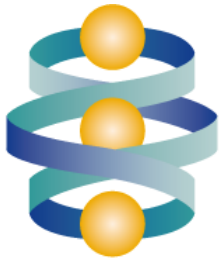

DoReMi
Integrating Low Dose Research

Summary of the methodology for DoReMi TRA setting, key and subquestions

Structuring the key and subquestions to the related tasks, and outline of future TRA

Dietrich AVERBECK, WP2

IRSN/CEA, France

DoReMi TRA Position meeting - Consensus meeting
for position papers on risk assessment and radiation protection
•Hotel Port Sitges , Barcelona, Spain 29-30 April 2015

DoReMi Integrating Low Dose Research

DoReMi TRA (1)

- **The DoReMi TRA** played a central role in defining the short, mid term and long term scientific goals of DoReMi (and also for the MELODI SRA). It identified the main questions concerning the remaining scientific uncertainties in radiation protection (i.e. low dose radiation health effects) and translated them into relevant and feasible research projects on the basis of HLEG recommendations, dedicated meetings and workshops (brain storming*), periodic DoReMi and MELODI meetings and related congresses. Most recent scientific developments were taken into account. The TRA was implemented by launching corresponding **internal and competitive calls** in Europe. The TRA progressed stepwise.

***meetings in Saint- Feliu de Guixols, Barcelona, Spain May 201 and in Vitri sul Mare, Italy, Oct 2012)**

DoReMi Integrating Low Dose Research

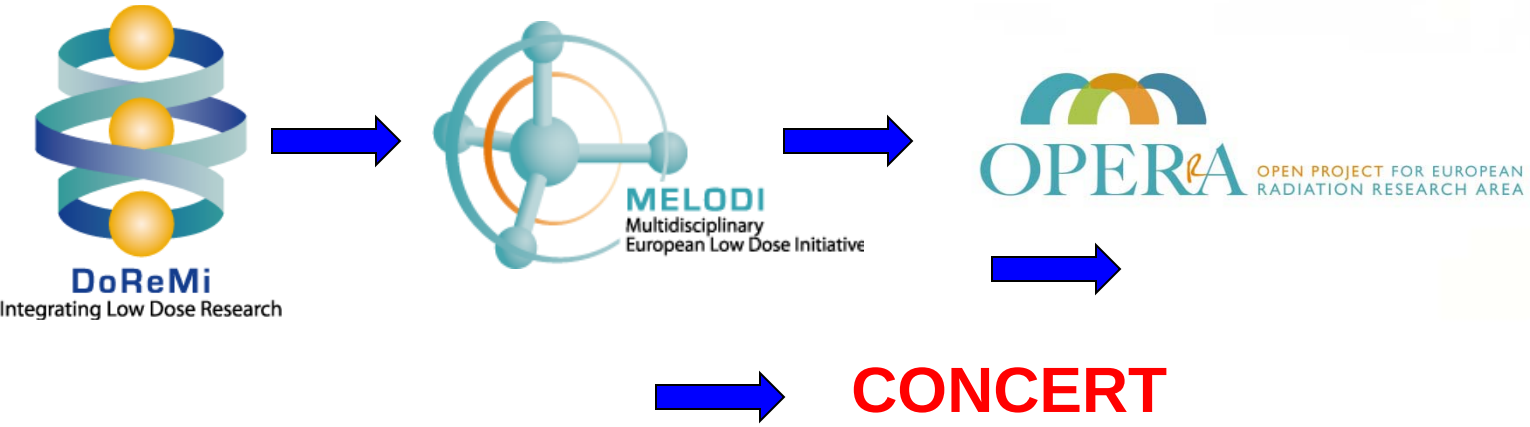
DoReMi TRA (2)

- The first DoReMi short term Transitional Research Agenda (TRA) has been worked out by DoReMi WP2 and the DoReMi consortium in accord with the MELODI association in 2010 (**www.doremi-noe.net)** .
- TRA 1st version was prepared at month 6 (June 2010) (see publishable version 20 September 2010), and a
- The second TRA version foreseen for months 36 (December 2012) came out as publishable version on 30 January 2013.
- Both were subsequently updated by **three short TRA statements** (22 Sept 2011, 6 March 2013, 23 Oct 2013). Now,
- a **final TRA** is foreseen at the end of the DoReMi project in December 2015.

DoReMi Integrating Low Dose Research

Overall aim of DoReMi and MELODI:

- **promoting and integrating research in Europe with focus on questions essential for assessment of low dose radiation health risks and radiation protection**

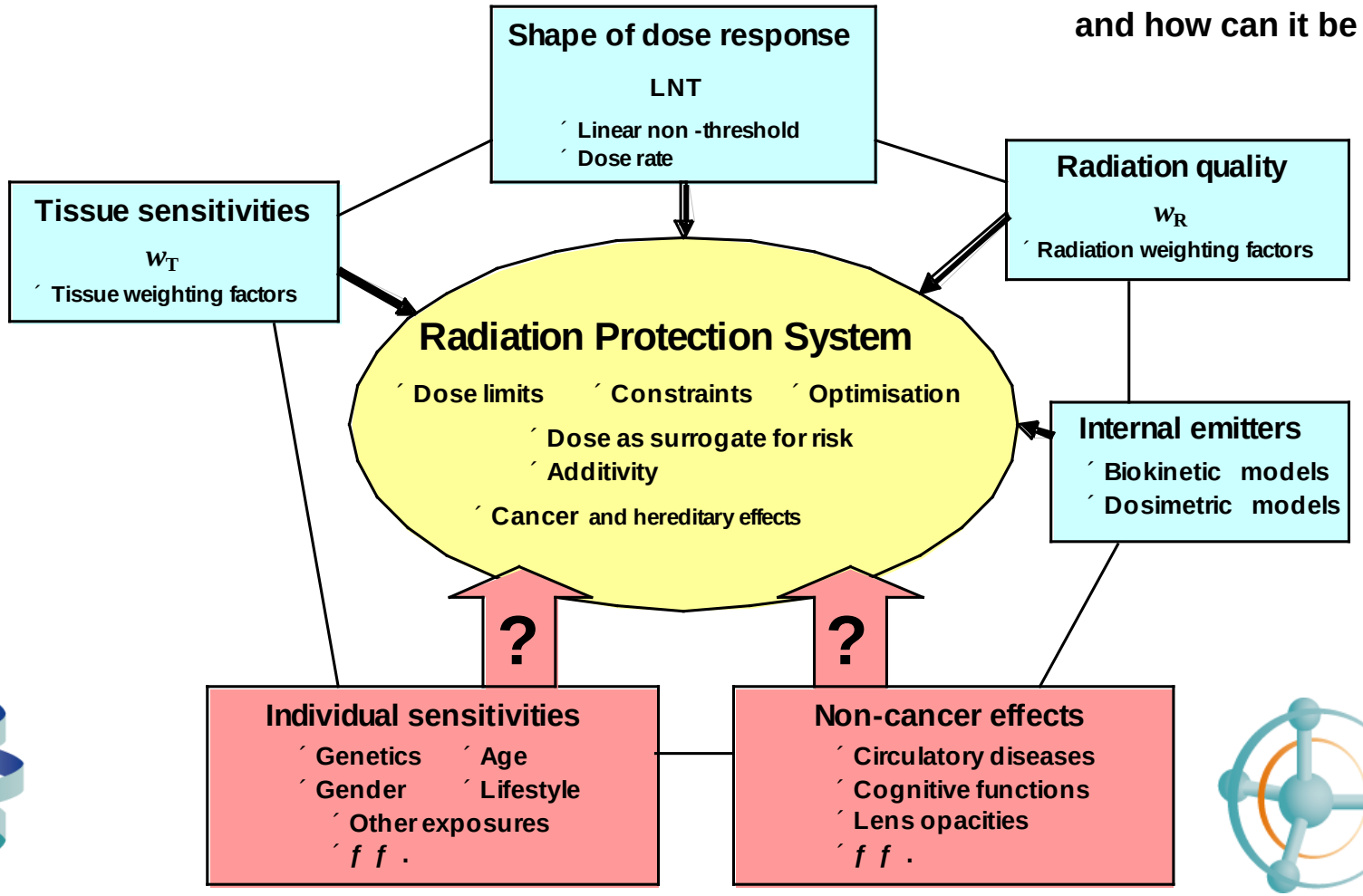


High Level Expert Group

The DoReMi TRA (and MELODI SRA) follow the HLEG concept

How robust is the system of radiation protection and risk assess ment?

and how can it be improved ?



DoReMi
Integrating Low Dose Research

MELODI
Multidisciplinary
European Low Dose Initiative

The specific challenge of low dose health risk research

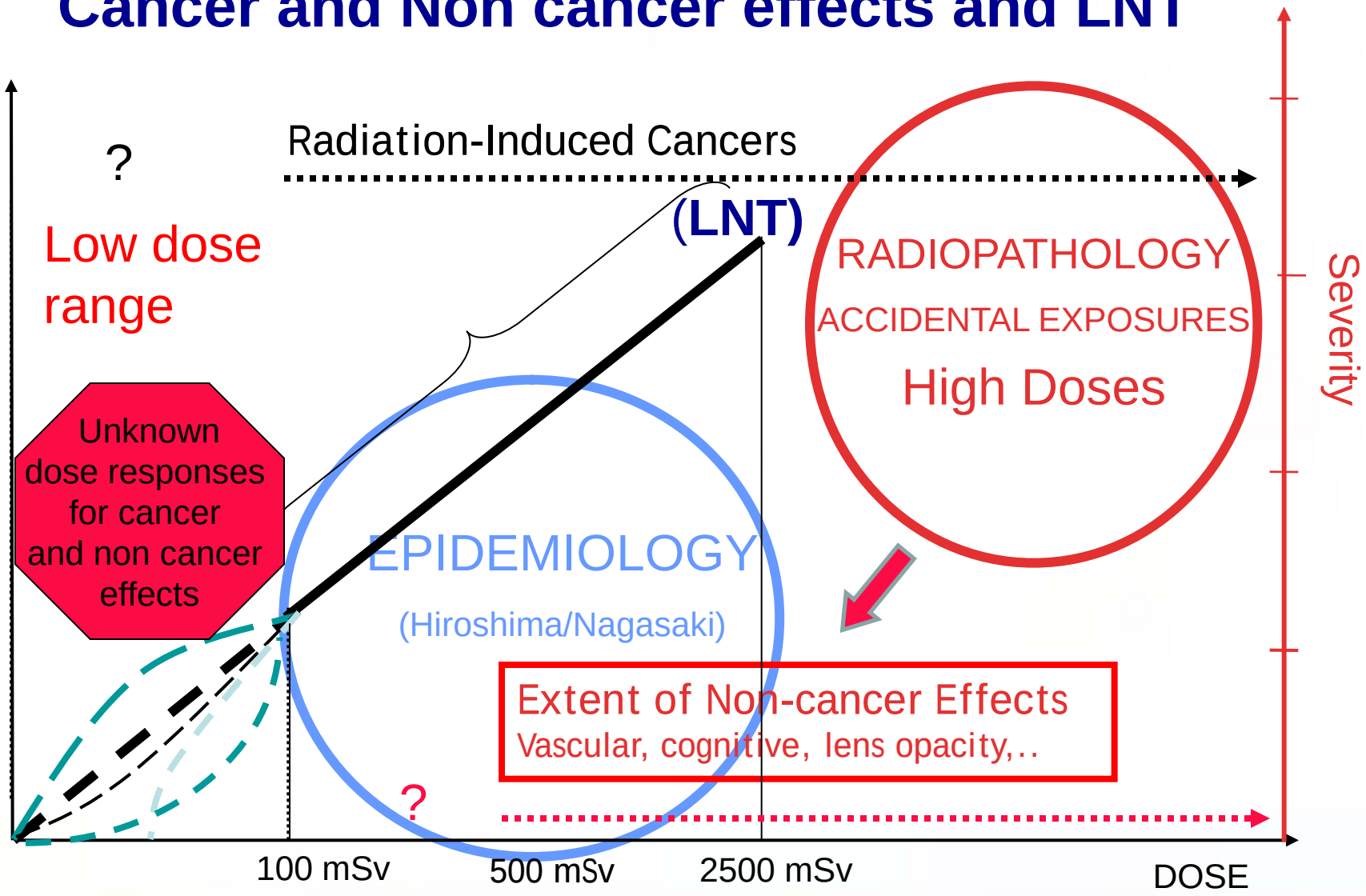
- **Radioprotection for high radiation doses** is well established, mostly on the basis of **epidemiological studies**. Assessments for low doses are mainly based on extrapolations following the LNT hypothesis.

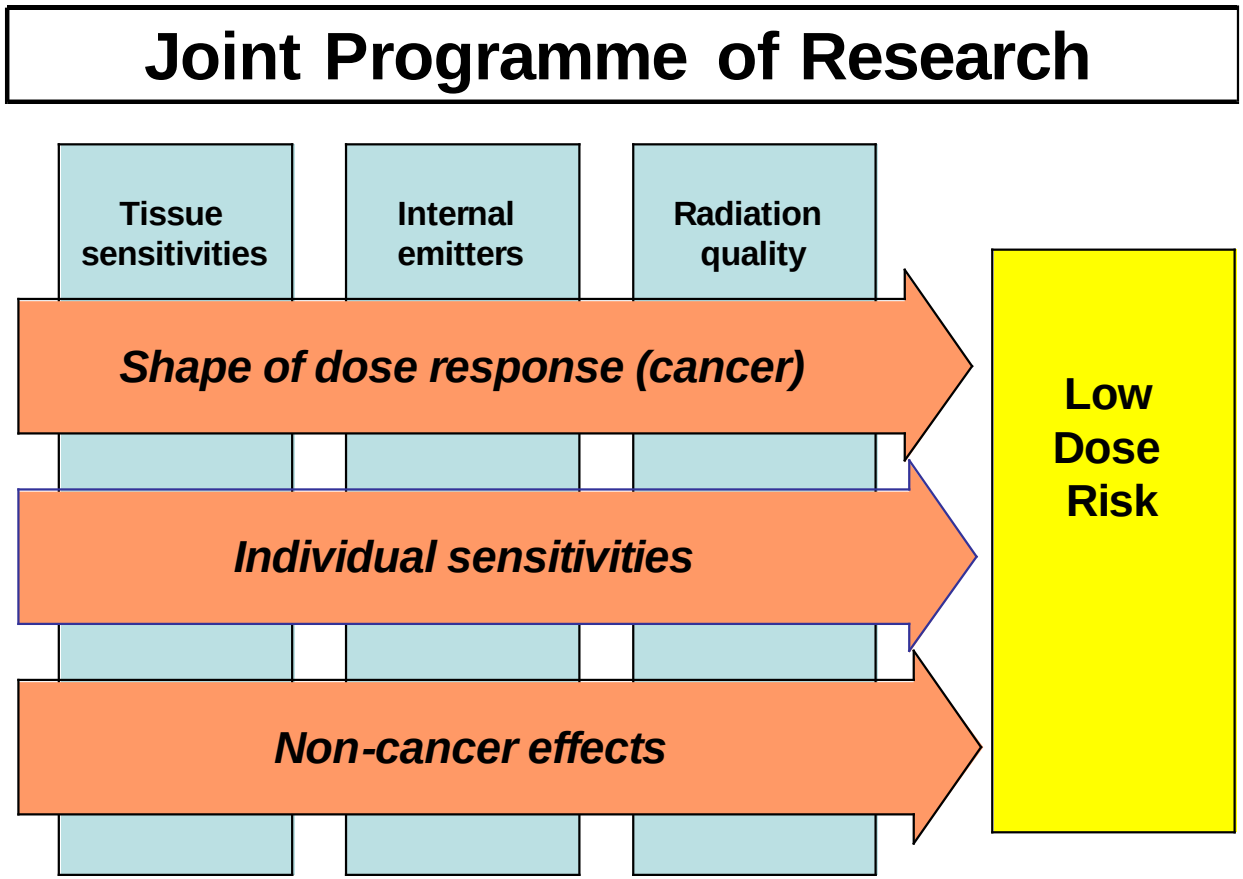
- However, at **low doses (<100 mGy) and dose rates (1 mGy/h) many uncertainties and open questions still exist that need to be backed up by mechanistic studies**

- *This constitutes a great scientific challenge because this needs development and use of new and extremely sensitive approaches Based on new experimental concepts and technologies.*

- *The DoReMi project was designed to take up these new challenges with well focused innovative feasibility and RTD studies.*

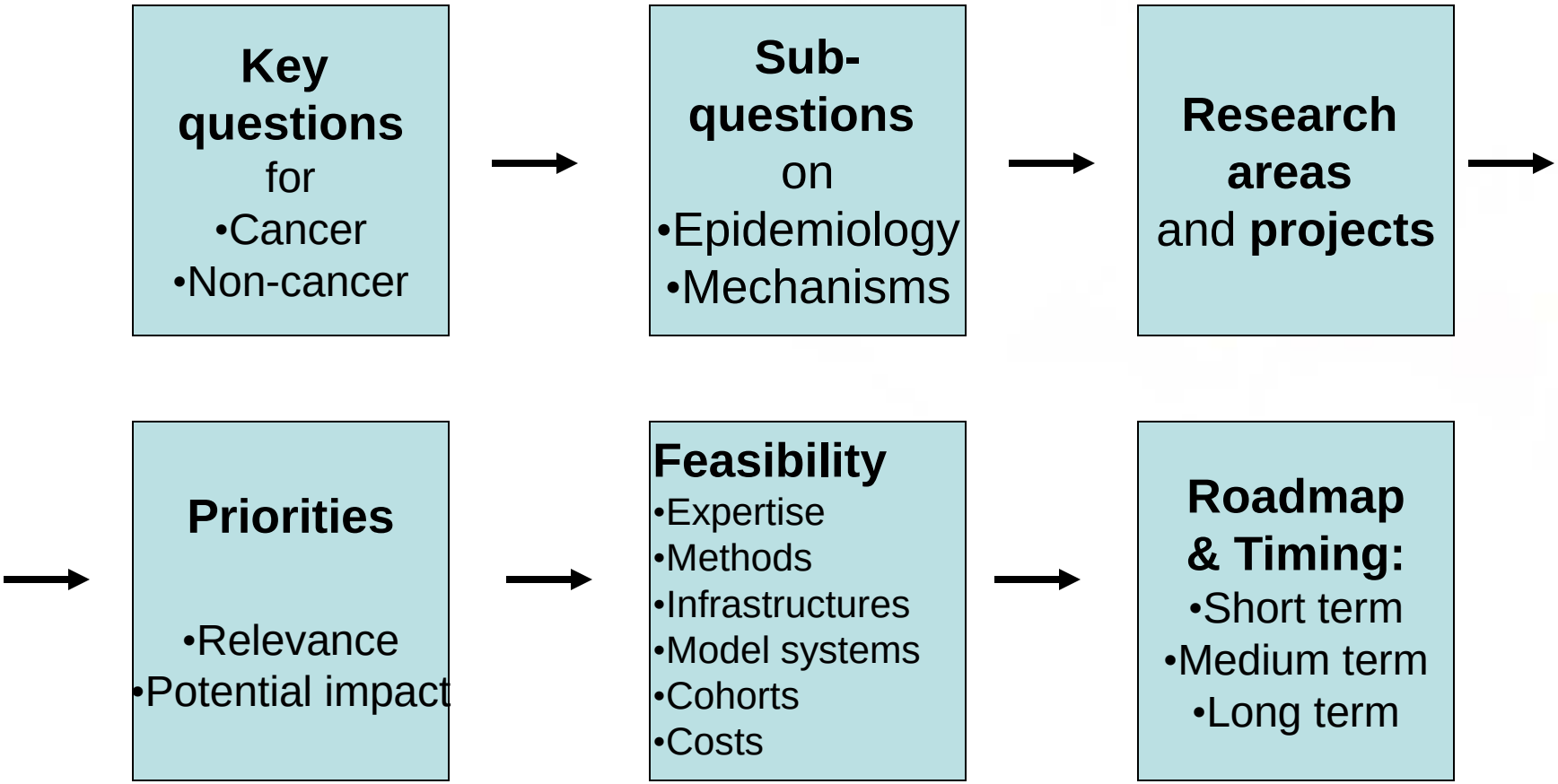
Cancer and Non cancer effects and LNT





This indicates the three main research questions addressed in RTD WPs 5, 6 and 7 . Each WP Includes cross-cutting issues (in blue): tissue sensitivities, internal exposures and radiation Quality . The interconnection between research themes is schematically illustrated (see Annex 1)

Stepwise development of the TRA



Identification of 9 key questions in DoReMi (from TRA 1st version 2010)

1. What is the dependence on energy deposition?
2. What is the dependence on dose rate?
3. What are the tissue sensitivities?
4. What is the modification of risk by genetic and epigenetic factors and gender?
5. What is the effect of age on risk?
6. What is the effect of lifestyle and/or other exposures on risk?
7. What is the effect of physiological state?
8. Is there a hereditary component in risk?
9. What is the role of non-targeted effects in health risk?

DoReMi Tasks with their Subquestions (1)

(derived from the 1st version of the TRA and the work plans, Annex 1)

WP5 cancer induction

Overriding questions:

- What is the role of radiation quality? (dose and dose-rate?)
- What is the role of DNA damage, intra-and intercellular signaling and repair?
- What is the involvement of genomic instability?
- What is the involvement of stem cells?
- What is the role of genetic predisposition?
- Can be more basic knowledge provided concerning the mechanisms driving radio-carcinogenesis and allowing low dose/low dose rate risk modeling?

DoReMi Tasks with their Subquestions (2)

(derived from the 1st version of the TRA and the work plans, Annex 1)

WP5 cancer induction

WP5.1 :

-Are the underlying processes contributing to radiation-induced carcinogenesis uniformly over the entire dose range

-Are there non-linear responses?

-Are the responses dependent on LET and radiation quality?

WP5.2:

-Are there non-targeted and systemic (inflammation, immune function) processes involved?

(see also WP7)

DoReMi Tasks with their Subquestions (3)

(derived from the 1st version of the TRA and the work plans, Annex 1)

WP5 cancer induction

WP5.3:

-What are the key events in neoplastic transformation (normal--→ tumor cells) and in mouse leukaemogenesis

-Are there suitable (molecular) biomarkers to indicate radiation induced tumorigenesis (see also WP6)

WP5.4:

-Can suitable models for carcinogenesis be developed that integrate mechanistic and epidemiological studies? (example: lung cancer?)

WP5.5:

-What is the health risk from internal emitters (contamination)?

-Can be a best suitable study design proposed?

DoReMi Tasks with their Subquestions (4)

(derived from the 1st version of the TRA and the work plans, Annex 1)

WP5 cancer induction

WP5.6:

- Can track structures, initial events and radiation quality dependency be modeled by an integrated approach?

WP5.7:

-Does chromothripsis play a role?

WP5.8:

-Can a Concerted action (biology-dosimetry-epidemiology) set up for Occupational Uranium Exposure (CURE)?

WP5.9:

-What is the mechanism of NTE in vivo?

WP5.10:

-Can one design a study on Gastrointestinal tumorigenesis (CLOGICAT)?

DoReMi Tasks with their Subquestions (5)

(derived from the 1st version of the TRA and the work plans, Annex 1)

WP5: Expected priority outcomes

- High standard dosimetry related data
- Validation of signatures and strengthening of attributability (radiation-induced cancers)
- Proper conservation of biosamples for further studies (WP3)
- New biomarkers from molecular and new generation sequencing data
- Understanding of stem cell involvement in the carcinogenic process
- Progress in *in vivo* follow up (genetic and epigenetic imprinting) and real time imaging of radiation carcinogenesis
- Integration of systems biology approaches in models on radiation-induced carcinogenesis and epidemiological studies to facilitate health risk assessments

DoReMi Tasks with their Subquestions (6)

(derived from the 1st version of the TRA and the work plans, Annex 1)

WP6 Individual radiation sensitivity

General questions

•Does individual variability significantly affect low dose radiation and radiation quality responses such as the induction of cancer and non-cancer diseases?
•Are there molecular approaches that can be validated by *in vivo* animal studies and epidemiological studies
•Is there a dependency of individual radiation sensitivity on dose and dose rate and radiation quality?
•What are the influences of gender, age, genetic and epigenetic factors, lifestyle (smoking, alcohol consumption..) and co-exposures and other confounders on individual sensitivity?
•Do also physiological parameters (hypertension, obesity…), reproductive (hormonal) factors (and immunological factors) play a role?
•Are there suitable biomarkers to determine different types of exposures (radiations, chemicals….?
•With the help of (genetic and epigenetic) biomarkers can one define radiation sensitive sub-populations?

DoReMi Tasks with their Subquestions (7)

(derived from the 1st version of the TRA and the work plans, Annex 1)

WP6 Individual radiation sensitivity

WP6.1:

-Are there suitable cohorts for supporting (joint with molecular studies) an epidemiological approach to individual radiation sensitivity? (mammography, children CT scans), uranium miners, Mayak workers, nuclear workers)

WP6.2:

-Is there a specific molecular signature for the sensitivity of children in the Chernobyl accident and for radiation-induced thyroid cancers?

- What is the contribution of individual genetic variability on cancer development (taking into account different cell types and tissues, age effects and radiation quality)?

WP6.3:

-Can specific modifier or susceptibility genes (and or variants) be identified that are associated with varying degrees of IR sensitivity and that can be validated in animal models?

DoReMi Tasks with their Subquestions (8)

(derived from the 1st version of the TRA and the work plans, Annex 1)

WP6 Individual radiation sensitivity

WP6.4:

-Are there specific modifier genes in humans that are relevant for susceptibility to radiation-induced osteosarkomagenesis, mammary tumors or medulloblastoma that can be validated in animal models using high or low dose rate exposure?

WP6.5

-Can epigenetic (chromatin related) factors be identified contributing to individual IR- induced cancer susceptibility?

WP6.6:

-Can a pilot study be performed to answer the question whether specific genetic factors influence individual susceptibility to low dose radiation-induced cancers?

-Does an individual susceptibility exist for IR induced non-cancer diseases (cataract, neurological and cardiovascular disorders) (in collaboration with WP7)?

-Can the familial predisposition (cancer among parents and siblings) be assessed?

WP6.7:

-Can the research portefolio on individual radiation sensitivity further expanded?

DoReMi Tasks with their Subquestions (9)

(derived from the 1st version of the TRA and the work plans, Annex 1)

WP6 Individual radiation sensitivity

WP6.8:

-Can individual radiation sensitivity be predicted by Raman spectroscopy?

WP6.9

-Can a molecular epidemiological study be performed on post-Chernobyl thyroid cancers in Belarus?

WP6.10:

-Can DNA lesions be characterized in the nuclear ultrastructure of differentiated and tissue-specific stem cells after protracted low dose radiation?

WP6.11:

-What is the mechanism of low dose radiation responses and its significance for radiation protection?

DoReMi Tasks with their Subquestions (10)

(derived from the 1st version of the TRA and the work plans, Annex 1)

WP7 Non-cancer effects
General questions

•What is the biological impact of different radiation qualities and radiation dose levels in terms of perturbing homeostasis and induction of pathological non-cancer effects (cardio- and cerebro-vascular diseases, neurological and cognitive effects, lens opacities)?

•What is the importance of acute versus chronic r fractionated radiation exposures for non-cancer effects?

•What is the molecular basis to expect that low dose radiation can cause or modulate pathological non-cancer effects?

•Can molecular alterations of cellular homeostasis, redox potential and energy metabolism induced by low dose radiation induce or promote non-cancerous diseases?

DoReMi Tasks with their Subquestions (11)

(derived from the 1st version of the TRA and the work plans, Annex 1)

WP7 Non-cancer effects

Additional overriding questions:

- What do we know about the radiation sensitivity of disease relevant cell types (epithelial cells, cells of central nervous system, stem cells..)?
- To what extent oxidative and genetic damage contributes to non-cancer effects?
- Can relevant biomarkers be developed from transcriptomic, proteomic and metabolic analyses and physiological markers?
- Can relevant biomarkers be identified (from proteomics and gene expression data) that may be useful for molecular epidemiological studies?
- Can a systems biology approach be used to explain specific non-cancer responses?
- Are low dose exposures relevant for the induction of non-cancer effects (diseases)?
- Can the dose-responses be modeled?
- Play genetic variations, effects of age and radiation quality (dose and dose rate, mixed fields) a role in individual radiation sensitivity in terms of the induction of non-cancer effects? Do heavy ions induce or promote non-cancerous diseases?

DoReMi Tasks with their Subquestions (12)

(derived from the 1st version of the TRA and the work plans, Annex 1)

WP7 Non-cancer effects

WP7.1

•Can priorities be set for exploring IR-induced vascular effects, cognitive effects and lens capacities?

WP7.2

•Can a molecular epidemiological study be conducted on low dose IR induced vascular damages (circulatory diseases)?

WP7.3 (cardiovascular)

•Is there a threshold for induction?

•What is the contribution of radiation dose, inflammatory (immunological) effects, cellular signaling, cellular senescence?

•What is the role of endothelial, smooth muscle cells, bon marrow progenitor and stem cells?

•Are vascular effects induced that can be revealed by epidemiological children CT studies?

•Can high throughput technology (proteomics) be used to get mechanistic insights into the radiation response of the endothelium after acute and chronic exposure including internal contamination with radio-nuclides ?

DoReMi Tasks with their Subquestions (13)

(derived from the 1st version of the TRA and the work plans, Annex 1)

WP7 Non-cancer effects

WP7.4 (lens opacities)

-Can a threshold dose for the induction of lens opacities (posterior sub capsular) be determined?
-Can one define the risk of cataract induction by IR?
-Can lens opacities can be detected in a cohort of interventional cardiologists chronically exposed to IR <150 mSv?
-What is the involvement of DNA damage, protein cross-linking, disruption of membrane channels and ion pumps as well as genetic factors such as Rad9 and ATM in IR-induced cataractogenesis?
-Can more accurate methodology implemented (ELDO)

WP7.5 (cognitive and neurological effects)

•Can we increase our knowledge on the molecular mechanisms of cognitive effects induced by acute and chronic radiation exposures?
•What are the effects of internal contamination?
•What is the contribution of oxidative stress to changes induced in neurotransmission and neuromodulation?

DoReMi Tasks with their Subquestions (14)

(derived from the 1st version of the TRA and the work plans, Annex 1)

WP7 Non-cancer effects

WP7.6

-Are there anti-inflammatory effects of low dose IR?

WP7.7

-Is there a gene expression signature for IR-induced cardiovascular disease?

WP7.8

-Is low dose IR contributing to catarctogenesis and influencing genetic and cell communication factors?

- WP7.9

- Are there epigenetic and functional changes in brain microvascular pericytes after low dose IR?

WP7.10

-Do low dose and low dose rates modulate the development of parkinson disease in predisposed mice?

-WP7.11

- Can an Epi-pilot study be performed on cataracts in interventional cardiologists?

-WP7.12

-What is the effet of low dose IR on impaired vascular endothelium?

-WP7.13

-- What is the mechanism of low dose cataract induction in mice?

Steps in DoReMi TRA development (1)

- **Key Questions**
- **Subquestions**
- **Definition of Research areas: cancer and non cancers (epidemiology and mechanisms) and related main issues and projects**
- **Definition of Scientific (RTD) WPs 5-7:** Cancer induction, Individual sensitivity, Non cancer effects and **operational WPs**. WP 3 : Education & training, and WP4: Infrastructures

- Definition of Research needs and Priorities
- Feasibility check
- Roadmap and timing

DoReMi TRA for operational WPs

Work packages for implementation of research and operational aspects: Operational WPs (WP3 and WP4), respectively:

•**Infrastructures** (radiation facilities, bio-and data banking, cohorts, analysis) (facilitating research) and

•**Education and Training** (ensuring the necessary human resources)

•Through TRA statements in collaboration with MELODI and the MELODI SRA and MELODI statement settings (promoted by WP2) internal and external competitive calls were proposed and successfully launched after EU- processing .

•This led to a substantial increase in DoReMi tasks (completing the original DoReMi Joint research plan of integration and defining urgent needs of research, infrastructures, education & training).

DoReMi Tasks with their Subquestions

Questions derived from TRA versions 1 and 2:

WP3 (Education & Training)

WP3.1:

-Can a sustainable Integrated Training and Education Network (ITN) be developed?

WP3.2:

-Can a specific low dose risk ITEN be set up promoting (MSc or PhD level) University courses and radiation protection related training events (Bologna-accredited) as well as in particular topics (ad-hoc workshops and one-off specialist courses)?

WP3.3:

-Can sustainable funding for such courses be developed (in collaboration with WP2)?

WP3.4:

-Can a special FORUM be organized for E&T coordination and integration in collaboration with MELODI?

WP3.5:

-Can new funding of training activities in ITEN developed in collaboration with MELODI and in the framework of the EC-funded project OPERRA?

DoReMi Tasks with their Subquestions

Questions derived from TRA versions 1 and 2:

WP4 Infrastructures

Overriding questions

- Can external (low dose, low dose rate, neutron charged particle beams, microbeams) and internal radiation facilities assessed and their access and use promoted?
- Can suitable data and biobanks be assessed, made accessible and promoted for optimized radiation research?
- Can suitable cohorts be identified and/or set up for well-defined epidemiological (classic and molecular) studies?
- Can suitable platforms for high throughput analysis be assessed and their access and use promoted?

DoReMi Tasks with their Subquestions

Questions derived from TRA versions 1 and 2:

WP4 Infrastructures

WP4.1: can a survey on existing facilities for low dose risk research be made?
WP4.2: can infrastructure needs be defined?
WP4.3: can DoReMi support activities for shared infrastructures be implemented?
WP4.4: can infrastructure development and access be implemented?
WP4.5: can open access to the UMB low dose IR facility (FIGARO) provided?
WP4.6: can dose/dose-rate effects be assessed for Brain Cancer risk?
WP4.7: can a IR low dose/dose-rate facility be developed for in vitro biological research (LIBIS)?
WP4.8: can STORE be integrated into DoReMi and sustainability assured?
WP4.9: can the ion microbeam IR facility SNAKE be provisioned?
WP4.10: can the Laboratory infrastructure for radon and throron dosimetry be used?

Table of DoReMi key and subquestions according to task publications: What every DoReMi task is up to?

	Cancer (1)		Non-cancer (2)	
Key question	**Subquestions** *DoReMi Task number*		**Subquestions** *DoReMi Task number*	
	Epidemiology	Mechanisms	Epidemiology	Mechanisms
1. What is the dependence on energy deposition?	*5.1, 5.4, 5.5, 5,8*	*5.1, 5.1.1,5.2, 5.2.1, 5.3, 5.6, 5.7, 6.2, 6.8, 4.6*	*7.9*	*7.3*
2. What is the dependence on dose rate?	*4.8, 5.8, 6.4*	*4.5, 4.6, 4.7, 4.8, 5.1, 5.10, 6.10*	*4.8*	*4.5, 4.7, 4.8, 7.3, 7.10*
3. What are the tissue sensitivities?	*5.4, 5.5, 5.5.1, 5.5.2, 5.8, 6.2, 6.3, 6.9*	*5.3, 5.8, 6.21,6.1, 6.9, 4.6, 4.9*	*7.4, 7.4.1*	*7.3, 7.5, 7.8*
4. What is the modification of risk by genetic and epigenetic factors and gender?	*6.1, 6.5, 6.6, 6.9*	*5.5.1, 5.2, 5.3, 6.1, 6.2, 6.3, 6.4, 6.5, 6.9, 6.11*	*6.1*	*7.3, 7.7, 7.8, 7.9*

Table of DoReMi key and subquestions according to tasks: What every DoReMi task has been up to? (2)

5. What is the effect of age on risk?	*5.4*	*6.4*		*7.10*
6. What is the effect of lifestyle and/or other exposures on risk?				
7. What is the effect of physiological state?		*5.2.1, 6.8*		*7.3, 7.6*
8. Is there a hereditary component in risk?				
9. What is the role of non-targeted effects in health risk?		*4.9, 5.2, 5.2.1, 5.3, 5.7, 5.9*		*4.9, 7.6*

Background of TRA methodology

(see S. Salomaa 170113):

- Follow-up of on-going research
- Exploratory DoReMi workshops for brainstorming
- Definition of emerging topics and multidisciplinary consortia
- Surveys among scientists (not too effective, since few responders)
- Definition of key questions and research areas/projects
- Systematic Identification of topics for internal and competitive calls (however, there are too many sub-questions and potential projects that could be initiated).
- Initiation of feasibility studies
- Assessment of feasibility studies (Go/No-Go steps) by individual working groups groups and WP leaders to launch TRA updating process
- Designing a **ROADMAP** giving the time schedule of foreseen research activities.

Background of TRA methodology

(see S. Salomaa 170113):

- Updating of DoReMi TRA (months 36 and 72).
- Participation in MELODI workshops (link to broader scientific and radiation protection communities with important feedback on research priorities in terms of relevance and potential impact)
- Consulting of MELODI consortium (particularly fruitful for integration aspects and joint programming in Europe).
- Consulting of EAB (crucial for evaluation of scientific and technological quality and feasibility, evaluation of calls for proposals).
- Consulting other relevant EURATOM projects and the general scientific community (essential for scientific opening, finding synergies, avoiding duplication).

The DoReMi TRA methodology may well be helpful for identifying best practices for MELODI, OPERRA and joint programming of CONCERT during Horizon 2020.

Main TRA work focus

•Definition of questions and corresponding research needs

•**Priority setting** following(as much as possible) **defined criteria**:

-Relevance:

- -Is the project in line with HLEG strategy and DoReMi TRA?
- -Relevance of the topic for radiation protection
- -Repeating old or creating new?
- -Multi-disciplinarity of approach

-Potential impact:

- -Prospects for improved protection of citizens, workers or patients
- -Addressing needs of stakeholders
- -Applicability of the knowledge to RP
- -Change in paradigm?
- -May change RP system?
- -May change RP procedures?

•**Definition of the Roadmap (timing of research activities)**

Proposed Structure of DoReMi Final TRA (1)

-Purpose of TRA
-Questions to be answered
-Uncertainties in RP to be considered:
Radiation quality factors (WR), DDREF (ICRP proposal= 1.5-2), Tissue sensitivity weighing factors (WT), Influences of genetic and epigenetic control, Individual sensitivity responses, effects of sex, age and lifestyle, metabolic status, chronic internal and mixed exposure, transgenerational effects, non targeted effects (immunological effects)
-Update of TRA methodology
-Priority setting and evaluation criteria
-Experiences in TRA Updating
-Research issues addressed by DoReMi WPs , 6 and 7
-Operational issues addressed by DoReMi WPs 3 and 4

Proposed Structure of DoReMi Final TRA (2)

-Highlighting results obtained (**list of DoReMi publications**) for the different research issues (WPs)

Scientific results achieved:

•Some **answers to key questions** concerning dose rate dependence, tissue sensitivities and modification of risk by genetic and epigenetic factors.

•Evolution of level of analysis:

-from detailed cell, tissue and organ specific effects towards integrated responses on the cellular, tissue and organ and whole body level.

-from single pathway analysis towards integrated pathway network analysis and systems biology, omics- proteomics-metabolomics

-from whole body analysis towards single cell analysis-

-from genetic control analysis towards analysis of epigenetic control

- Towards mechanisms of specific radiation-induced cancers

- Towards evidence for non cancer effects at relatively lower doses < 1 Gy

- From bystander effects at the cellular level -→non targeted effect-→ effects of the microenvironment and cell-cell interaction-→ immunological and systemic effects (ascopal effects)

Proposed Structure of DoReMi Final TRA (3)

-Results obtained in WPs 3 and 4: Education & Training and Infrastructures

List of unanswered questions and missing items:

Quasi-total absence of work on the 3 key questions:
-what is the effect of age on risk, -what is the effect of lifestyle and/or other exposures to risk and - is there a hereditary component in risk (radiation quality effects?

Proposed research lines for follow-up and reinforcement of low dose radiation protection and anticipated additions:

- medical diagnostic and therapeutic issues?
- ethical issues?
- societal issues?
- environmental issues?
- urgency management?
- Relationship to MELODI SRA and other SRAs
- Design of Future Roadmap

Where are we with the scientific progress made?

Scientific discoveries paving the way to a better understanding of low dose radiation effects - and vice versa

	Past	Recent and present	Future
Scientific discoveries and key disciplines	X-rays, radioactive decay Physics and biophysics DNA helix DNA repair Molecular biology Oncogenes and tumour suppressor genes	Sequencing human genome, less genes than proteins Non-targeted effects Intra-and intercellular signalling Tissue responses Single nucleotide polymorphisms Epigenetics Integration of radiobiology and epidemiology	Molecular epidemiology Systems biology Stem cells: cell reprogramming Synthetic biology Integration of systems biology and molecular epidemiology

New tendencies in Future TRA

- From low dose IR (<100 mGy) to medium and high dose IR including environmental and medical options.

- From DNA oriented work towards RNA, stem cell, immunological and multi-exposure oriented work?

- From understanding of most relevant metabolic pathways in the induction of cancers and non cancer effects towards Systems biology and modeling of IR health risks

- From classical epidemiological work towards **molecular Epidemiology, integrated and individual health risk assessment**

Lessons learned from DoReMi

- Clear scientific questions are stimulating research in health risk assessment and radiation protection
- Scientific experiments and biological samples (from animals, humans) should be explored as much as possible with different techniques and as wide ranging as possible.
- Access to suitable infrastructures (irradiation facilities,cohorts, data-and biobanking, analysis and imaging platforms) is essential.
- All scientific disciplines should be consulted and included.
- The best is collaborative and multi- and interdisciplinary work.
- Well-defined EU calls (fundings) are essential in stimulating new approaches and research activities.
- The young scientific community should be stirred up by inter-institutional and international training and education and exchange programs.

Thank you for your attention!