



European Low Dose Risk Research

Report by

High Level and Expert Group (HLEG)

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3rd EURADOS Winter school, 28 January 2009
“Low-Dose Radiation effects”





High Level and Expert Group (HLEG) on European Low Dose Risk Research

Objectives

- Formulate and agree the **policy goals** to be addressed
- Develop a **strategic research agenda** and road map
- Specify elements of and next steps for establishing a **sustainable operational framework** for low dose risk research in Europe





Membership of HLEG on European Low Dose Risk Research

Formative members

W Weiss, BfS

M Belli, ISS

G N Kelly, EC

P Legrain, CEA

J Repussard, IRSN

S Salomaa, STUK

H Walker, DH

(D Goodhead)

Co-opted experts

M Atkinson, HMGU

E Cardis, CREAL

R Cox, HPA

A Elliot, NHS

J Hall, Inst Curie

M Harms-Ringdahl,
Stockholm Univ

J-R Jourdain, IRSN

A Ottolenghi, Pavia Univ





Responsibilities of HLEG Members

- **Formative members:** responsible for the **content** of the HLEG report and the **proposed way forward**.
- **Co-opted experts:** responsible for input on **scientific matters** and identifying **research directions** most likely to respond effectively to policy questions.

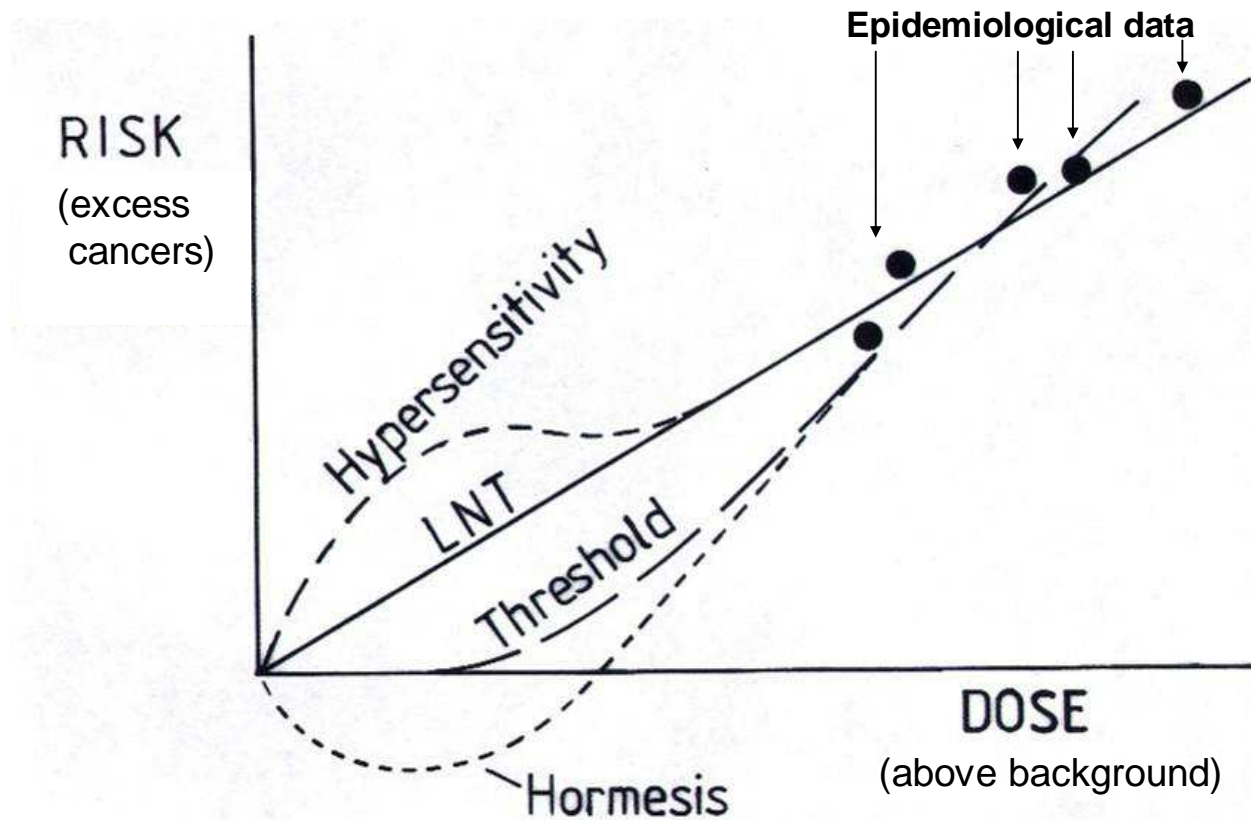
Over-arching policy questions

- How robust is the current system of Radiation Protection and risk assessment?
- How can it be improved?

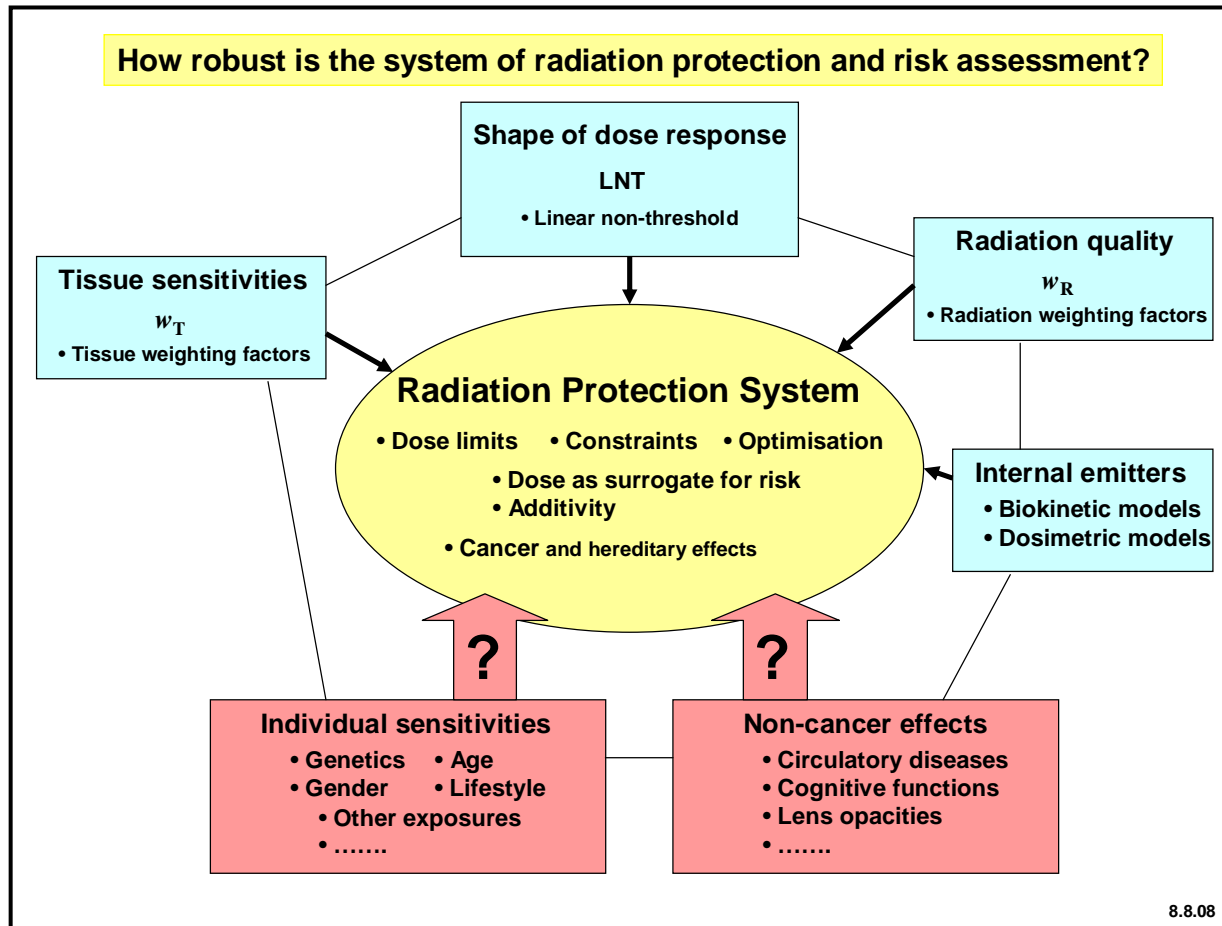
Key value judgements/simplifying assumptions underpinning RP

- Shape of dose-response for cancer
- Tissue sensitivities for cancer
- Individual variability in cancer risk
- Effects of radiation quality
- Risks from internal exposure
- Non-cancer diseases (risks and shape of dose response relationships)

Low dose risk extrapolation



Key value judgements in the radiation protection system



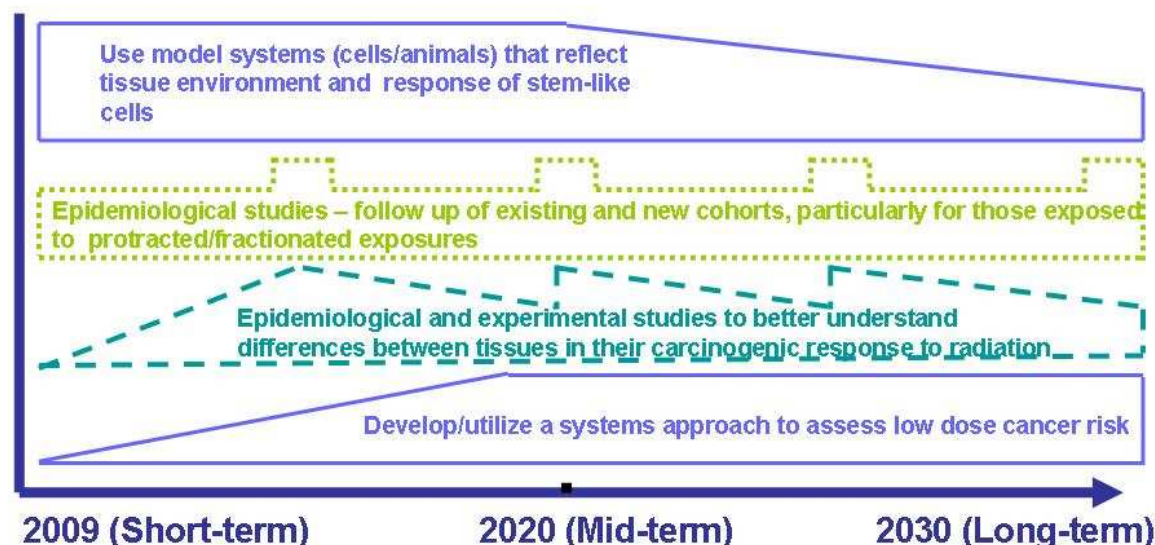
Report Content

- Policy Issues
- State of Science and research challenges
 - Current state of knowledge
 - Most promising research directions
 - Indicative time course for research
- Proposed European research strategy
 - Trans-national structure
 - Scientific strategy.

Indicative research directions to address issues on the shape of dose response relationship and tissue sensitivities for cancer

Objective: To improve the understanding of dose-response for radiation carcinogenesis – to judge whether approaches using the LNT model might under- or over- estimate risk in different tissues

Relevance: projection of risk to low doses and doses rates – judgments on tissue weighting factors



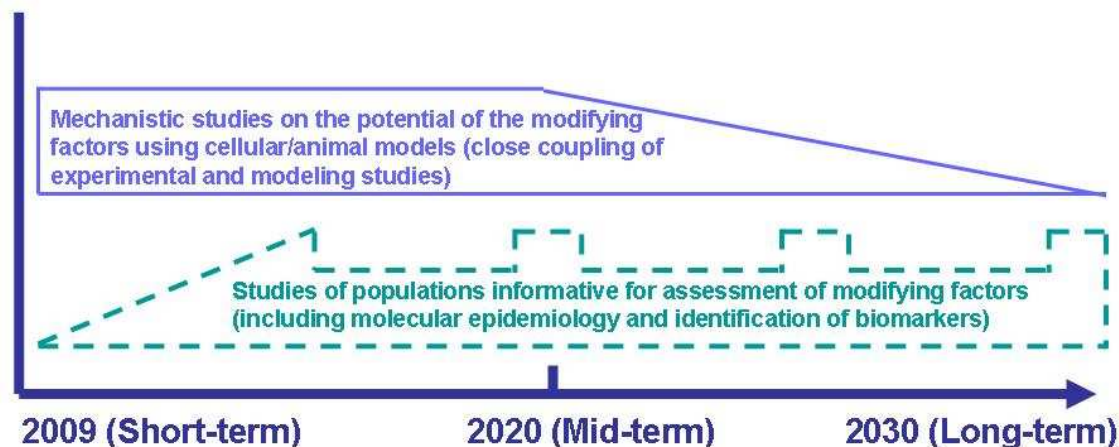
Indicative research directions to address issues on the shape of dose response relationship and tissue sensitivities for cancer

- To continue epidemiological studies of low-dose responses, in different tissues, and to combine these with experimental studies.
- Further experimental approaches need to be developed and utilized in order to understand better the biological mechanisms that underpin the responses
- Mechanistic studies should be closely coupled with computational approaches that incorporate biological processes in models of low-dose response.
- A systems biology approach is needed that will combine quantitative experimental data and mathematical modelling of critical biological processes in the radiation response.
 - Such an approach would involve experiments performed at low doses at different scales (cell, tissue, organ, organism and population)
 - Predictive models of the behaviour of the complex systems to radiation, allowing a better understanding of the risks to health from exposure at low doses and low dose rates, and from different radiation qualities.
- Cooperation between the fundamental radiobiological research and mathematical-modelling communities is needed.

Indicative research directions to address issues of individual variability and genetic susceptibility to cancer

Objective: To quantify how the sensitivity of individuals (or population subgroups) to induction of health effects depends on gender and age, genetic and epigenetic factors, lifestyle factors and concomitant exposure to other agents

Relevance: protection of particular subgroups of population



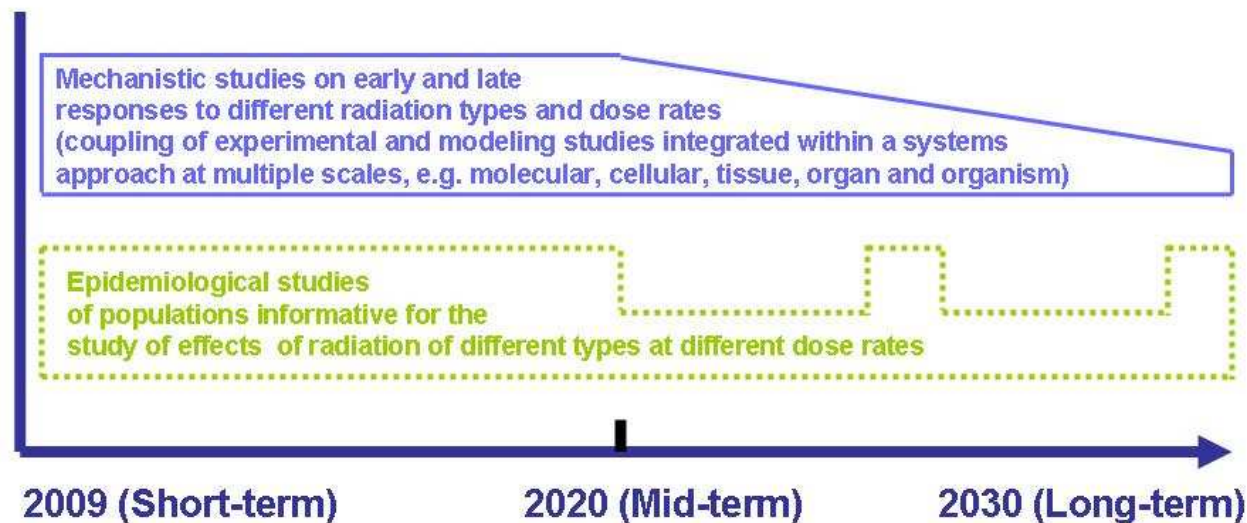
Indicative research directions to address issues of individual variability and genetic susceptibility to cancer

- To obtain better scientific information on the extent of the variations in sensitivity in the population
 - the sizes of the variations in sensitivity
 - the proportions of the population that are affected
- To identify the factors that affect individual sensitivity to radiation risk
- Epidemiology is the most direct way to estimate human risks. However, because low-dose risks are small and difficult to detect, additional approaches are also needed.
- To study genetic effects, including functional polymorphisms, and epigenetic effects that could modulate radiation risks:
 - epidemiological studies with sufficient statistical power must be enhanced by combining with molecular characterisations of the individuals
 - supplement with laboratory studies aimed at identifying the underlying mechanisms.

Indicative research directions to address issues of radiation quality

Objective: Quantification of health effects of different radiation types and mixed fields

Relevance: use of radiation weighting factors in radiation protection and application of different types of radiation in medical practice



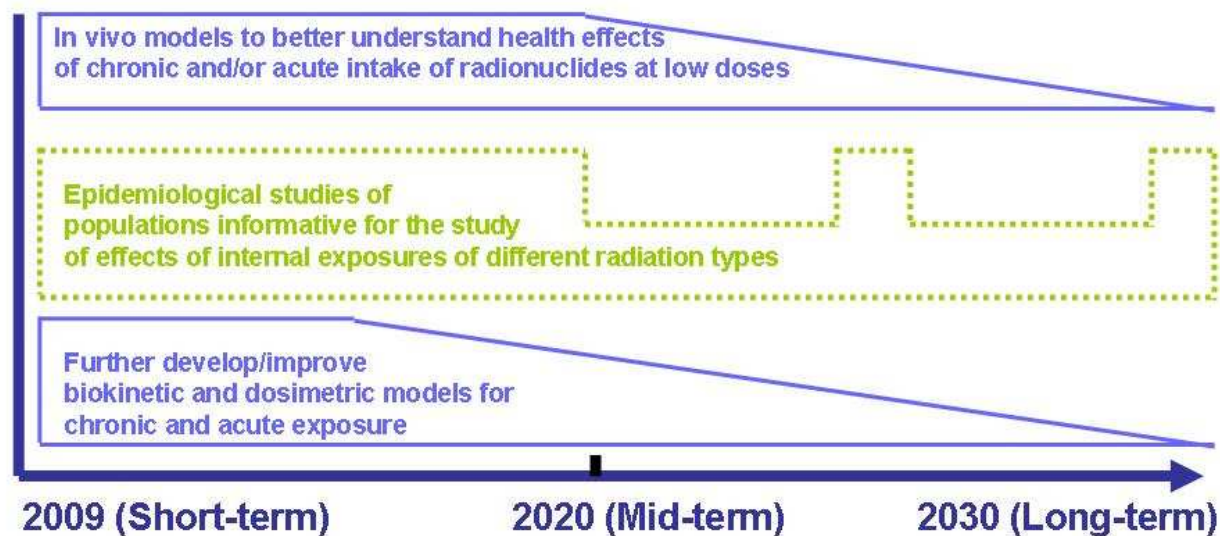
Indicative research directions to address issues of radiation quality

- Well designed epidemiological studies of relevant populations that can provide significant information.
- Mechanistic understanding is required of:
 - processes involved in radiation carcinogenesis and in non cancer diseases,
 - the impact of radiation quality on key aspects, starting from track structure and physical interactions with various biological “targets”
- How radiation quality affects the initial damage (DNA and non-DNA) and its time evolution: repair and mis-repair processes, the intra and intercellular signalling, non-DNA-targeted effects
- The relevance of clustered DNA damage from a single track in inducing chromosome aberrations, mutations and carcinogenesis
- The role of dose-rate, together with mixed field effects (including possible synergistic and adaptive phenomena).
- A systems biology approach for these radiation effects is advisable, with coordinated experimental, modelling and epidemiological studies to encompass the key processes from the initial radiation tracks to the final health risks.
- How radiation quality influences epigenetic phenomena and the occurrence of genomic instability.

Indicative research directions to address issues of internal exposure risks

Objective: To better quantify the risk estimates from internal exposure

Relevance: To improve the robustness of the systems of protection



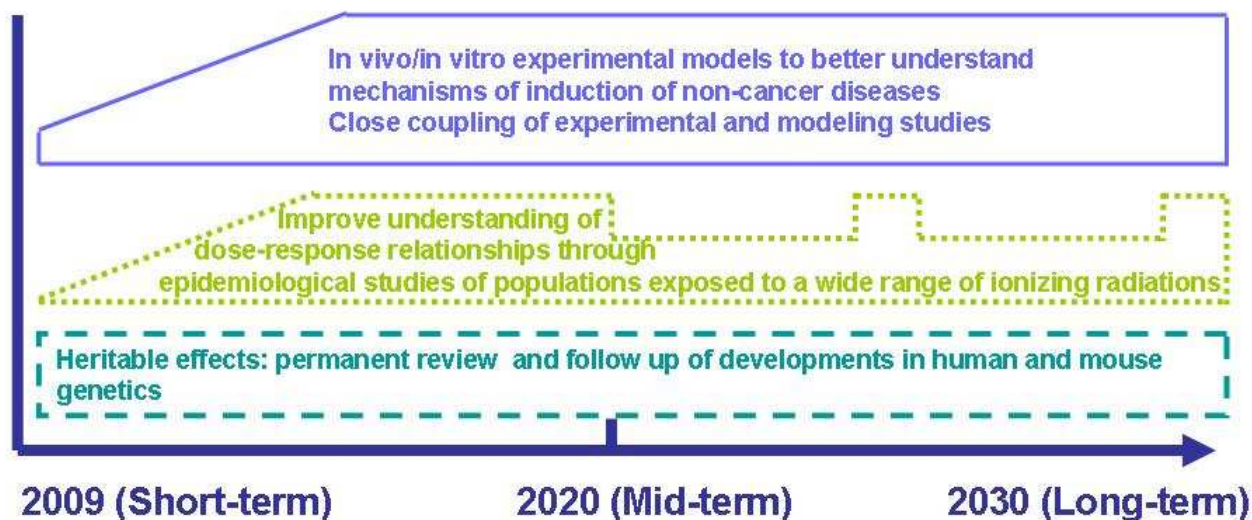
Indicative research directions to address issues of internal exposure risks

- Epidemiological studies of groups with reliable exposure/dosimetric information could provide further quantification of effects (both cancer and non-cancer) from internally-deposited radionuclides.
- These groups could include:
 - patients from diagnostic investigations and therapeutic treatments,
 - well characterised cohorts of workers and the public with substantial exposures to internal emitters incurred, in particular, during the early stages of the development of nuclear weapons (e.g. tritium, strontium, caesium, uranium, plutonium)
- Experimental studies, particularly using in vivo animal models:
 - to improve understanding of the mechanisms of health effects from heterogeneously deposited radionuclides in the body
 - to improve biokinetic and dosimetric models for their assessment

Indicative research directions to address issues on risks from non-cancer effects

Objective: To better understand the mechanisms of and quantify the risks for non-cancer health effects resulting from exposure to low and protracted doses

Relevance: Implications of contribution of non-cancer diseases to radiation risk for the system of radiation protection



Indicative research directions to address issues on risks from non-cancer effects

- Circulatory diseases (i.e. heart disease and strokes), effects on cognitive function following radiation exposure in infancy and occurrence of opacities in the lens of the eye (cataract)
- Well-controlled epidemiological approaches will continue to be essential in addressing each of these areas.
- New more-suitable animal models also need to be developed for mechanistic studies of circulatory effects at low doses and for effects on learning and cognitive functions.
- Better understanding is needed of the extent to which some biological modifications observed in animals exposed chronically to low levels of radionuclide contamination (eg, uranium, caesium) could lead to clinical effects.
- Although judgements on heritable risks following gonadal dose are relatively well developed, it remains important to keep the topic under review and to retain scientific competence to undertake further studies if new issues are revealed.



The **M**ultidisciplinary **E**uropean **LOW** **D**ose **I**nitiative **MELODI**

Establish trans-national governance structure to:

- Integrate national, bi- and multi- lateral research programmes within an agreed SRA
- Interface with broad range of stakeholders
- Oversee investments in key infrastructures, knowledge management and E&T
- Ensure consistent research methodologies.



Some underlying principles of MELODI

- **Open process** – mechanisms to involve any research organisation/funding body able to contribute to MELODI goals
- **Actively engage** with potential contributors from the wider scientific community and stakeholders
- **Step by step process** in the development and implementation of MELODI
- **Focus initially** on developing fully integrated and sustainable approach to low dose risk research

Scientific Strategy

Four key elements

- Holistic approach
- Periodic review of objectives
- Dissemination of research outcomes and interaction with users
- Ensuring pre-requisites are met.

Elements of a more holistic approach

SRA will engineer programmes/projects that:

- fully integrate mechanistic studies, modelling at all scales, epidemiology, dosimetry, etc
- accommodate most recent paradigms in radiobiology (eg, NTE) and in biology more generally (eg, systems biology, etc)
- utilise the most recent investigative techniques (eg, tracer biology, track analysis, micro-dosimetry)

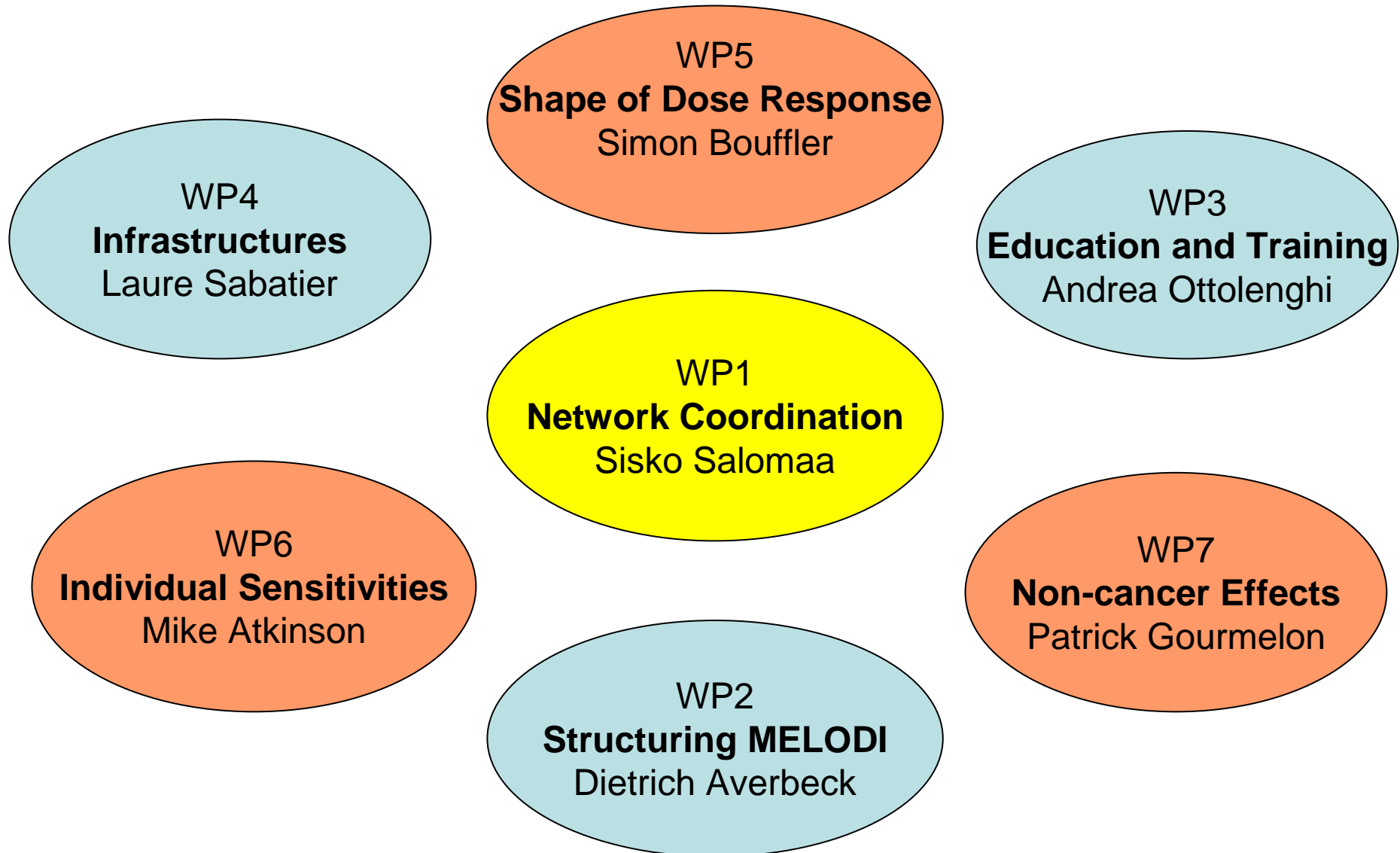
Next Steps

- Final HLEG report to be published in January 2009 taking account of comments from web consultation (www.hleg.de)
- Establishment of governance structure and detailed strategic research agenda (SRA) and road map
- Implementation of SRA

Next Steps: Network of Excellence

- Euratom Call for Network of Excellence
 - dead line April 2009
 - evaluation June 2009
 - if funded, start January 2010
- 5-7 years project
- max 15 MEuros EC contribution
- Operational tool to initiate MELODI

Workpackages / contact points



Network of Excellence

- Workshop open to all interested parties is tentatively planned for September 2009 in Germany
 - presenting the concept
 - exploring ideas and possible contributions
 - preparing for the first call (2010)
 - three competitive calls planned
- Linking with other programmes and projects