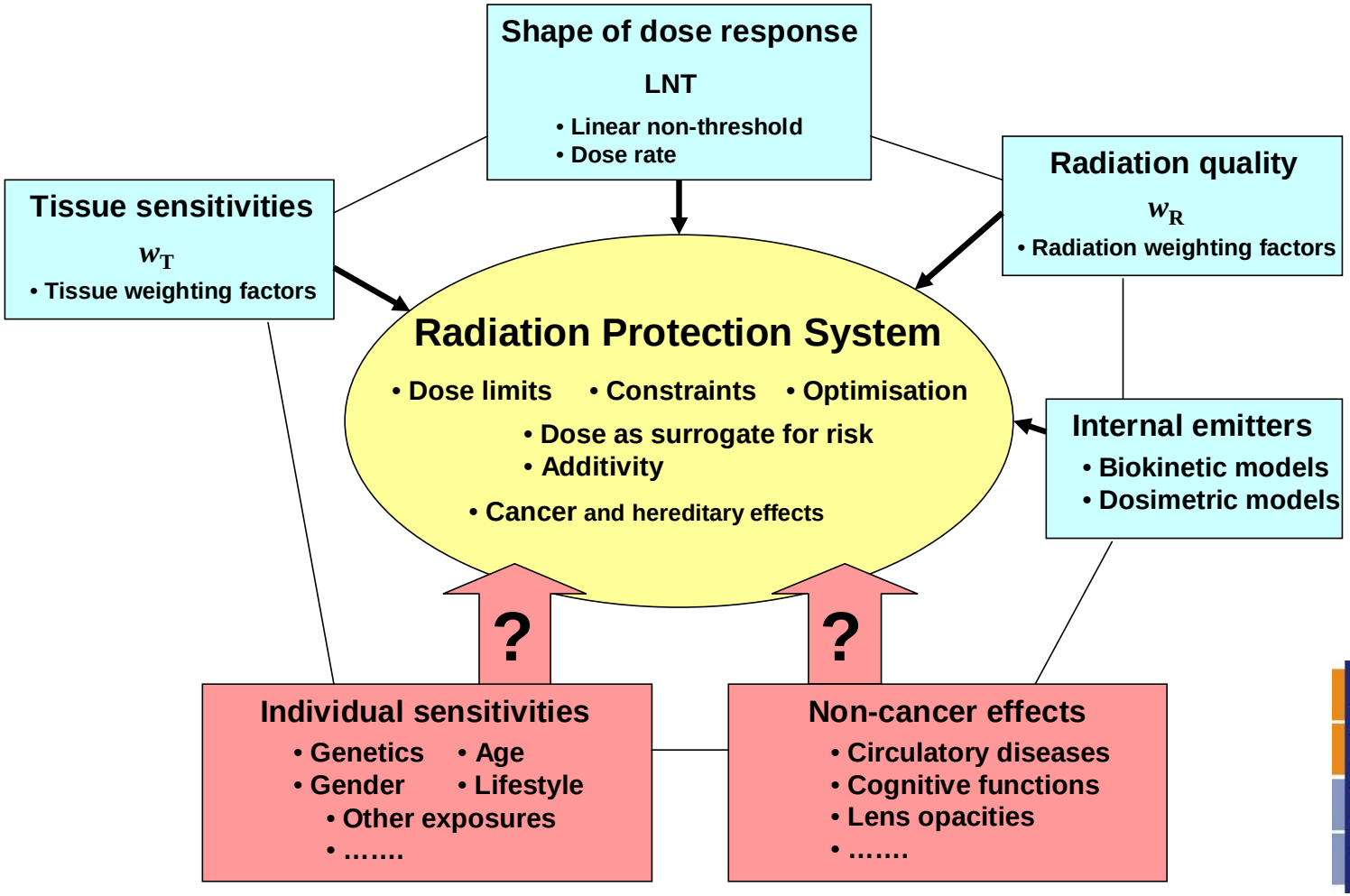
Starting points (2)

How robust is the system of radiation protection and risk assessment?



High Level Expert Group

Starting points (3)

The key scientific issues are:

- (1) the shape of the dose-response for cancer
- (2) the investigation of individual radiation sensitivity
- (3) a consideration of induced non-cancer effects

and the **cross-cutting issues**

- (1) radiation quality
- (2) tissue sensitivity
- (3) internal emitters

MELODI SRA

Contents of 2nd Draft

1. **Status of SRA**
2. **Scientific vision:**
   - **The present situation**
   - **Fundamental research lines**
   - **Proposed Research Priorities for key scientific issues** (including cross-cutting issues)
3. **Next steps**

MELODI SRA contents (1)

1. **The Status of the SRA introduces**

   the purpose, key issues, current scientific consensus and key questions; early developments due to HLEG and the Network of Excellence DoReMi, and long term issues of the MELODI SRA

2. **The Scientific vision describes**

   the present situation referring to ICRP and existing uncertainties (DDRF, extrapolation to low doses using LNT), tissue and radiation quality weighting factors, sensitivity of children.., dosimetry issues.

MELODI SRA contents (2)

2. Scientific vision also indicates

- Fundamental interactions in relation to cancer and non cancer effects
- Proposed **research priorities** for the scientific key issues: Dose response relationship for cancer, Non cancer effects, Individual sensitivity

3. Next Steps:

- Research areas to be exploited, Infrastructures, Education and Training, maintaining the SRA, Roadmap, major MELODI considerations, consultations, Scientific Committee

4. 5. & 6. Executive Summary, References and Annexes

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Current consensus

on Health effects which should be addressed are:

- Cancer – including secondary cancers
- Vascular effects
- Neurological effects (neurological and cognitive effects)
- Lens opacities
- Low dose adverse effects to normal tissue from radiation therapy (including individual sensitivity)

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Scientific vision

Low dose research

- **Epidemiological studies have limitations for statistical reasons** for estimation of radiation risks at low doses (<100mGy) and very low doses (<10mGy). Nevertheless, it is important to extend risk estimation down to environmental exposure levels such as mGy or µGy *(Smith 2010, J Radiol Prot. 2010 Mar;30(1):93-101, Wakeford and Tawn 2010, J. Radiol. Prot. 30(2010)1-3).*
- According to the HLEG, **refinement of low dose risk estimates will necessitate the close association of epidemiological with experimental mechanistic studies.**
- For this, dosimetry issues are important.

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Scientific vision

Dosimetry issues

- Research on micro- and nanodosimetry
- Dosimetry of internal contamination
- Dosimetry of medical exposures
- Small animal dosimetry
- Hadron and high LET dosimetry
- Biological dosimetry*

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Scientific vision

Radiation protection

- The present system of radiation health risk evaluation and radiation protection is based on current scientific knowledge and societal considerations of acceptance. It is steered by the ICRP protection system (ICRP publication 103) which, for low doses, has evolved around the perceived risk of induced malignancies and, to a lesser extent, heritable effects attributable to cancer. **It does not refer to non-cancer effects.** It uses the linear-no-threshold (LNT) assumption to estimate, derived from high dose radiation effects, the risks associated with low doses.
- For high radiation doses for which epidemiological studies are particularly significant the radiation protection system is reasonably well established. Nevertheless, **uncertainties still exist** and continue to need attention.

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Scientific vision

List of uncertainties (1)

- Shapes of dose response curves for different types of cancers and non-cancer diseases;
- Sensitivity variations dependent on 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 diseases.

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Scientific vision

List of uncertainties (2)

- Biological effectiveness of different types of radiation;
- Sensitivity of different cell types and tissues;
- Mixed radiation exposures;
- Dose-rate effect, including fractionated exposures;
- Interactions of radiation with chemical agents;
- Effects of radionuclides and internal contamination;
- Non-targeted effects of radiation.

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Why are we confident that these uncertainties can be reduced?

This is because **the science of low dose ionising radiation effects has made great progress** in recent years:

- The low dose range <100 mGy) is not anymore a black box and has become experimentally accessible to mechanistic research.
- Striking differences are observed in molecular and metabolic changes induced when comparing high and low doses (see results from 'Omics': transcriptomics, proteomics, metabolomics..).
- New paradigms specific to the low dose range include changes in intra-and intercellular signalling, bystander effects, modifications in cellular redox response, adaptive responses, genomic instability…
- Cellular defence systems play a crucial role at low doses: antioxidant defences, DNA repair, genetic and epigenetic regulation, metabolic regulation, hormonal and immunological activities.

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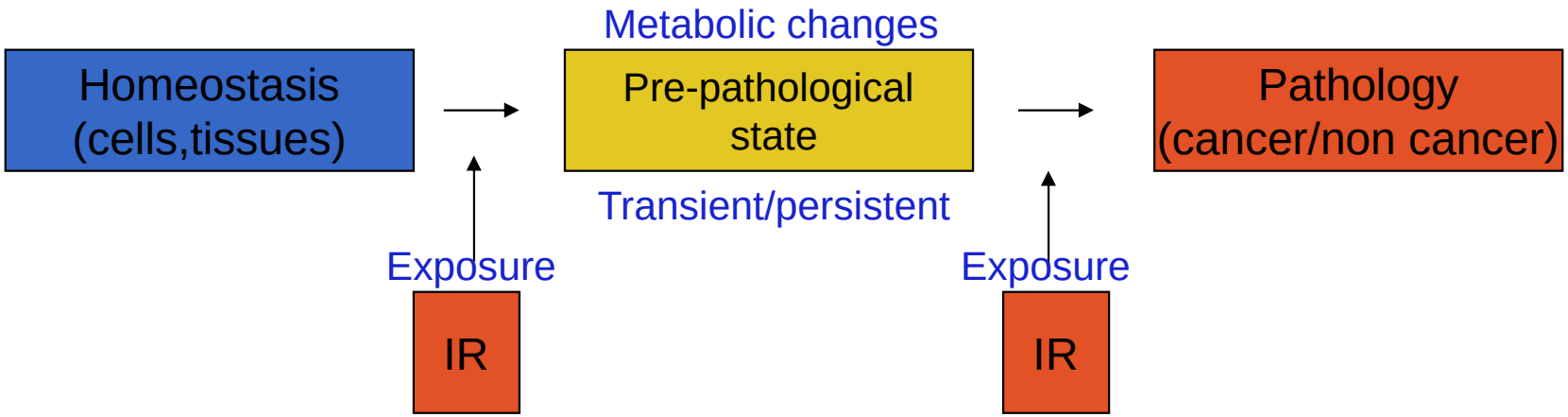
A closer look into the Scientific vision (1)

The scientific vision includes the notion of normal metabolic cell and tissue functions (homeostasis) coping with daily oxidative stress and metabolic changes in cells, tissues and organs that may be perturbed reversibly or non reversibly by ionising radiation of different quality *(by direct and indirect (free radical mediated stress) radiation effects)* and at different dose-rates causing transient changes in metabolic functions or persistent cellular, tissue and organ dysfunction and disease (specific cancer and non cancer effects).



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Scientific vision (2)

From this follows

- the necessity **to ensure sound dosimetric measures** of exposure (micro-nanodosimetry…biological dosimetry)
- the necessity of getting a solid **understanding of normal and perturbed metabolic functions** in relation with the initiation or not of disease, and
- the development of **suitable biomarkers** that are able to indicate **exposure**, to distinguish radiation **exposed cells with transient metabolic changes** from **exposed cells with persistent changes** acting as precursors and signalling the onset of specific types of cancer or non cancer effects.
- Biomarkers are likely to be developed from **molecular studies** using **high throughput technologies** (transcriptomics, proteomics, metabolomics, genetic and epigenetic profiling, sequencing, as well as detailed pathway analysis) and **systems biology** approches.

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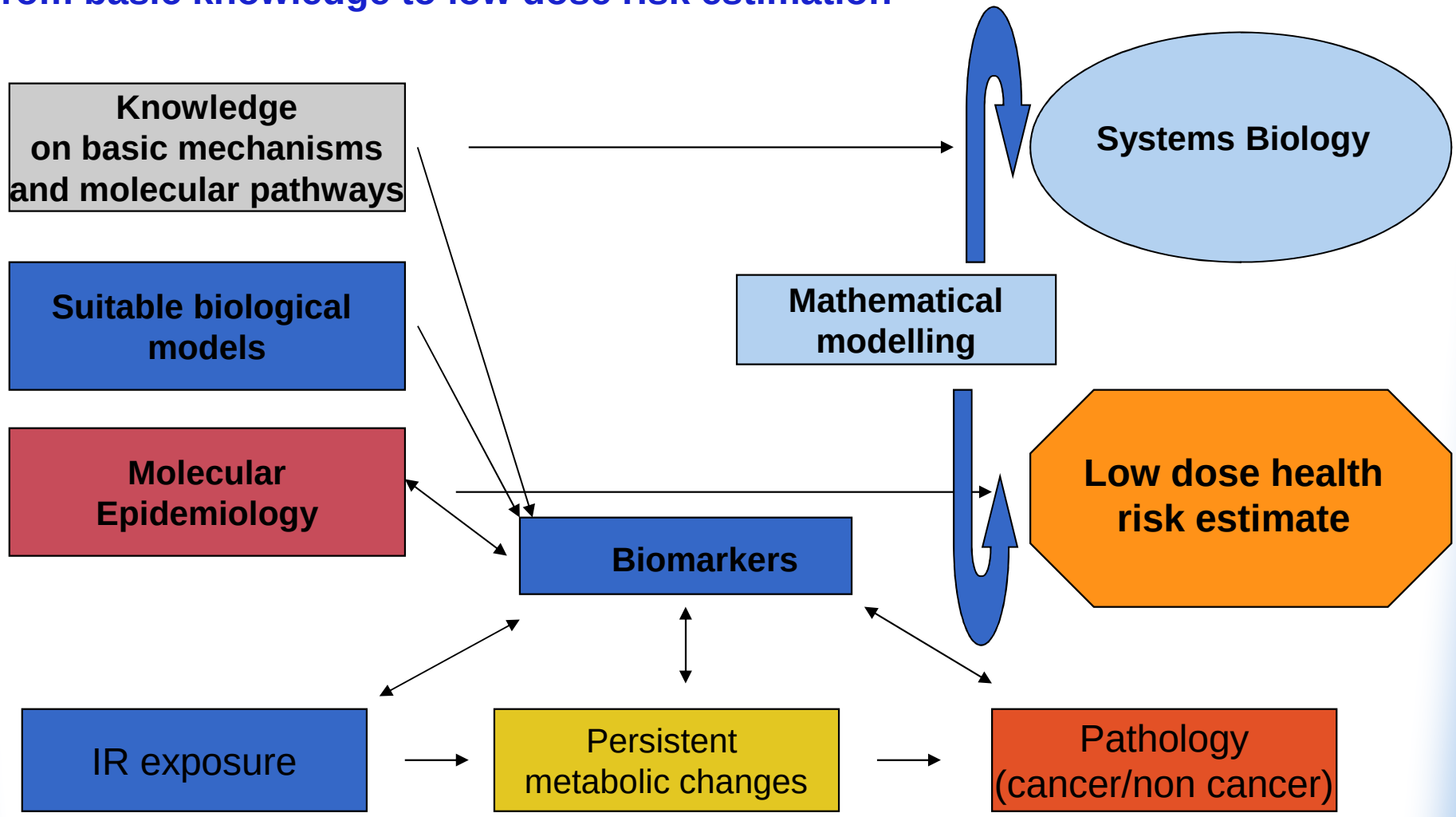
From basic knowledge to low dose risk estimation



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Research Priorities

- Following a somewhat mixed ‘top down/bottom up’ approach the present SRA is proposing research priorities for

(a) Shapes of dose response curves for cancer,
(b) non cancer effects,
(c) individual radiosensitivity

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Shapes of dose response curves for cancer: priorities (1) as an integrative package:

Epidemiological research on suitable cohorts, studies of the spectrum of damage, use of susceptibility biomarkers, bio- and databanking, studies on radiation quality effects (low dose, low dose rate, dose fractionation, chronic and internal exposures), animal studies, studies on suitable cohorts, mathematical modelling to assess health risks

together with the development of relevant dosimetric approaches to quantify exposure.

Shapes of dose response curves for cancer : priorities (2)

- **Association of epidemiological research on suitable cohorts (with sound dosimetric and well-defined medical bases) with fundamental mechanistic studies to include most recent technologies (Omics and sequencing). Information on dose response for specific cancer types, as well as gender, age and lifestyle effects should be included.**

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Shapes of dose response curves for cancer : priorities (3)

Suitable Cohorts

- Cohorts : retrospective and prospective (for example : diagnostic x rays (CT scans of premature babies and young children, CT scan children (congenital deformities e.g cleft palate, and trauma, dental cone beam, CT breast cancer screening, colorectal cancer with virtual CT colonoscopy, primary cancer patients from radiation or hadron therapy with out-of field effects and patients with secondary cancers) were biosamples are (or can be made) available. (associated with bio-and data banking).

➢ *Advantage : for most of these reliable dosimetry is available.*

- Cohorts allowing epidemiological studies on internal emitters (actinides, tritium in nuclear industry and radium, radon and thorium, uranium exposures in mining industries).
- Cohorts of thyroid cancer and breast cancer patients.

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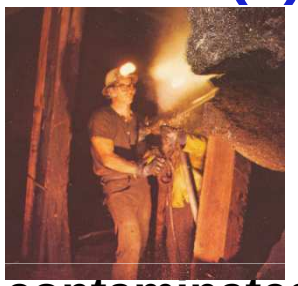
Shapes of dose response curves for cancer : priorities (4)



Suitable Cohorts

Other reliable cohorts are from

- **Chernobyl, the Mayak workers, uranium mining and other contaminated sites where relevant biomaterial is available and accessible.**

- **Also, populations of workers involved in the nuclear fuel cycle give good opportunities to construct a** combined cohort (compatibility of databases), with a precise reconstruction of past exposures to insoluble uranium oxides and other exposures (good dosimetry, availability of data, job exposure matrix construction), including the feasibility of biological sampling and biomarkers testing (legal and logistic procedures), and the collection of additional medical information (hypertension, serum cholesterol levels) from the occupational medical files. Such a cohort would allow to assess cancer as well as non cancer effects.

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Shapes of dose response curves for cancer : priorities (5)

as an essential part of low dose research:

Fundamental research on mechanisms

- The role of RI induced damage its repair (including dose-rate, radiation quality and external and internal exposures effects), its effects on metabolic pathways, the role of genetic, epigenetic and non-targeted effects, immunological, inflammatory effects as well as cell- and tissue type specific and developmental stage effects.
  - *See for example: miRNA regulatory effects on carcinogenesis (Koturbash et al. 2011, Mut. Res. 722,94). Non-tageted effects and epigenetic regulation (Illnytskyy, Kovalchuk 2011, Mut. Res. 714, 113)*
- Mechanisms of radiation-induced cancers (involvement of gene mutations, gene silencing and stem cells, effects of age)
- Radiation-induced changes in regulatory and metabolic processes and their possible dose dependent disruption (including effects on tissue specific microenvironment) (see changes in transcriptomics, proteomics, metabolomics).

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Shapes of dose response curves for cancer : priorities (6)

Fundamental research on mechanisms

- Development of biomarkers *indicative for radiation exposure, biological (early and late) effects, i.e. pre-pathological and pathological states, and radiation susceptibility based on omics, genetic and epigenetic profiling as well as sequencing.*
- *Studies on specific animal models are also important for mechanistic studies.*

Mathematical modelling

- *Suitable mathematical modelling will bridge the gaps between epidemiological and radiobiological studies and should allow the quantification of low dose health risks.*
- *Wherever possible mathematical modelling should help to define low dose radiation health risks at low doses of internal or external exposure.*

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(b) Non cancer effects : priorities (1)

There is increasing evidence that some of these effects (lens opacities) can be induced at much lower doses 500 mGy than previously anticipated (1-2 Gy) (ICRP 2011). Thus, **there is an urgent need to analyse the possible induction of vascular, lens opacities and neurological (cognitive) impairments by low/medium dose ionising radiation.**

- **For each of these pathologies the age and developmental-specific mechanisms involved should be determined. Particular attention has to be put on the involvement of specific tissue, and overall metabolic, hormonal, immunological, inflammatory (tissue micro-environmental) status in the different pathological responses.**
- ***Molecular approaches such as omics, genetic and epigenetic profiling as well as sequencing may be used at some stage to further elucidate mechanisms and to identify relevant biomarkers.***

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Non cancer effects : priorities (2)

- **Research on vascular disease should be carried out on low and medium doses of ionising radiation (as a follow up and extension of the previously more high dose oriented EU project CARDIORISK).**

- **Research on lens opacities needs to be launched if possible, combining epidemiological research and mechanistic studies on the dose response relationship including acute and chronic exposures to ionizing radiation.**

- **Research on neurological disorders and cognitive dysfunctions induced by low dose ionising radiation should be undertaken in order to determine low dose and dose-rate related responses (including radiation effects in utero , children and adults).The development of CT dosimetry tools for brain perfusion CT and other (repeated) brain CT examinations may allow accurate monitoring of this cohort of patients.**

Non cancer effects : priorities (3)

Epidemiological studies on suitable cohorts

- **Epidemiological and fundamental mechanistic studies should be undertaken in order to determine the dose-effect relationships (absence or presence of thresholds) for the induction of cardiovascular, lens opacities and neurological (cognitive) impairments. Suitable cohorts (some retrospective already existing cohorts, most prospective) with sound dosimetry and medical control have to be identified and/or set up.**
- **Most importantly, we have to find out whether these effects are of deterministic nature (with thresholds) or of stochastic nature.**

➢ *See for example: lens opacities in interventional cardiologists. S. Jacob et al. 2010, BMC Public Health 10,537*

Non cancer effects : priorities (4)

Fundamental research on mechanisms

- Given the ethics constraint of research with humans, animal studies are essential complements for these studies. **In particular, animal studies are needed for the analysis of low dose acute and chronic effects from external as well as from internal (contamination by intake of radionuclides) exposures.**

➢ *Recent animal experiments suggest possible links between ingestion of low doses of radionuclides and effects on the central nervous system, liver and major metabolic functions. Chronic uranium exposure at low doses affects metabolisms of xenobiotics, vitamin D, cholesterol and iron and exerts behavioural and cognitive effects in addition to the known nephrotoxic effect of uranium. In humans bone metabolism is affected. (see for example Bensausson H et al. 2009, Toxicology 26,59)*

➢ *Chronic contamination by cesium-137 could affect cardiovascular functions but the effects of radiation as opposed to chemical toxicity need to be clarified. (see Bertho JM et al 2011,J. Radio Prot. 32,25).*

Non cancer effects : priorities (5)

Fundamental research on mechanisms

- Furthermore, **radioactive contamination studies** should be backed up by investigations on the effects of particle size, distribution and specificity including research on nanoparticles.

➢ *Recent animal studies have reported a high sensitivity of the brain and cognitive impairment after low doses of external X-irradiation during the perinatal period, in particular, in neurite outgrowth and in neuron connectivity.*

Mathematical modelling

Wherever possible mathematical modelling should help to define low dose radiation health risks at low doses of internal or external exposure.

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Individual radiosensitivity : priorities (1)

- Clinical evidence from diagnostic and therapeutic uses of ionising radiation clearly shows that individuals respond differently to ionising radiation.
- There is thus an urgent requirement for **identifying biomarkers, gene markers and phenotypic traits to indicate specific radiation risks in individuals.**

  However, this research is not easy to perform. It highly depends on the availability of suitable data-and biobanking associated with suitable cohorts for which retrievable DNA (frozen or possibly fixed blood cells) and samples from blood serum or even skin biopsies can be collected. At present, there are formidable ethics restrictions placed on this type of research in Europe and of course logistical limitations (especially for cohorts of children) on what may be collected from human subjects.
- The establishment of **suitable prospective cohorts** (for example children exposed to low radiation doses and with long life expectancy) will be essential to identify human traits of radiation sensitivity in relation to individual predispositions to cancer and non cancer pathologies.

Individual radiosensitivity : priorities (2)

Associated epidemiological research

- **For the detection of individual sensitivity, it is essential to set up suitable (dosimetrical and medical) cohorts that are well controlled together with appropriate infrastructures of proper data-and biobanking allowing concomitant fundamental research (molecular studies) to be carried out using recent technologies.**

➢ *Interesting functional cohorts could come from human longevity studies (cancer susceptibility and radiation response) and from cancer susceptible individual and radiation therapy patients with aberrant responses.*

➢ *See for example: genetically defined sensitivity in mammography C. Colin et al. 2011,IJRB early online, 1-10*

Individual radiosensitivity : priorities (3)

Fundamental research on mechanisms

- **Research should cover : sensitivity of different cell types (stem cells and progenitor cells) in different types of tissues, determination of the range of radiosensitivity, redox profiles (oxidative stress), genetic (SNPs, sequencing) and epigenetic (miRNAs) profiles, the DNA repair capacity, capacity for radiation-induced death, the immunological, hormonal, inflammatory, general health status of radiation sensitive and resistant individuals, latencies for different pathologies (cancer, non-cancer diseases).**
- **Using well-defined 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 roles in individual low dose radiation responses..**

➢ Risk variants can be determined by combining epidemiological and model animal studies.

Individual radiosensitivity : priorities (4)

Fundamental research on mechanisms

- **This knowledge can then 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 or from mixed radiation fields as well as the amount of radiation sensitive tissue (example the amount of glandular tissue versus adipose).**

❖ *Tests of G2 sensitivity, dicentric chromosomes or micronuclei have not been able to serve as reliable individual predictors of radiation sensitivity*

❖ *Applying some newer assays for markers of radiation exposure (gH2AX, 53BP1) and specific DNA repair activities (RAD50, MRE11) have shown some promise for indicating intrinsic individual radiation sensitivity and repair capacity, and this work should be encouraged. It is possible that compilation and integration of results from several markers will emerge as the most reliable way to specify an individual's sensitivity. (see A.Granzotto 2011CR Biologie 314,140)*

Individual radiosensitivity : priorities (5)

Fundamental research on mechanisms

At present, it is unclear to what extent

- **inflammatory and immunological factors or non-targeted** *effects are involved in modulation of individual radiation responses.*
- *individual sensitivity is dependent on* **genetic background, developmental stage (child-adulthood)** *and modifiable lifestyle factors (the amount of radiosensitive tissues: see glandular tissue vs adipose tissue in the breast).*
- *Radiation responses differ for exposure in utero, in childhood and in adulthood.These investigations should, where possible, be factored into studies of mechanisms.*

Individual radiosensitivity : priorities (6)

Fundamental research on mechanisms

- *From this will emerge the potential usefulness of embarking on programmes of systematic genetic profiling or sequencing of individuals within cohorts such as radiation workers.*

- *Moreover, 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.*

Individual radiosensitivity : priorities (7)

Fundamental research on mechanisms

- **Combined epidemiological and animal model studies should be useful in identifying risk variants.**
  - *In-bred laboratory animal models 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 congenital malformation risks or for cancer risks like osteosarcomagenesis (RB1), mammary tumours (Aps) and medulloblastoma (ptch or thyroid rRET-PTC) cancers).). Radiation quality and dose-rate effects can be determined as well.*
- *See for example: importance of FOXE2 locus as determinant for individual sensitivity to radiation-related thyroid carcinoma in Belarussian population after Chenobyl : Takahashi et al. 2010, Hum. Mol. Gen.19,2516*

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Scientific vision

Cross-cutting issues : priorities (1)

*Research on the **cross-cutting issues radiation quality, tissue sensitivity and internal emitter effects** has to be actively pursued since they directly fit into all issues mentioned above. Some are already included in specific EU projects (see for example, DoReMi..)*

- ***Radiation quality** does concern micro-and nanodosimetric issues as well as the interaction with biological matter, and further understanding is essential also because of the use of devices such as microirradiation, synchroton irradiation, heavy ion and proton beams, conformational radiation therapy, immunological and pharmacological radioactive matter.*

➢ *see for example: induction of clustered or tandem lesions in DNA by radiations of different quality, their repair and biological consequences. Bergerand et al. 2010 PNAS USA, 197, 5528, Eccles IJ et al. 2011 Muta.Res. 711,134)*

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Scientific vision

Cross-cutting issues : priorities (2)

- ***Tissue sensitivity*** *is focussing on elucidating of intercellular signalling, tissue microenvironmental,and tissue regulatory effects (miRNAs) and the behaviour of different cellular compartments (progenitor and stem cells).*
  - *See for example: tissue specfic response, Harfouche et al. 2010, Stem cells 28, 1639; FGF2 signalling involved in DNA repair in Human keratinocyte stem cells.*
- ***Research on internal emitters*** *needs to be extended: Chronic exposures due to internal contamination is a permanent concern and needs more work on specific radionuclides Iode 125,131, Césium 137, 3H, 14C etc. analysing the chemical toxicity (nanoparticules) versus radiation-based toxicity as well as biokinetics of uptake and excretion.*
  - *See for example: tissue specfic response, Bertho JM et al*

MELODI SRA Next Steps (1)

Summary of research areas to be exploited :

- Metabolomics, homeostasis, signalling mechanisms, stem cell biology, cellular stress, proliferation, genetics, epigenetics, systems biology, toxicology, genotoxicology, physiology, pathology, immunology, inflammation research, hormone research, research on cell death (apoptosis, mitotic catastrophy, autophagy), central nervous system, recognition and behavioural effects, embryology, teratology, molecular markers for imaging, effects of nanoparticles (nanotechnology), heredity, trans-generational transmittance, diseases (medical treatments and diagnosis of cancer and non-cancers, …).

MELODI SRA Next Steps (2)

SRA recommendations on organisational and practical issues

Infrastructures

- *The availability of and access to proper infrastructures (**cohorts, radiation facilities, data-and biobanks, platforms** for high through put analyses) is a basic requirement for successful low dose radiation research.*
- *High Priorities are: **upgrading and establishment of suitable infrastructures***

MELODI SRA Next Steps (3)

Infrastructures

Suitable cohorts

- *Establishment of suitable cohorts with dosimetric, medical and molecular follow up.*
- *A number of retrospective cohorts from industrial and nuclear workers, medically exposed groups and residential radon exposure are at least partially available and should be further explored.*
- *Prospective cohorts should be initiated, wherever possible, because methods of dosimetry, data and biological sample collection (data-biobanking) as well as associated molecular analyses can be easier harmonized.*
- *Furthermore, Ethics approval of epidemiological studies is an important issue. The establishment of a Europe-wide infrastructure to facilitate ethics approval and consensual national interaction of ethics committees should be considered.*

MELODI SRA Next Steps (4)

Infrastructures

Suitable radiation sources

Suitable Radiation facilities are essential requisites for low dose radiation research. The existing and forthcoming radiation facilities including microbeams, devices for alpha, beta, gamma, x-ray; neutron, proton exposure as well as facilities for low dose rate exposures have been listed by DoReMi.

- *MELODI is asked, wherever necessary, to help in getting access.*

MELODI SRA Next Steps (5)

Infrastructures

Bio- and databanking

Suitable data-and biobanking facilities have been part of several EU projects (e.g. STORE)..

- *MELODI should be able to facilitate access to future users and to help in organising proper data-and biobanking in connection with suitable well-defined cohorts. It may become necessary to create a dedicated biobanking infrastructure within the MELODI programme.*
- *Ensuring medium term or long term maintenance will be an important organisational and financial challenge of MELODI.*

MELODI SRA Next Steps (6)

Infrastructures

Analyses platforms

Analyses platforms for high throughput 'omics' exist in several institutions in Europe. Access is usually possible via collaborative projects or through direct individual contracting.

- *MELODI should seek support for this type of collaborative and integrative efforts in low dose research and facilitate access to forthcoming high level sequencing activities (often done commercially) in the framework of defined low dose radiation research projects.*

MELODI SRA Next Steps (7)

SRA recommendations on organisational and practical issues

Education and Training

In order to counteract the loss of key competences in radiation research and radiation protection in Europe **MELODI proposes:**

- **an integrated approach to education and training** of research research and teaching at universities and non-university research organisations., i.e. strengthening of the European MSc course and achieving compliance with the Bologna process which creates the European Higher Education Area (EHEA) based on cooperation between ministries, higher education bodies, students and staff from 46 countries with participating international organisations.

MELODI SRA Next Steps (8)

Education and Training

At present, only few universities can offer a full educational programme in radiation biology and radiation physics. Thus, an integrated approach is needed. The following steps are proposed:

- ***Audit of radiation courses in Europe*** *(undertaken by DoReMi) and establishment of European course (and/or summer school) in radiation biology and radiation protection with conventions with European Universities and institutions*
- ***Identification of stakeholders able to provide long term sustainability***
- ***Proposition of EU calls directed to education and training*** *promoting new ways for multidisciplinary interactive courses (including recent research developments in the field of low dose radiation research and the evaluation of health risks) with Bologna compliance and conventions with leading universities and research organisations.*

MELODI SRA Next steps (9)

Proposition

Education and training in radiation physics, biology and protection:

- Increase competences in the field by attractive scientific programmes (multidisciplinary and interactive courses with European universities and institutions, check Bologna compliance and take an active part in European Higher Education Area (EHEA)),
- Identify and check existing courses (audit)
- Increase attractiveness by multiple approaches: Summer schools, Master schools, PhD and post-doctoral European training programmes
- Establish links to job opportunities
- Establish sustainability by long-term commitment of funding bodies (identify interested stakeholders)

Maintenance of the SRA

- **Yearly updating of the SRA in connection with the open MELODI workshop is proposed.**
- The MELODI Scientific Committee (SC) should review and approve successive revisions of the SRA and pass them to the Governing Board for formal endorsement. Maintenance of links to DoReMi WP2 and to the MELODI SRA Working group will be obvious. The chairman of the DoReMi Sientific Advisory Committee has accepted to be a member of the MELODI SC.
- **A short MELODI statement derived from the updated SRA should be useful for the preparation of future calls.**
- **The SRA should 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.**

MELODI Roadmap

At present, the SRA Working Group considers it premature to outline already a **ROADMAP** for MELODI at this stage:

- Most prioritized research items will have to follow a more or less preset time scale.
- The search for suitable biomarkers for defined radiation exposures (internal or external), predictions for sensitivity, for the activation of pathological pathways and for final pathological effects will come first in the research on radiation related Systems biology.
- The development of biomarkers is expected to **stimulate molecular epidemiological studies and the establishment of suitable prospective or retrospective cohorts.**
- The **detailed analysis of metabolic pathways** is expected to provide **useful information for a systems biology approach associated with mathematical modelling of low dose radiation health risks.**
- A preliminary roadmap may be established at the end of 2011.

Major Considerations :

MELODI is an open structure

- promoting multidisciplinary integrated low dose research in Europe
- bringing in **'new blood'**, i.e. also specialists with skills in research areas that previously have not yet been associated with ionising radiation.
- Aming at sustainability of infrastructures, education and training
- Promoting open **interaction and communication** with the scientific community, stakeholders and the public.

➢ (see also the MELODI Website).

Consultation (1)

- Regular consultation is foreseen of the general scientific community through workshops and expert group meetings.
- DoReMi and MELODI workshops open to a large scientific community will be held to attract new scientific competences.
- Links to other relevant European research projects will be sought.
- Specific working groups may deal with specific research issues (including technological and ethical problems)
- Selection of actual research needs as well as topics for future calls will be established based on criteria for relevance, feasibility, sustainability and expected outcomes.
- Regular surveys of national research and education and training activities will be required to identify original and novel research lines to low dose research.
- 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.

Consultation (2)

The following additional activities are recommended:

- Interdisciplinary working group meetings will be held
- to attract fundamental scientists a variety of disciplines (radiation physics, medical physics, dosimetry, biophysics, radiation chemistry, toxicology, imaging, physiology, immunology, cancer research, DNA repair, genetics, oxidative stress, epigenetics, molecular signalling, developmental research, nanotechnology, inflammatory and immunological research, 'omics', protein research, miRNAs, systems biology, medicine)
- MELODI sponsored forums-conferences-seminars-colloquia will be held on

➢ for example: Intra-and extracellular signalling, cellular damage/epigenetics; nanotechnology/toxicology/internal contamination, 'omics' and systems biology, stem cell research/cancer/non cancer, Infrastructures; epidemiology (suitable cohorts); education and training (degree courses); meetings for regulators and researchers etc.

Establishment of the MELODI Scientific Committee (SC)

- The committee should be composed of experts with well-founded reputations embracing a wide range of disciplines and competences (see list of disciplines to be considered)
- In order to ensure regular updating and some continuity in the work on the SRA, members of the MELODI SRA working group may also be active members of the Scientific Committee. The chairman of the DoReMi Scientific Advisory Board has accepted to be also a member of the MELODI SC.
- The MELODI Governing Board is going to formally invite and appoint the future SC members who should not represent their specific institution or country, but should be serving the cause of MELODI as individual experts.

Research areas and disciplines to be considered (1)

- Radiation Physics (spectroscopy, dosimetry, space research
- (Biophysics
- Radiation Chemistry
- Radiation Biology
- Molecular Biology and Biochemistry
- High throughput processes (Sequencing, screening, genotyping)
- Physiology, Metabolism
- Cancerology
- Medicine : Radiology, Radiotherapy, Radiodiagnostics, Nuclear Medicine, Pathology, Histology, Cancerology, Cardiology, Ophthalmology,, Hematology..

Research areas and disciplines to be considered (2)

- Physiology
- Toxicology
- Genetics, Epigenetics
- Biology of Development (Embryology, Germ cell Research)
- Immunology (Inflammatory research)
- Stem cell Biology
- Molecular Epidemiology
- Biomathematics and Bioinformatics
- Modelling
- Systems Biology

The SRA of MELODI contains also :

- **An Executive Summary**
- **References to ICRP publications,**
- **HLEG: www.hleg.de,**
- **MELODI : www.melodi-online.eu/**
- **DoReMi: http://www.doremi-noe.net**
- **Papers on Low dose radiation**
- **Annexes:**

- Questions identified as being key issues for MELODI

- MELODI statement (18 November 2010)

Conclusions

The SRA MELODI promotes the following ideas:

Fundamental research:

- **Opening the way towards mechanistic understanding of low dose radiation effects** on metabolic pathways in relation to **cancer and non cancer diseases and individual responses**. For this, **development of suitable biomarkers and system biology approaches with mathematical modelling** appear to be most promising.
- **Animal studies** are very useful for *in vivo* mechanistic and whole lifespan studies.
- **Take advantage of technical advances**: high through-put detection and imaging, flow cytometry, microarrays, molecular profiling (mRNA miRNA),sequencing, nanotechnology

Molecular epidemiology:

- Setting up of **suitable cohorts** with access to precise dosimetry, medical check and biosamples for **associated biological studies as well as for mathematical modelling for health risk evaluation**. Examples are: large scale cohorts (Mayak workers, nuclear power workers, uranium miners, CT scans…).

As a conclusion: A musical metaphore for MELODI

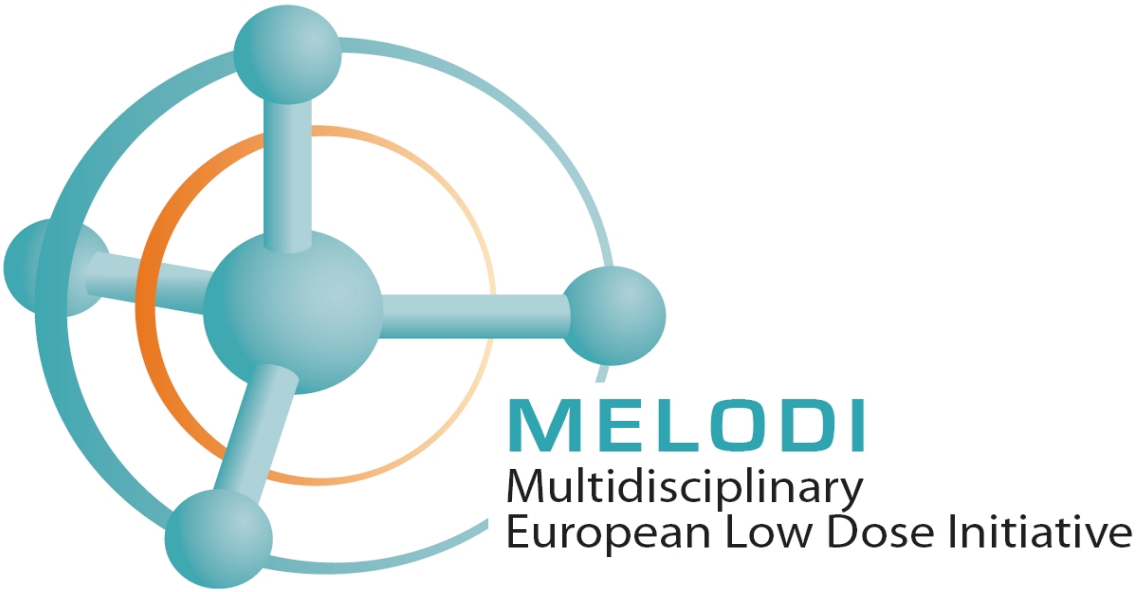
At the end of this presentation, the reference to DoReMi and MELODI sounds somewhat very musical:

Indeed,

- To get a well integrated sound (orchestra) the many players (MELODI members) and also DoReMi partners) have to be well conducted by the **MELODI platform,** and a **common (integrative) partition** has to be agreed upon to be effective and successful**.**
- **The Strategic Research Agenda (SRA)** may be taken as **common partition to be played and continously worked on. DoReMi helps in promoting relevant research lines to get a nicely coordinated ensemble, the MELODI.** The total refers to an operational framework that relies on scientific engagement, institutional support (EC), on stakeholders and the public.
- ***I do hope that the 3rd MELODI workshop will be like a great concert that gets us all further tuned up and does inspire sound and memorable future work.***

Thank you very much for your attention.

The presentation is open for discussion!!



MELODI SRA

Contents of 2nd Draft

1. **Status of SRA**
2. **Scientific vision:**
   - **The present situation**
   - **Fundamental research lines**
   - **Proposed Research Priorities for key scientific issues** (including cross-cutting issues)
3. **Next steps** (Research areas to be exploited, infrastructures, education and training, maintaining the SRA, Roadmap, major MELODI considerations, consultation activities, scientific committee)
4. **Executive summary**
5. **References**
6. **Annexes:** Questions on key issues, MELODI statement 2010

MELODI SRA

Epidemiology

Many cohorts are of interest:

They may be suitable for answering specific questions:

Mayak cohort: dose range 500- several Gy (European study SOLO): in some parts reasonably good dosimetry, medical surveillance, availability of biological samples (data-and biobank: SUBI)(exploitability and accessibility has to be clarified) man and women, internal contamination, plutonium cancer and non cancer

Uranium miners: 100 000 men, radon, gamma IR, uranium, biological samples available for some molecular biology (HPA, BfS)

Nuclear workers: 70 000 men, numerous, uranium fuel cycle, internal contamination, good medical information,physiological parameters, possible blood samples, doses correctly monitored,

Cardiovascular, lens opacities, neurological problems, cancer may be monitored (IRSN)

Techa River: 30 000 individuals, 100mGy-1Gy, cancers, cardiovascular, cesium, strontium, dosimetry OK?,quality of biol. samples? F1 generation

MELODI SRA

Epidemiology

Other cohorts of interest:

Chernobyl: *liquidators and children follow up important, F1 generation*

ARCH

EPICE: *life in contaminated areas (Chernobyl): external 200 mSv, internal doses, cardiac rhythm disorders (2009-2013) and lens opacities (2014-2018) in a cohort of 18 000 children in Russian contaminated § 9 000 children) and non-contaminated (9000children) territories of the Bryank oblast.*

Fukushima-Daishi: *prospective cohorts*

Nuclear veterans, military essays in the pacific: CEA: 4500 persons, blood, doses external/no internal doses?

Tritium: USA, Canada, UK : workers, maybe in the future also in France

Kerala (Japan, USA): natural radioactivity

Yang-Yang (China): natural radioactivity

MELODI SRA

Epidemiology

Other cohorts of interest:

Medical radiology, nuclear medecin

Interventional cardiologists: *lens opacities follow-up in time necessary, cardiovascular, neurological behaviour, brain tumours may be monitored as well.*

CT children and EPI-CT: *> 30000 (France) prospective studies, children cancers in children (leukemia, brain tumours), dosimetry OK*

Hemangioma treatment:

Secondary cancers, cancer du sein, cancer survivors (precise doses, cardiovascular doses > 500 mGy, control/case study