



**Proceedings of the
First International MELODI Workshop
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1. Background

The Bundesamt für Strahlenschutz (BfS), on behalf of the MELODI signatories, organized the First MELODI Open Workshop in Stuttgart on September 28th and 29th 2009. 156 scientists, representatives of the regulatory community and interested stakeholders from 23 European states, the USA and Japan took an active part in the workshop and discussed the future development of low dose radiation research in Europe. Prior to the workshop start, each workshop participant received a folder with the following papers: the workshop programme; a flyer with a short version of the programme as a help for orientation; a general questionnaire to guide the discussion during the parallel sessions; a brochure about the High Level Expert Group (HLEG); draft MELODI document no 1 (September 2009): "Low Dose Risk Research: The MELODI European Platform Project"; draft MELODI document no 2 (September 2009): "Relationship between MELODI and DoReMi".

The workshop's objectives were to present the multidisciplinary approach proposed by HLEG to the broad scientific community and to advise of the instruments to implement these recommendations on the EU level, namely MELODI and the DoReMi network. This approach includes the process of open participation of all interested parties in the platform as well as in the future research programme calls. Furthermore, the state of knowledge on low dose radiation effects at the international level with a focus on identifying open questions and uncertainties relevant to radiation protection should be reviewed during the workshop.

All presentations given in the course of the workshop are posted on the internet (www.hleg.de/melodi.html).

The results of the Stuttgart workshop will provide a good basis for the development of an SRA for low dose research in Europe as well as a road map to implement the SRA. In the medium term MELODI plans to prepare a MELODI document describing more precisely the process for establishing and maintaining SRA + Roadmap and for implementing priority projects. These activities should be based on a feasibility study (organized and funded by MELODI). Additional actions will be the identification of specific thematic topics which require further in-depth discussion before they can be discussed during the 2nd MELODI Workshop in October 2010.

2. Introduction

The workshop participants were informed about the recent initiatives launched to organise the low dose risk research in Europe by introductory talks given by representatives from the European Commission (Simon Webster), the WHO (Maria del Rosario Perez) and HLEG (Wolfgang Weiss). An introduction to MELODI and to the planned working group sessions was given by Jacques Repussard.

Following these, the workshop participants split up into three working groups (WG 1-3), each focussing on one of the scientific key themes "shape of dose-response curve for cancer", "individual radiation sensitivity for cancer" and "non-cancer effects". To allow for a vivid and theme-oriented discussion, each working group was further split into subgroups of 16 to 24 participants, related to the cross-cutting themes "radiation quality", "tissue sensitivity" and "internal/external exposure". A total of 8 parallel sessions were held, 3 on the focus theme "shape of dose-response curve for cancer" and "non-cancer effects", 2 on "individual radiation sensitivity for cancer". A questionnaire with standardised questions formed the basis for structured discussions in the parallel meetings and helped to ease the

chairpersons' and rapporteurs' duty to sum up the results of each session and working group.

During the second day open parallel sessions on “infrastructure” and “education and training” were held. Parallel to these sessions, the outcome of the 3 workshops of day 1 was summarized by the chairs together with the rapporteurs. The results were presented in plenary to the workshop attendants for further discussion.

A panel discussion with Jacques Repussard and Simon Webster (EC) was held to provide further information on the role and the working arrangements of MELODI and to clarify the relation between MELODI and DoReMi NoE. During a second panel discussion, experiences in the field of low dose risk research in USA and Japan were discussed.

The presentations and the outcome of the open working group sessions, summarized as reports of the chairs will build the basis for a SRA for low dose research in Europe and a roadmap with prioritized topics of immediate and medium term action in each of the key research fields. The results of the discussions in the working groups as well as in plenary are summarized in chapters 3 to 5. This summary is based on reports received from the chairs and rapporteurs of the 5 working groups and from Dudley Goodhead who was invited to the workshop as an independent observer. No attempt was made to harmonize the style and structure of the individual reports received.

3. Results of the Working Groups

In the following the results of the parallel sessions are described for WG 1 to WG 5. The summaries were compiled by the chairs and rapporteurs of the working Groups; they include the key issues discussed in the Working groups and in the plenary sessions on Tuesday.

3.1 WG1 “Shape of Dose-Response Curve for Cancer”

3.1.1 Where are the greatest uncertainties on the shape of the cancer dose-response?

- In the low dose region (generally below 100 mGy low LET).
- For low dose-rates.
- For high LET radiations.
- Dosimetric uncertainties in studies of cancer dose-response.
- Generalising to a single dose response relationship for all radiation-induced cancers is a major simplification. Cancer is not a single condition, dose-responses for each cancer type are likely to differ. Indeed epidemiological and experimental data back this up. It has to be recognised that cancer aetiology is complex and there are modifying factors such as age, gender and exposures to other agents. The need for simple ‘all solid cancer’ risk estimates will nonetheless remain for radiation protection purposes.

3.1.2 Which types of investigation are needed to reduce the uncertainty on the cancer dose-responses?

- The key point made was for interdisciplinary investigations which are planned and carried out in an integrated fashion from the start. The key individual disciplines are given below.

- Epidemiological investigations - particularly where it is possible to analyse by individual cancer site/type will continue to produce risk information. Future studies will require long term follow up, good dosimetry and individual data.
- Molecular/biomarker epidemiological studies - these were seen to be potentially very useful but work is needed to identify suitable biomarkers of radiation-induced disease. Nonetheless consideration of study design and cohort recruitment can go ahead in the absence of defined validated biomarkers.
- Experimental work at many organisational levels - there are likely to be infrastructure access requirements, e.g. to low dose rate exposure facilities associated with this.
- Dosimetric investigations - to ensure robust and reliable dose information in all studies, particularly for internal contamination. MELODI workshops to define minimal acceptable dosimetric criteria could be useful in this respect.
- Mathematical modelling - including biophysical modelling and mechanistic modelling of the cancer process.

3.1.3 *Which populations/exposures are most likely to provide useful information?*

- It was noted that experimental and epidemiological studies have limits to their ability to detect risks of low level radiation exposures – about a 1% increase in risk may be detected reliably.
- Nested designs can provide information for several areas (e.g. cancer, non-cancer disease etc) and are more suited to molecular epidemiology
- Minimal criteria for good study design are needed, again MELODI may help facilitate such discussions. Basically all studies require good dosimetry, long follow-up and good data quality including personal history, other exposures, smoking etc.
- It was pointed out that some specific populations/situations perhaps do not receive sufficient attention, e.g. *in utero* exposures.
- A view was expressed that sufficient information is available for radon epidemiology and the gain through further studies will be small. Not all agreed, especially regarding non-lung cancer risk or microdosimetric aspects.
- A view was expressed that second cancer studies in irradiated populations could be useful, especially in far-out of field sites, where low doses are delivered. This was not agreed by all.
- Some championed non-human, ecological epidemiological studies, for example of animals living in contaminated areas.

3.1.4 *What are the prospects for molecular epidemiology?*

- This will be a long term endeavour.
- Populations need to be identified – ideally with several exposure conditions and backed up by experimental cancer models.
- A two level approach was suggested, starting with large prospective cohorts followed by nested studies providing detailed health data and biological samples.
- A common EU understanding on the ethical approval required for tissue sampling and banking is needed. A MELODI action on this could be beneficial.

- Tumour causality will be an issue in such studies. Robust radiation cancer signatures are required. There was considerable optimism expressed that such signatures will become available.
- Any study will require reliable biomarkers of radiation-induced disease to be identified. This will require experimental work.
- It was suggested that MELODI may be able to help access existing biobanks or facilitate the establishment of biobanks.

3.1.5 *In which areas will experimental work provide useful information for risk assessment?*

- The cancer process. Very little is known of the steps between initial radiation exposure and disease presentation, which can span a significant proportion of an organisms lifespan. Good animal models with low spontaneous cancer incidence will be required. A good model of radiation-induced acute myeloid leukaemia is available and yielding useful data. Models for other cancer sites are needed. These studies must take note of advances in the wider area of cancer research.
- Clarification of the role of non-targeted effects. There are several phenomena described under this umbrella. It is critical to determine if these processes operate *in vivo*, particularly following internal contamination or inhomogeneous irradiation studies. Also whether the effects are cancer risk enhancing or decreasing and the nature of interactions between phenomena are important issues.
- Information on dose-response relationships for *cancer relevant endpoints*. While some relevant endpoints are known, e.g. DNA damage, chromosomal damage etc, we do not yet have a full inventory. Many additional candidates are available including cellular senescence, stress response, apoptosis, among many others. If high and low doses provoke different responses, this may be important in determining the proportionality of dose and risk. Studies at both high (>100mSv) and low doses (<= 100mGy) are needed to establish the correct basis for extrapolation.
- Clarification of the role of systemic responses to radiation such as inflammation and immune modulation. Such systemic factors may affect the growth of pre-existing pre-cancerous lesions or the growth and development of radiation-induced cancer.

3.1.6 *Which experimental systems will be most useful?*

- The main issue here is the need for consideration of all organisational levels and an integrated approach. Ultimately however the process of cancer has to be followed *in vivo* in animals or humans.
- New information on the radiation physics and chemistry of interaction with biological materials continues to emerge. This highlights the need to keep research on this level of interaction.
- Human stem cell models were viewed as having good benefits as cancer is seen as a disease of stem cells. Limitations are imposed by the lack of a full understanding of stem cell biology (MELODI may help forge links) and by a non-uniform ethical framework for stem cell studies across Europe (MELODI pressure in this area may be beneficial).
- Good tissue models are available for only certain tissues, notably skin. Other systems will require careful characterisation, mixed culture systems were viewed as being useful for some non-targeted effect studies.

- Animal model systems are the only systems in which the cancer development process can be followed in its entirety, therefore these are of particular importance. Access to large facilities capable of delivering chronic exposures over long periods to large numbers of animals is required. Improved models are required as noted above. Animal maintenance facilities and irradiation facilities are on the decline, at least in radiobiology labs. A MELODI action on this could be beneficial.
- Systems approaches are being championed in most if not all areas of biology. These are highly costly and if embarked upon will need a large budget, in the several tens of millions of Euros. Significant computing power would also be needed.
- It was considered that non-human cell studies are now of limited value, particularly where there is no clear relationship to human cancer. It should nonetheless be remembered that much of our current knowledge of DNA double strand break repair, for example, has its foundation in somatic cell genetic studies in Chinese hamster cells.

3.1.7 Are there specific issues in respect of internal emitters?

- It was noted that exposure through inhalation and ingestion are very important in radiation protection.
- Improved dosimetry and biokinetic information is needed, the chemical form and toxicity have also to be taken into account.
- Each radionuclide is different and extrapolation across radionuclides is not possible. Therefore there is a need for a discussion to identify a limited number of radionuclides in which to focus research efforts. Such discussions have many facets. MELODI could help facilitate these discussions and the DoReMi proposal includes a task on scoping internal emitter studies.
- It was noted that a well planned series of linked epidemiological, experimental and mechanistic modelling investigations on a particular radionuclide could potentially yield results from an integrated approach in the relatively short term. Such a study would also help facilitate dialogue and therefore promote good working relationships across the disciplines.
- The difficulty and cost of disposal of contaminated waste was noted and MELODI might help in dealing with waste from experiments.

3.1.8 Are there specific issues regarding tissue sensitivities?

- It was noted that tissue weighting factors have a poor scientific basis. Analyses of epidemiological data by cancer site could improve on this situation.
- It is particularly the case that there is uncertainty on tissue weightings for high LET radiations.
- Concern was expressed that radiation weighting/RBE might vary in different tissues. Thus site/tissue specific studies using a range of radiation qualities continue to be needed.

3.2 WG2 “Individual Radiation Sensitivity for Cancer”

The key research questions and tasks defined by WG2 agreed broadly with the aims and key questions previously identified by HLEG. Participants decided that the need to identify

the pathways and molecular mechanisms involved in making individuals at increased risk is the overriding priority for the research area. Slightly lesser importance was given to the cross-cutting issues of radiation quality and tissue sensitivity, as these were seen to first require progress in the mechanistic and candidate side before becoming relevant.

The consensus view was that a combined approach, linking molecular epidemiological and laboratory experimental studies, is essential to address the issue of individual sensitivity. A focus on genetic and epigenetic factors and their role in modifying susceptibility was seen as the biggest priority. Other factors such as age and gender were discussed. Caveats describing the application of molecular epidemiological cohort studies were recognised. A multilevel approach for studies using experimental systems (cell culture, tissue culture, as well as non-mammalian and mammalian models) was recommended. These were seen to be essential to validate epidemiological results, as well as for the provision of new biomarkers for epidemiological analysis.

The relevance of modelling activities for the long-term goals of the programme was only recognised after suggestions from the chairman. No clear support for immediate studies on modelling was given. The lack of suitable quantitative data for modelling activity was seen as a roadblock. Classical epidemiology was only tangentially discussed and support for continuing these studies was present, although not strong.

Areas for initiating new research programmes were identified. A consensus for adopting stem cell studies and modelling/systems biology approaches in radiobiology was agreed upon, although again here the general view was that there was first a need for considerable preparatory work. More controversial was the discussion on the appropriate use of non-mammalian models for susceptibility studies. Caution was urged in the use of these systems for identifying new candidate markers of cancer risk, unless clearly relevant end points for validation were demonstrated. Both mammalian and non-mammalian *in vivo* systems were seen to be suitable for validation studies of candidate biomarkers derived from epidemiology.

On the specific issue of tissue sensitivity a majority opinion saw value in animal studies following different tissue responses. An alternative approach, using organotypic or mixed tissue cultures was seen as a valuable supporting strategy. The value of studies on stem cell/progenitor cell biology in answering this question was recognised by a number of participants. Whilst epidemiological approaches for identifying modifier action in determining differences in tissue susceptibility may be suitable, they were not discussed.

Discussion of radiation quality saw the need for identifying suitable epidemiological cohorts exposed to different radiation qualities. Recommendations receiving attention here were the expansion of current and future studies to include comparisons between photon and non-photon irradiation. A plea from a number of participants indicated the need for an alternative way of representing dose, to allow comparison between qualities. Dosimetry was discussed in some depth by one group, where a Europe-wide lack of expertise in the field was noted and future problems with accurate dose estimations were seen as a potential problem.

Although no direct prioritisation was made, it is possible to generate a ranking of research tasks *post hoc*, as a number of topics were raised by both subgroups and were unanimously agreed upon as being the critical areas for future research. These have been de-

defined as **level 1 topics** in the following report. Other areas were agreed upon by a majority of the participants in both groups, or were accepted unanimously only by one subgroup and were not discussed by the other (**level 2 topics**). The **level 3** topics represent either the unchallenged opinions of a minority, or were subjects that were controversially discussed and not accepted by the majority of participants.

3.2.1 Identify the key questions to be addressed to improve protection of individuals from low dose/rate exposure

Level 1 topics

Three level 1 topics were identified. As these were unanimously recognised as key questions by both subgroups we are confident in assigning these the highest priority for research funding. The main focus of the discussion in both subgroups concentrated upon the question of evaluating individual risk. Discussion focussed on genetic modifiers. Age was discussed. The panels did not recommend significant effort be expended on studies of non-genetic effects such as age and gender unless they were added value end points arising from genetic studies.

- 1) The question raised was whether an evidence-based assessment of individual risk could be based on quantitative data provided by epidemiological and mechanistic studies. This should allow the scientific community to evaluate the probability that some individuals within a radiation-exposed population are at greater or lesser risk of developing malignant disease after exposure to low doses. The answer to this question should allow the identification of individuals at greater risk rather than identifying broad groups of individuals or populations at risk.
- 2) The research effort should focus upon quantifying those "at risk" individuals exposed to realistic low doses, and include protracted exposure scenarios, such as medical imaging, nuclear workers, and flight crew, rather than extrapolation from acute dose high exposures. However, radiation therapy effects, such as secondary cancers in tissue volumes exposed to low doses, were seen as a valuable resource and an issue of increasing importance.
- 3) The third key question asks if it is possible to use validated surrogate indicators of susceptibility (e.g. biomarkers, gene markers or phenotypic traits) to identify at risk individuals? Here a deeper understanding of the mechanisms of modifier action is required, for which model systems must be employed. A further question was which in vitro surrogate markers, such as apoptosis, are indicative of the biological end point cancer?

Level 2 topics:

- 1) Is it possible and advisable to transport risk factors identified at the population level to the risk of an individual? Concerns were raised that the multifactorial nature of individual risk may prohibit risk assessments based upon only one or a few individual parameters. Thus, it must be established if there is a hierarchy or interaction between different modifiers of risk such as between genetic background and age or gender. The question then can be formulated as: is it possible that single risk factors identified between populations lose their power when applied to individuals within that population?
- 2) Are the mechanisms and factors governing cancer susceptibility independent of dose rate and quality, or are there differences in the degree to which risk modifiers contribute to individual risk at different rates and qualities?

- 3) It was asked if there are any means to quantitatively compare the magnitude of the effects due to individual sensitivity. This would lead to a ranking of the contribution of different modifiers such as age, gender or known gene mutations. Can these factors be weighted and is this an improvement or an unnecessary complexity?

Level 3 topics:

- 1) Is the epigenome relevant as a modifying factor? (This may be included in the more general question of mechanisms above).
- 2) Are mouse models of radiation-induced cancer relevant to the human situation?
- 3) Are non-mammalian models relevant to humans?

3.2.2 *Identify strategies, resources and infrastructures to answer to the key questions:*

Level 1 topics:

- 1) The first priority identified was the need for an integrated effort to identify which genetic factors influence individual sensitivity. This was recognised as the single most important point in the working group discussions. Such studies should be performed on cohorts that have identifiable risk (direct end point cancer, or an as yet unknown surrogate), These studies should have tissue available for genetic analysis, and/ or have sufficient information on gender, age at exposure, lifestyle, and environmental exposure. Such a cohort must offer the realistic possibility of obtaining high quality dosimetry. These studies were recognised to require large-scale and long-term investment, needing a strong commitment from the community to ensure follow up of the cohorts. An immediate priority set for molecular epidemiology was the validation of both statistical power and feasibility of obtaining the necessary data and materials.
- 2) A significant part of such studies will be the involvement of epidemiological and experimental researchers in their design and implementation. This can be best achieved by setting up joint think-tank structures to leverage cooperative planning. The panels agreed that the design of such a study must meet these criteria to guarantee success. Doubts were raised by a minority of participants that an ideal cohort, as such, may not exist. Ethical concerns were also raised, and it is recommended that ethical implications of individual sensitivity testing be covered by MELODI. A lack of dosimetric expertise was seen as a major barrier to progress in low dose epidemiological studies as the variations in dose estimates may provide false information.
- 3) A close relationship was identified between experimental and epidemiological studies, with each requiring input from the other to identify and validate susceptibility modifiers. It is recommended that a panel of model systems be developed and deployed to allow the experimental verification of any factors identified in a molecular epidemiological study. These models should include *in vitro* cellular and tissue level models for functional analysis of the identified factors. For verification involving more complex interactions, culminating in end points relevant to cancer, *in vivo* models (mammalian and non-mammalian systems) will be required. Model systems are also required for hypothesis-generating studies to identify new candidate biomarkers and pathways for subsequent study and verification in epidemiological cohorts.

- 4) Further research areas seen as being promising for addressing the problems of defining individual sensitivity were stem cell / progenitor cell radiobiology and modeling/ systems biology (quantitative and predictive approaches). A clear definition of how exploration of these scientific areas should be implemented into current radiobiological experiments was not discussed. This topic can only be adopted as a research priority when it is clear how it will address the problems of low dose risk.

Level 2 topics:

- 1) The study of inflammatory and immunological responses to low dose may provide insights into non-DNA damage mechanisms of cancer induction by low dose radiation. Studies in this area were recommended by a minority of participants.
- 2) The application of cell and tissue models for in vitro study of non-targeted effects and stress responses was proposed.

3.2.3 Tissue differences

A lack of time prohibited in depth discussion on these issues. No consensus was attempted due to the lack of detailed discussion.

- 1) It was agreed that different biological responses exist in different tissues (e.g. development of different cancer types). It was not clear however, if or how individual differences would modify such a basic biological process. A clear need for biological mechanistic studies exists, and may be met by stem cell/ progenitor studies. However, it was not unanimously agreed that stem cell biology can answer the question, nor if appropriate models yet exist.
- 2) Tissue level responses were seen to require complex biological models, such as in vivo or multicellular in vitro studies. It is not clear if simpler models can provide answers to tissue sensitivities.
- 3) The molecular epidemiological studies described above should incorporate tools to allow identification of sensitivity modifier effects acting upon different tissues. However the panels did not recommend a strategy.

3.2.4 Radiation quality and dose rates

- 1) The effects of modifier genes may not be universal, with the effects of different radiation qualities possibly being subjected to different influences. Thus, a modifier of high LET-induced cancer that exerts its influence through genomic stability may not have as strong an influence on radiation of lower LET. Consequently caution is needed in interpreting and applying modifier functions to different qualities, and both epidemiological and experimental studies must address this possibility.
- 2) Studies into the role of dose rate effects and the action of modifiers upon them were seen to be underrepresented in the EURATOM programme. Effort must be made to redressing this imbalance, as modifier action may well be most pronounced in situations of protracted exposure.

3.3 WG3 “Non-Cancer Effects”

The participants were asked to define the non-cancer effects that need immediate attention and for each type of effect, to identify the open scientific questions to be investigated.

They were asked also to think collectively about the endpoints and populations of interest to be explored, the research projects to be launched (e.g. phenomenological studies, mechanistic studies, epidemiological studies –classical/molecular, methodologies to be used, and modelling tools to be developed), the infrastructures to be enhanced and the needs in terms of education and training.

The final objectives of the working group were (i) to make priorities among the issues identified as to be addressed in the future to better understand the mechanisms behind the non-cancer effects resulting to an exposure to low dose of ionizing radiation; (ii) to provide an indicative timescale to help in designing the strategic research agenda and the road map to be followed.

3.3.1 Terms of reference

It was thought useful to establish broadly, as part of the terms of reference, what range of doses was to be considered as low dose of ionising radiation, what non-cancer effects were to be explored in priority and then what level of biological entity should be the focus of investigations?

- 1) The participants concluded that, while acknowledging the complicating factors of dose rate, accumulated dose, intrinsic radiation quality and disparities between internal and external delivery, a good working range would lie between 0.3-3 mSv per year as the dose below which it would not be worth making investigations at least in the first instance (corresponding to the range of background environmental doses), and an upper level of 100-300 mGy as an acute dose of low LET radiation of the same order as diagnostic radiation. The group emphasised that the range of doses of relevance to “low dose effect” might well be heuristically determined as investigations proceeded but that therapeutic exposure should be excluded. However, the participants in one session thought that information at doses at above 0.1 Gy (low LET) may be useful in considering dose-response relationships. The group considered the question of the dose quantity to be considered (effective dose, equivalent dose, absorbed dose?) especially where evaluation of the role of heterogeneity in dose distribution is needed to better understand the differences between non-cancer effects resulting from external exposure *versus* internal exposure. The participants agreed that comparison between consequences of an acute and/or sum of acute exposure *versus* chronic and/or protracted exposure is of the utmost importance. The group laid stress on differences in effects resulting from whole-body *versus* partial-body exposures, recognizing they are both relevant to radiation protection.
- 2) The traditional paradigm of radiation risk is focussed on organs and tissues but existing data suggests that this approach is inappropriate for low dose effects, which affect processes and systems. It was therefore agreed that focus should be on systems or processes. Examples where data is already available are the cardiovascular system (cardio- and cerebrovascular), the immune system (inflammation), the central nervous system (neurogenesis) and behaviour, with also possibly the digestive system. Reproductive biology and transgenerational effects are also of interest but there are problems with the availability of embryology expertise for most model organisms; need for exploration of biomarkers of teratogenesis and pregnancy outcomes was recognized. The group also agreed that there was a place for an anatomic-based approach in some cases and supported the idea that cataract might be a useful system to pursue.

Indeed, whatever the non-cancer effect considered, the group agreed that input from other disciplines is essential: cardiology, neurology, toxicology, dosimetry, radioecology, embryology, bioinformatics, pharmacokinetics, and more generally, specialities relevant to non-cancer endpoints; as a result, the group emphasised that establishment of bridges among various disciplines is crucial.

- 3) The participants had concerns with making priorities among non-cancer effects to be explored in the future, mainly due to a lack of decision-making elements to be considered in defining such a priority list: public health impact (mortality, morbidity), level of proof, opportunity to link the observed effects to a dose value, populations of interest? In addition, considering the issue as wider and complex, the group recognized the need to balance risks against benefits, pointed out the possible need to define dose constraints/recommendations for medical exposures, and raised the question of what to do if there is evidence of a beneficial effect. The group stressed also the need to distinguish systemic effects from those that are organ-specific.

3.3.2 *Experimental Approaches*

Epidemiology is vital but so is the use of validated animal model systems and cell cultures and the group recommend a multi-level approach combining epidemiology, tools for microdosimetric calculations, model organisms and cell culture.

The group strongly recommended a systems biology approach to the low dose non-cancer problem and given some of the caveats below suggest that one of the priority systems with most potential for investigation at the model organism, cellular and epidemiological levels would be the immune system. The central nervous system was also recognized as a promising system for assessing individual radiation sensitivity at different stages of the development.

The group recommended developing an integrative systems biology approach also to better understand the respective contribution of individual characteristics and effects resulting from the radiation exposure. The question of how to assess the role of confounding factors (e.g. diet, smoking, other lifestyle factors, or underlying disease in the case of medical exposures) was raised; as an example, the group emphasised that interactions between chemical compounds and radioactive materials need to be better understood with the view of better evaluating the respective contribution of chemical toxicity and radioactive toxicity.

1) *Model organism*

Model organisms are essential to allow mechanistic investigation of physiological systems and have many other strengths. The possibility of genetic dissection of effects and sensitivity and the use of genetically sensitised organisms, e.g. mutant fish and mice, was seen to be a great advantage of the model organism approach and the participants would be able to leverage research using the large scale pangenome knockout projects currently underway as well as the European strength in phenotyping as exemplified by the German mouse clinic in Munich and the *Institut Clinique de la Souris* in Strasbourg.

It should be mentioned that two sub-groups disagreed about the relevance of using fish as a model organism: one saw a great advantage in this model, while another recommended to avoid “fishing exercises”. However, the group recognized a need for a variety of animal models.

2) *Cell/Tissue culture*

The group recommends that primary cell culture systems be exploited over established cell lines, and that multi-cell type “tissue model” cell culture systems be validated for low dose research. The participants supported paying special attention to studies on endothelial cells, coupling *in vitro* and *in vivo* experiments in coordination with on-going projects such as CARDIORISK.

3) *Epidemiology*

Given the lack of knowledge about the magnitude and nature of low dose effects three major problems were raised for epidemiology:

- The effect of confounding factors when it is difficult to estimate the sensitivity of a study. It was suggested that studies on the immune response effects might be more tractable in the first instance than the cardiovascular system for this reason.
- Potential problems in finding large cohorts exposed to a range of radiations and dose rates and following these cohorts to ascertain non-cancer effects.
- Uncertainties in dosimetry.

It was agreed that discovery of end-points or markers, possibly derived from experimental research might be vital in the construction of useful epidemiological studies and that the necessity for large cohort sizes might require a coordinated approach to studies, maybe making use of existing large cohorts although from the point of view of radiation quality reconstruction of doses for existing cohorts could be difficult. Indeed, the group recognized the importance of determining the shape of dose-response curves for non-cancer effects, by combining data from different cohorts where it is possible and relevant.

The group identified several potential populations of interest:

- *Patients*: cancer patients treated with radiotherapy (impact of new technologies, e.g. impact of dose volume histograms, use of alpha-emitters, effects on tissues on edge of treatment volume?); CT patients (large number of patients, wide ranges of ages, availability of blood samples and dose estimates); nuclear medicine patients (possible consequences of internal radiotherapy, e.g. using radioactive antibodies? Risk for patients to develop vascular diseases? Risks associated with new medical imaging technologies, especially in infancy and childhood? Is an administration of antioxidant relevant to protect the patient receiving a radiation dose? Need for evaluating the efficacy and toxicity of such a medical countermeasure).
- *Workers*: nuclear workers (e.g. research and industrial sectors, defence – including DU exposed, staff preparing radiopharmaceuticals - especially for PET imaging, workers exposed to alpha-emitters – need for a continuation of the ALPHA RISK project, Mayak workers); uranium miners and other groups of miners (fluorspar) (where gamma exposures may be important, rather than radon alone); aircrew; medical workers (e.g. interventional cardiologists, dentists).
- *Environmental exposures*: background (limited range of exposures, at least in Europe: concerns about comparability of populations); naturally-occurring radionuclides (e.g. in drinking water); Chernobyl; Techa River; Semipalatinsk test site; Scandinavian populations such as Sami; tritium; radium (industrial waste); radon.
- *Vulnerable subgroups*: paediatric groups; smokers; people with metabolic disorders; pregnant women.

Whatever the population of interest, the group pointed out ethical issues (ability or inability to provide consent) and the issue of availability of biological samples.

3.4 WG4 “Infrastructure”

The ultimate objectives of the infrastructures work package under MELODI and DoReMi are:

- to describe available facilities
- to identify the needs for existing facilities and for new ones
- to define the infrastructures to be implemented within DoReMi and those implemented with MELODI support in order to set-up sustainable funding
- to facilitate access to infrastructures in collaboration with Training activities
- to launch calls for infrastructure accesses in collaboration with scientific projects

The aim of Stuttgart meeting is to contribute to the identification of the needs for existing facilities and for new ones, without giving, at this stage, priorities, as the SRA for scientific topics is a prerequisite for the infrastructure prioritisation.

3.4.1 What should be considered under infrastructures

The following types of infrastructure (HLEG, DoReMi) were identified and discussed:

- Large irradiation facilities;
- Human cohorts;
- Databases, tissue banks;
- Platforms for analysis.

The objective would be to make common infrastructures open for access by European scientists, prepare standard research agreements and evaluate the possibility of providing funding through open calls to provide support for the use of infrastructures.

Standard procedures, protocols and even a possible glossary (including the various definitions of terms used by different scientists in radiation protection research) can also potentially be considered under infrastructures.

The general discussion (during the Workshop and the plenary session) also identified needs for:

- Animal facilities for irradiation of large numbers of animals;
- A shared platform for analysis, bioinformatics tools;
- A central facility for all types of chromosome analysis;
- A central facility for measurement of DNA damage, for DNA sequencing, phenotyping;
- Tissue banks with stem cells from different human tissue to assess individual radiosensitivity;
- A forum to exchange experience, problems (for example with antibodies);
- Infrastructures that will help training in radiobiology in European universities (webtools);
- Educational material in Radiobiology (training lectures, slide files);
- Dedicated infrastructures for information and dissemination to populations of radiobiology/radioprotection/radiotherapy

It was felt important not to recreate facilities which already exist (EURADOS, ERA, ...) or are in the stage of feasibility (STORE, ...). It will be important therefore to make a comprehensive survey of existing facilities and create a network to allow access to them. The survey should not be restricted to the EU, but should include facilities in Canada, Japan and elsewhere. For the benefit of research, openness of access will be essential. The survey should focus on low doses.

An important aspect which was brought up was the need for long-term financial support of infrastructures and it was suggested that consideration be given to what has been done to secure important infrastructures in other areas, such as for ecology and the biota.

3.4.1.1 Irradiation facilities

There is a need for facilities for different types of radiation, namely:

- X-ray tubes ($E < 300$ kVp);
- X-rays from LINAC ($E < 25$ MeV);
- monoenergetic X-rays (from SLS);
- γ -rays (^{60}Co , ^{137}Cs);
- α -particles (from sources);
- β -rays (from sources);
- Electrons;
- neutrons;
- protons;
- heavy ions.

Several websites exist already which provide a list of accelerators, including ELSA (http://www-elsa.physik.uni-bonn.de/accelerator_list.html) and the IBER report (<http://iber.na.infn.it>). It is important to collect information not only on radiation type but also on the possibilities provided for biological research, including cell culture facilities, animal facilities (and capacity), availability of microbeams, dosimetry support and staff for experiments.

The subsequent discussion revealed that very many facilities are available and that a careful survey will be needed.

- For charged particles, existing large scale facilities (FAIR; GSI, GANIL) are sufficient and there does not appear to be the need for new ones, though improved access is needed.
- For chronic low dose and low dose-rate exposure to low LET radiation, the situation is somewhat different. There are existing facilities in Japan and Canada but access is very difficult (subsequent discussions in a later session revealed that the difficulties in accessing the Japanese facility were related to administrative and jurisdictional problems and were being resolved).
- For internal exposures, it was reminded that there are tricky problem to deal with cell cultures and animals.

The issue of dormant facilities was also raised and will need to be addressed in the survey. It will be important to review the needs before decisions are made to decommission these facilities.

Whether an additional facility in Europe will be needed must be assessed carefully, taking into account the fact that the costs of dosimetry and support for biological labs will also need to be factored into the cost of any new facility. It was reminded that for low doses and

low dose rate exposures, it is necessary to eliminate background radiation exposures. Underground facilities exist and might be included in the review.

Finally, it was indicated that the European Space Agency might be willing to co-fund some studies if relevant for them (radiation quality).

3.4.1.2 Cohorts – Europe's epidemiological infrastructure

Concerning epidemiological cohorts, much effort has been invested both nationally and at the level of the EU to set-up national and multinational cohorts. These include occupational cohorts (for example nuclear industry workers, Mayak workers, uranium miners, airline crew, Chernobyl liquidators, Radiologists, Radium luminisers), environmental cohorts (such as the Techa river cohort, a cohort of persons environmentally exposed to Radon in the Czech Republic and cohorts of evacuees from the 30 km zone around Chernobyl), medical cohorts (cancer survivors, survivors of benign diseases such as ankylosing spondylitis, tinea capitis and haemangioma, patients with diagnostic exposures – including exposures to ^{131}I and new and planned cohorts on paediatric CT scans and interventional radiology – and cohorts of sensitive persons such as BRCA1 or BRCA2 mutation carriers and AT heterozygotes).

A careful, critical review of existing cohorts is needed, focusing on cohort designs, study size, adequacy of dosimetry and quantification of dosimetric uncertainties, information collected and, where relevant, biological samples collected, data and sample storage conditions, status of the cohorts and availability for European research. Such a survey would allow the identification of the cohorts that are most informative for RP research and of what may be needed to maintain and exploit them (it is known that some databases are dormant and could be lost if efforts are not made to convert them to new versions of data management software and new servers and that funding is not always available nationally for additional follow-up). Once these important cohorts are identified, it may be possible to build upon past investments by allowing additional follow-up and, if needed, collection of additional information on study subjects to maximise the information that could be obtained from these studies for RP.

Based on this review, the most suitable cohorts for answering specific questions in radiation protection could then be identified. For example, it may be possible to use existing cohorts of patients treated for cancer and non-cancer diseases for studying individual sensitivity, collecting additional information on risk factors and biological samples to maximise their informativeness. Similarly, cohorts of uranium miners or of nuclear workers could provide a good basis for studies of dose-response for cancer and on non-cancer effects and their informativeness could be improved by additional follow-up (to increase statistical power) and, in the case of nuclear workers, efforts in dose reconstruction for specific radionuclides. Where appropriate cohorts do not exist yet, surveys could also suggest important populations for answering specific questions (for example studies of paediatric CT scan patients could provide information on cancer and non-cancer effects of low to moderate doses in childhood, studies of the Chernobyl accident might provide information on mixtures of internal and external exposures or studies of AT heterozygotes information about the importance of genetic predisposition).

The subsequent discussions highlighted:

- National efforts (secondary cancers, CTs, ...) where combination may be needed, where it does not exist yet, at the European (or international) level, ensuring consistency of information collected through standardization of study instruments. Conditions to provide data for European access will need to be determined.

- The possible need for new cohorts for studying risk of cataracts, cardiovascular morbidity.

It was concluded that there is a need for a careful review of existing cohorts and their status (databases status, logistics of continued follow-up), for coupling data with biological samples where they are available and for storage of all relevant information on study subjects (including results of biological and bioinformatics analyses).

A critical point and non trivial issue which will have to be addressed is the ethics approvals needed and the logistics for making data and samples from available cohorts accessible to the broader research community.

3.4.1.3 Databases and tissue banks

A huge work has been going on in recent year to create the European / International Radiobiological Archives (available online) and making a non-exhaustive list of existing databases and tissue banks, including

- for humans: NOTE: EU FP 6 EURATOM, CTB: EU FP 7 EURATOM, LUCY (Lung Cancer in the Young), WISMUT miners: national funding, MAYAK workers: USA and national funding, individual radiosensitivity (patients): national funding, GENEPI: EU FP 6 EURATOM, ALLEGRO: EU FP 7 EURATOM, BBMRI (Biobanking and Biomolecular Resources Research Infrastructure): EU FP 7 Capacities.
- from experiments CASIMIR (Coordination and Sustainability of International Mouse Informatics Resources); EU FP 6 Life science, STORE – data and material from animal studies (EU FP 7 EURATOM).

However the results of a recent survey of databases and tissue banks which highlighted the fact that samples are not always available to go with databases and that tissue banks may be located elsewhere, with the risk of tissue being lost. Within STORE, a questionnaire is being prepared to identify what data and material are available and whether the investigators are willing to share them. The OECD and MELODI have made recommendations about data sharing and the Rome Agenda for sharing data from mice experiments has been published (Schofield et al., Nature, Sep. 2009).

An issue which will need to be addressed is the form in which data and material will need to be stored – in data bases or a data warehouse – and, for material, physically in a "central depository" or virtually (for example scanning histological preparations and making them available on the internet). Whichever approach is chosen, there will be the need for developing a sustainable platform

The discussion highlighted the need for such a platform and raised questions about how the material would be stored and who would take care of it, the need for ensuring long term-funding as well as for cooperation – not just within EU but also with Russia, US, Japan, and the need for a constant overview (with prospective surveys to identify new databases and tissue banks).

Sharing of data is an essential but difficult aspect, if one wants to avoid loosing data or biological material. The question of whether *publicly funded institutions and projects could be obliged to share material and whether this could be ensured* by introducing research commons was discussed. It was pointed that applications for biological materials need to be under open review in order to select the best proposals.

Finally, it was suggested to explore the use of other large biobanks (e.g. EPIC – the European Prospective Study on Diet and Cancer, led by IARC) collected outside the radiation area to explore radiosensitivity in existing cohorts.

3.4.1.4 *Wrap-up*

At the end of the session, the question was raised if there were any issues related to infrastructure which had not been discussed. The following issues were suggested

- The need for a facility to screen large number of samples in human populations;
- The need to store material for future, as technological developments are underway. It was suggested that in projects funded by public money, a clause be included stating that samples will be available for future analyses with future technology.

The audience was also reminded of the importance of dosimetry as an essential cross-cutting issue in all areas, and of the need for interoperability of databases, including standardisation of semantics to allow linking of database and accessibility in a standard fashion.

3.4.2 *What issues are identified in other WP*

3.4.2.1 *Issues identifies by WG 1*

- Access to low dose/dose rate exposure facilities particularly for animals, possibly obtainable through collaboration.
- Data/bio-sample storage and sharing infrastructures both for epidemiology and experimental work. This might be developed through the STORE project.
- Conservation of large epidemiological databases. MELODI could assist in obtaining agreement from ethics committees and data protection agencies in respect of development of these infrastructures.
- A decline in expertise in several critical areas such as pathology and dosimetry needs to be stopped.

3.4.2.2 *Issues identified by WG 3*

- By and large the technology is available for experimental low dose research, and specifically for the investigation of radiation quality. There are two problems. Firstly the availability of chronic irradiation facilities for animal models (e.g., rodents) in Europe and secondly the expertise for dosimetry, specifically microdosimetry and that these issues need to be addressed as part of infrastructure and training. There exist facilities for chronic animal irradiation and/or contamination in Japan, Norway, Canada and France. The group recommends that the capacity and availability of these centres and any others be looked at from the point of view of either justification of a new central resource or the possibility of supporting and federating access to the existing ones. The group also recommends defining mechanisms and tools (web site?) allowing research groups to share databases (e.g. tissue banks, microarray data, etc.) and performing meta-analysis of existing information.
- With regard particularly to radiation quality experiments, acute doses using different qualities of radiation are no problem, but information on chronic doses is limited to external gamma radiation. This problem can be solved using internal emitters but it

was noted that there would be considerable expense in dealing with solid waste disposal in these experiments, which would increase costs significantly.

- Mechanistic approaches have already been identified: genomic instability, oxidative stress, signalling, bystander effect, membrane channels, cytokines, senescence, respective roles of DNA/RNA/proteins, epigenetics and these should be supported as a set of priorities. At the moment there is insufficient evidence available to say which of these should be prioritised over the others and indeed many may be inter-linked. Most of the technologies needed to investigate these aspects of non-cancer effects were felt to be already in place, though in some cases expertise was not readily available.
- A systems biology approach would benefit from the setting up of central resources for proteomics, transcriptomics and particularly the emerging 'omics technologies such as proteomics and epigenomics. Expertise is thin on the ground and, with the high costs of this technology, establishment of a central, accessible, service platform would be very helpful.
- The group raised the question of the use of electronic patient records, including information on diagnostic exposures if possible.

3.5 WG5 “Education and Training”

3.5.1 *What are the training and education needs for low dose research*

- Provision of an education/career programme for the next generation of researchers in low-dose radiation risk. This is the fundamental requirement to enable a productive long-term European research programme to address the uncertainties in radiation risk.
- Radiation protection for professionals – doctors, regulators, radiation protection officers/advisors. In the area of practical radiation protection, as applied to all uses of radiation, there is a need for a deeper understanding of both the assessment and management of radiation risks. This need can only be fully addressed by a deeper understanding of the science, together with well informed instructors and well structured training courses.
- Provide cross-discipline courses. The science of radiation risk is multidisciplinary, and researchers may enter from the disciplines of radiobiology, radiation physics, epidemiology, mathematical modelling, molecular biology, etc. There is a perceived need for cross-discipline courses that would be suitable for scientists wishing to gain a fuller perspective on the subject.
- Focused short courses on single topics/techniques. There are many requirements for single topic short courses, designed to give greater accessibility to a particular laboratory/measurement technique, or as a prerequisite to the use of a particular facility or piece of equipment.
- The MELODI workshop offered a wide range of suggestions for T+E needs. There are two conclusions to this. First, that there are many areas where T+E are critical to the science underpinning radiation protection, and that the initial terms of reference should be as wide as possible. The second conclusion is that in any activities sponsored by MELODI, it is essential to maintain a focus on the fundamental purpose, and target the support where it will be most effective.

3.5.2 *What types of courses and programmes are needed?*

- Courses that will confer internationally recognised qualifications (e.g. Bologna-compliant). It is essential that qualifications are perceived as valuable career steps.
- Modular, allowing students to pick and choose. This recognises that fact that post-graduate courses will attract students from diverse backgrounds
- Attractive. The design and targeting of courses must be sensitive to what the student wants as well as what MELODI thinks the community needs.
- Focused courses. There is a demand for focused courses designed for scientists already in the field (at all levels) that deal with a particular training need, and extend no further in syllabus or time than necessary.
- Comprehensive courses. These in particular would be designed to attract high-level students from the standard sciences. They must be seen as job-tickets and interesting. Rather than exclude students by being too narrow in scope, they could be part of wider topics like environmental ecology, normal tissue radiobiology, etc. This could be useful in attracting a wider student and support base in order to give greater viability to the courses.
- As in the previous key question, the contributions from the MELODI workshop were very wide-ranging. Maintaining a focus on the fundamental purpose is essential.

3.5.3 *What training initiatives, schemes, and courses are already in existence?*

- EC funded training initiatives. There are a number of EC initiatives targeted at various training needs. Examples are:
 - European Fission Training Schemes (EFTS – FP7)
 - European Network on Education and Training in Radiological Protection (ENETRAN II, under EFTS)
 - TRISK (European Commission Second Programme of Community Action in the field of Health)
 - Erasmus Mundus – scholarships and academic cooperation.
- Many of the EC funded projects have training and education modules.
- Single-institution courses (several were described at the workshop).
- EC Masters radiobiology course.
- Before MELODI can take any initiatives to integrate and coordinate European training a significant exercise will be required to gain a comprehensive picture of the existing training environment.

3.5.4 *What are the key points that MELODI (DoReMi) should focus on?*

- Find the gaps. There is a very wide range of different types and areas of training required to support radiation protection. Many are already well catered for by successful courses. It is essential that from the start MELODI determines where the integration, coordination, and support are required. The primary focus should not be on the current practice of radiation protection (e.g. training radiation protection officers and experts) but rather on developing and fostering high-level expertise in the

research community that is investigating the science that underpins low-dose radiation risk assessment and management.

- Promote the field of study. Currently the brightest students are going to subjects where the big science and the big money are. Radiation science is not seen as ranking highly on either of these scales. MELODI must develop a strategic plan that will include E&T along with knowledge management and targeted promotion. Options to be considered should include strategic alliances with related sciences such as environmental ecology, radiation medicine. Making the topic attractive will not suffice if there are not also long-term career opportunities that can be offered with some degree of security. This is where MELODI has the potential to play a very valuable role.
- Make best use of what is already on offer. There are many single-institution courses in relevant subjects. It is important that MELODI should seek to integrate existing training and not compete with it.
- Take advantage of existing funding schemes such as the EURATOM Fission Training Schemes.
- Provide only what is needed and wanted. This will make the aim of long-term sustainability more realistic.

3.5.5 *Issues identified by WG 3*

- Lack of expertise and the need for training and access to centralised platforms were identified for:
 - Microdosimetry
 - Omics, especially emerging technologies, e.g. phosphatomics
 - Epigenetics
 - Modelling of energy deposition (considered too early to attempt to model non-cancer low dose effects as unlikely to fit into existing paradigms of stochastic effects)
 - Embryology.
- Importantly the group emphasised the importance of interacting with systems experts outside radiobiology, and suggest joint meetings based on systems biology not on radiobiology, maybe through integration with other FP7 projects in the Health programme. The participants also recognised the importance of radioecology to radiation protection issues and recommended interactions with the existing radioecology network of excellence, FUTURAE.
- The group emphasised also the importance of coordinating efforts with existing projects such as CARDIORISK, NOTE, STORE, or ERA-PRO. Thus, the group recommended to get more benefits from (i) approaches used in studying effects of high doses; (ii) new methodological approaches developed in projects addressing low dose risk associated to external exposure, in order to better use results arising from these projects to design studies on low dose risk associated to internal exposure.
- Dosimetrists within the group stressed that they need more interaction with and inputs from biologists and chemists to better understand physiological basis of radionuclide biokinetics and pharmacodynamic, to help improve existing biokinetic models.

- The group recommended harmonisation of training across Europe, while recognizing that few universities in Europe provide training in radiobiology. The group proposed a European Summer school as a permanent institution with broad perspective and organisation of workshops to assist interactions across disciplines. The group strongly recommends linking to other training initiatives in Europe and establishing tight contact with professional bodies.

4. General comments and recommendations of the participant

4.1 WG1

The discussions in WG1 provided an opportunity for open discussion of the major research needs to improve understanding of the dose-response relationship for radiation-induced cancer. Some initial consideration was given to prioritisation of research needs although it was recognised that this will require much effort in the future. Agreement was clear for the need for integrated studies combining epidemiology, radiobiology, dosimetry and probably other disciplines. Input from areas such as cancer research, toxicology and genetics was also viewed to be beneficial. There is a general need to appreciate that from a scientific and clinical perspective cancers at different sites are different and there will not be a 'universal dose response relationship'; rather, specific models will be needed for specific cancers and exposure conditions. These then may require generalisation for radiation protection purposes. Next steps will involve prioritisation of research needs and the establishment of an agreed *Strategic Research Agenda* to improve understanding of the radiation dose-response relationship for cancer.

4.2 WG 2

The following recommendations were prepared by the working group 2 to indicate future areas where the research scientists saw an opportunity for MELODI to improve the research effort within the low dose research programme.

- 1) The dissipation of the European research effort within the radiation protection community is seen as a major hindrance to a successful implementation of the research programme recommendations (strategic research agenda). The working group recommended that MELODI should engage in activities (other than sponsoring RTD activities) designed to maintain and even expand competence in the field. Examples of how this could be done were the organisation of summer schools for entry level and undergraduate scientists and on line access to teaching and training materials relevant for radiation research. Note of chairman: This recommendation was made prior to the role of the WP3 Training programme in DoReMi was presented to the participants.
- 2) The recognition level of the global goals of the EURATOM research programme in supporting radiation protection legislation and activities were not clearly recognised. Discussion of future research priorities sometimes deviated from the programme objectives of the HLEG. Consequently the working group recommends that MELODI play a more active role in disseminating the scientific/political objectives of the strategic research agenda. The panel felt that coherence between actual and planned RTD activity could be best achieved by information exchanges between MELODI, stakeholders and engaged scientists.

- 3) To facilitate optimal use of research funds, infrastructure and scientific skills the working group suggests that MELODI facilitate an exchange of research staff between different laboratories. This should be expanded to include creating opportunities for radiation protection legislators and laboratory scientists to create and sustain a dialogue.
- 4) The SRA should not be adopted as an immutable object but should be frequently revisited. In the opinion of the panel revision at 12-18 month intervals is a minimum period for revision. An alternative strategy to achieve sufficient flexibility would be to engineer into the SRA the means to allow rapid response to major developments in the field.
- 5) The panel sees the need for expansion of the knowledge base and attractiveness of research topics in the field by the recruitment of non-radiation science expertise. Key areas identified were clinical oncology, toxicology, biomathematics, stem cell biology and systems biology. It was felt by the panel that MELODI would be the ideal instrument to bring this new blood and new ideas into the field.

4.3 WG 3

The participants in the working group on non-cancer effects recognized that scientists need (i) to be open to challenging existing paradigms; (ii) to consider a system approach in studying non-cancer effects, in contrast to the approach for cancer which looks at organs; (iii) to integrate studies between classical and molecular epidemiology, model organisms, and *in vitro* system cultures (primary cells and tissue culture); and (iv) to involve various disciplines.

4.4 WG5

The strategic need for training and education, and the role for MELODI

Training and education are fundamental to a successful European research programme in low-dose radiation risks. It is the network of educational institutions that generate the continuing resource of researchers, they are the conduit for disseminating the new knowledge into the scientific community, and indeed they are where a significant part of the research takes place.

It was noted by HLEG (Report, January 2009) that many EU member states have lost key competences and are no longer capable of independently retaining their current research activities in radiation sciences. In order to answer the long-term questions of low-dose radiation risk, the research environment must continue to attract and hold top-level scientists. It must provide exciting scientific challenges and attractive career opportunities.

According to the HLEG Report, subject to further consultation, MELODI will aim to establish a sustainable integrated approach for training and education, including knowledge management. By forming a network of Universities and non-university research organisations, and coordinating both existing and new education and training programmes, it will be possible to broaden the scientific background of the training and contribute to increasing the mobility of the trainees.

5. Comments on the MELODI Workshop by D. Goodhead acting as an independent observer

5.1 General comments:

The MELODI and DoReMi initiatives are timely and very important. They have great potential and responsibilities for the field of low dose risk research in Europe. From the very beginning European nations have been in the forefront of research to understand and quantify radiation risks, bringing leading expertise and diversity to bear on the problems and with the EC playing an increasing role of coordination towards common goals. Diversity has been an essential strength but also a weakness. Several shortcomings are now well recognized, such as duplication of effort, gaps and a trend towards a reduction in the number of experts and the need for novel approaches and the drawing in of talent and ideas from other areas of science. Long-standing key questions on radiation risk remain unanswered (e.g. cancer risk at low doses) and new ones emerge (e.g. non-cancer diseases). The new initiatives are already becoming an important driver of Europe's effort in low dose risk research and if MELODI is successful it will dominate the field in Europe and make a major international contribution.

It seems evident from participation in the Workshop that there is widespread support for the success of MELODI, but with that success comes major responsibility - directing the research agenda on a large scale towards clear goals but also nurturing and reinvigorating the diversity and innovativeness of talent throughout Europe while engaging fully with the wider scientific research community as well as other stakeholders. The Workshop showed that the research community is willing and keen to engage. This early enthusiasm needs to be managed carefully in the short and medium terms, as well as the long term, in order to maximize the scientific engagement towards the key policy questions and not to dampen or lose parts of the community by inadequate attention to their interests and needs.

During the Workshop, I sensed some confusion amongst many of the scientists as to the precise purposes of their attendance, the ways and timescales on which they may be able to engage actively and on the transparency of the processes. The stated aim of the Workshop was to guide the development of a long-term SRA and road map for implementation, but it was apparent that in the shorter term an intermediate agenda was also essential and that this is likely to be most relevant to opportunities for their own active involvement in the field or, indeed, even whether or not they will remain in the field. The scientists are being asked for their best ideas and they have shown their willingness to engage by contributing their own resources to participate and contribute to the debate at the Workshop. But the potential return to them may have been less clear. Yes, the long-term is important for developing MELODI's strategy, but if the diverse research groups are not kept actively engaged in the field in the short and medium terms then to them the long term may become irrelevant as they instead take their expertise and ideas into other areas of science. This concern applies to senior investigators but probably applies even more acutely to the younger talent that has been drawn into the field by the recent large integrated projects in Europe and other activities. I strongly suggest that they need to know as soon as possible what the short- and medium-term opportunities might be to bring their research ideas into the fold, into the DoReMi 'club' or other routes that MELODI may offer. Will there be substantive open calls, within say the first six months of DoReMi starting, and over the next few years? Will the process be open and transparent to encourage their competition? While the main purpose of the Workshop was the longer-term strategy, the ongoing trust

and involvement of the scientific community may depend substantially on these shorter term issues. Such issues may become even more important in respect of the stated and essential strategy of MELODI to draw in new expertise and knowledge from advances in the wider disciplines of biology and medical sciences. The unwritten pact would be that you, the scientists, give your best ideas for future strategy (long term as well as shorter) and we (DoReMi and MELODI) will give you timely, open, equal and fair opportunities to bring your relevant research into the field with the common goal of addressing the overarching policy questions and the underlying scientific questions now and as the SRA develops.

5.2 Working Group discussions

Judging from the two WGs that I attended plus the plenary reports from each WG, my impression is that the WGs were quite diverse in the ways that they approached the discussion questions they had been given. This is unsurprising given the dependence on individuals within a WG and the breadth of the questions and underlying science. Some WGs focused in depth on particular issues, whereas others produced more generic sets of possible ways forward. Meaningful prioritization was not attempted in general, although there were some clear areas of consensus. The net output was a useful listing of potential research topics, approaches and techniques for addressing the key policy questions for low dose risk, with varying degrees of depth and, of course, strongly influenced by the particular interests of the individual participants. The WGs therefore served the very useful purposes of engaging the scientific community, increasing awareness of the goals of low dose risk research across Europe and of the MELODI initiative and they produced a useful general product.

The difficult challenge now is to select and prioritize so as to develop the SRA and road maps for the short, medium and long terms.

5.3 Prioritization

I can make only a few suggestions as to how prioritization may be approached. Clearly the overriding criterion should be relevance to the overarching policy question for low dose risk research and the key sub-questions, as identified by the HLEG, and the need to develop and maintain expertise in this area of science.

The *magnitude* of potential impact of the research on the overarching policy question and radiation protection standards provides a leading criterion for prioritization. Radiation-induced circulatory diseases are likely to be outstanding in this category, given that current data, from the A-bomb survivors in particular, indicates that the risks at intermediate doses are of similar magnitude to the totality of cancer risks on which standards are currently based. If these circulatory-disease risks extrapolate down linearly to low doses (the big question!) this must have a dramatic effect on total low dose risk (two fold) and hence on protection standards. It would also demand major rethinking of the concepts and applications of effective dose depending on tissue- and radiation-weighting factors, which could not apply equally to cancer and circulatory disease. Conversely, if circulatory risks were convincingly demonstrated to arise only above a dose threshold, there would be important public re-assurance of the standards and simpler ad hoc standards could be applied to protect against these additional risks above the thresholds.

A second useful criterion for prioritization could be aimed at key developments needed to enable longer term approaches to answering the intractable key policy questions. An example is building integration between different scientific approaches and techniques (such as epidemiology, experiment and theory) while drawing in new expertise and knowledge from the biological and medical sciences more generally. Relevance to the key policy question should underlie such prioritization, too.

A third criterion could be aimed at studies that are likely to deliver significant results (of relevance to the policy questions) on shorter timescales. These studies should ensure active ongoing engagement of the scientific community, including through open calls, and invigorate the field by demonstrating visible progress and new results.

A fourth criterion should be the development of *fundamental* knowledge and techniques for long-term scientific advancement of the field. Such activities should serve to maintain and enhance the field as an active and progressive area of science to attract and retain the best young minds and provide enticing career opportunities. As above, the key policy questions should provide a general framework of relevance within which fundamental scientific enquiry is encouraged.

Infrastructures require particularly careful prioritization. A very long and diverse shopping list of desirable infrastructures was drawn up. A few are of clear and general essential need within a programme of low dose research, such as a flexible low dose rate facility readily accessible to the European research community, probably within Europe (or possible through international collaboration if practical obstacles are not too great). But, in most cases infrastructures are expensive and long-term commitments, they often tend to be self-perpetuating and sometimes tend to dictate their own research strategy to justify and utilize their existence, rather than the strategy being driven by the external policy criteria of the low dose programme. The overriding requirement for prioritization should be the contribution that the infrastructure is likely to make towards answering the key policy questions. Within this, there should of course be optimization of infrastructures to provide pan-European access without undue overlap.

Running across all the above are the essential needs for training and career development within the field. These needs are of great importance and should be incorporated throughout the research strategy.

5.4 Concluding remarks

I feel that there is real danger that the MELODI and DoReMi initiatives may damage the field of low dose research for a generation instead of regenerating it. This is of course the exact opposite of what is intended. The perceived lack of transparency of DoReMi is a very serious concern. The FP7 Work Programme Call for an NoE stated that a large proportion of the resources were to be for research and for this reason the indicative budget was much greater than usual for an NoE. It is imperative for the trust of the scientific community that the research funds are substantial, are seen to be allocated only to properly reviewed research projects and that they are mostly open to full competition from the community. DoReMi will inevitably be seen as a child of MELODI and, if it does not open itself transparently, generously and fairly to the research community, not only may the whole initiative be in jeopardy but so too will the long-term trust and reputation of MELODI. To try to reduce such damage, MELODI may then need to ensure that its future SRA and road map are very clearly and visibly separated from potential self-serving interests of the DoReMi partners and that any future FP Calls suggested by MELODI to the EC are seen

to be not at all influenced by or tailored to suit the partners, but are driven only by the true policy and scientific goals and are equally open to the full scientific community. It may be that convincing separation could only be achievable by radical actions such as active exclusion of DoReMi partners from the processes. The problem is compounded by the close overlap of the DoReMi partners and the founding membership of MELODI.

The Stuttgart meeting marked a turning point in low dose research in Europe. Strong and wise actions are now essential and urgent to allay the disquiet in the scientific community and to do all that is possible to ensure that it is a turn for the better rather than the opposite. I feel that it is my duty to put these concerns to the founding members of MELODI and I trust that they will be read in the constructive way that I intend.

Annex 1

Work Shop Agenda

Introduction

The workshop's objectives are the following:

- (i) to present the recommendations proposed in the HLEG report and the EU-platform MELODI;
- (ii) to develop a successful strategic research agenda (SRA) for low dose research in Europe and to describe the roadmap for medium term scientific research agendas in each of the main fields identified in the HLEG report: 'shape of dose-response curve for cancer', 'individual radiation sensitivity for cancer' and 'non-cancer effects', also considering the three cross-cutting issues 'radiation quality', 'tissue sensitivity' and 'internal emitters'. Priorities within each roadmap should be set, taking into account the current international state of knowledge on low dose radiation effects. Efforts will be concentrated on collective thinking and establishing consensus within the research and regulatory communities;
- (iii) to elaborate an integrative road map, taking also into account the needs in term of infrastructure and education & training;
- (iv) to plan on the best ways to implement the SRA and the roadmaps, e.g. on methodology and practical actions for implementing the next steps of the European low dose research agenda.

After an opening session consisting of several presentations to inform the attendants about the recent initiatives launched to organise the low dose risk research in Europe, the participants will be distributed among three thematic working groups each of them addressing one of the main themes as identified by the HLEG (shape of dose-response curve for cancer, individual radiation sensitivity for cancer, non-cancer effects).

Each of the parallel sessions will be opened by a short introduction talk to stimulate and direct the discussions. To allow for a vivid and theme-oriented discussion, each working group will be split into sub-groups of 20 to max. 25 participants, related to the cross-cutting themes Radiation Quality, Tissue Sensitivity and Internal/External Exposure. In addition, sessions of the working groups "Infrastructure" and "Education & Training" will be held on the next day. Allocation and sub-division of the participants into the different working groups and sub-groups will be accomplished according to the preferences of each participant. To flag individual preferences each participant is asked to express her or his interest on the registration form. Among all participants interested in one specific topic, one chair person per working group and one rapporteur per sub-group will be nominated.

Before the meeting the BfS develops a catalogue of standardized questions, which should form the basis for structured discussions in the parallel meetings and which will ease the chairpersons' and rapporteurs' duty to sum up the results of each session or working group.

During the sessions, the participants will be invited to concentrate their efforts on collective thinking in order to provide appropriate research pathways and priorities to address a number of scientific open issues that will be submitted ahead the meeting. The results of this collective effort will form the basis for the report presented in a plenary session by the chair and rapporteur of each working group.

The next steps in the process of finalizing the first version of the SRA, and of setting up the MELODI research platform will finally be presented to the participants. This will include in particular the process through which the research priorities collectively identified as the outcome of the workshop will be drawn up into the European SRA on low dose research.

Annex 1

Workshop Agenda

Monday, September 28th, 2009		
<i>11.30–13.00 Welcome Coffee and Reception</i>		
13:00–15:00 - Opening Session		
13:00–13:10	Introduction and Welcome Address by the Organisers	Wolfgang Weiss
13:10–13:35	Expectations of the European Commission about the organisation of the low dose risk research in Europe	Simon Webster
13:35–14:00	Views of the World Health Organisation	Maria del Rosario Perez
14:00–14:30	Rationale and Recommendations of the HLEG on low dose risk research - overview of the actions launched during the two past years	Wolfgang Weiss
14:30–15:00	Introduction to MELODI and into the Working Group Sessions - Presentation of the questions which form the basis for discussions in the parallel scientific sessions (main topics: 1. Shape of Dose-Response Curve for Cancer; 2. Individual Sensitivity for Cancer; 3. Non-Cancer Effects; crosscutting sub topics: A - Radiation quality, B - Tissue sensitivity, C - Internal/External exposure)	Jacques Repusard
<i>15:00–15:30 - Coffee and Tea Break</i>		
15:30–19:00 – Open Working Group Sessions		
9 parallel open sessions with focus on ‘Shape of Dose-Response Curve for Cancer’, ‘Individual Radiation Sensitivity for Cancer’ and ‘Non-Cancer Effects’ are held		
Working Group 1	Working Group 2	Working Group 3
Shape of Dose-Response Curve for Cancer	Individual Radiation Sensitivity for Cancer	Non-Cancer Effects
Chair: Simon Bouffler	Chair: Mike Atkinson	Chair: Patrick Gourmelon
<i>Subgroups 1A, 1B, 1C</i>	<i>Subgroups 2A, 2B, 2C</i>	<i>Subgroups 3A, 3B, 3C</i>
Rapporteurs: 1A Mats Harms-Ringsdahl 1B Simon Bouffler 1C Dominique Laurier	Rapporteurs: 2A Anna Friedl 2B Rafi Benotmane 2C Kai Rothkamm	Rapporteurs: 3A Paul Schofield 3B Colin Muirhead 3C Jean Rene Jourdain
<i>19:30 Workshop Dinner</i>		
Tuesday, September 29th, 2009		

08:30–10:00 – Closed Concluding Working Group Sessions 3 parallel closed¹ concluding sessions to summarize the working group discussions and to prepare final reports <i>(only chairpersons and rapporteurs of working groups 1, 2 and 3 !)</i>		
Working Group 1 Shape of Dose-Response Curve for Cancer	Working Group 2 Individual Radiation Sensitivity for Cancer	Working Group 3 Non-Cancer Effects
Simon Bouffler (Chair) Mats Harms-Ringdahl Dominique Laurier	Mike Atkinson (Chair) Anna Friedl Rafi Benotmane Kai Rothkamm	Patrick Gourmelon (Chair) Paul Schofield Colin Muirhead Jean Rene Jourdain
In parallel to the closed concluding sessions of working groups WG 1, WG 2 and WG 3: 08:30–10:00 – Open Working Group Sessions 2 parallel open sessions with focus on ‘Infrastructure’ and ‘Education & Training’ are held		
Working Group 4 Infrastructure		Working Group 5 Education and Training
Chair: Laure Sabatier Rapporteurs: Elisabeth Cardis, Marco Durante, Bernd Grosche		Chair: Andrea Ottolenghi Rapporteur: Vere Smyth
<i>10:00–10:30 - Coffee and Tea Break</i>		
10:30–11:00	MELODI: European R&T Platform – The next steps (Some more Explanations)	Jacques Repussard
11:00–15:15 – Reporting and Planary Discussion		
11:00–11:45	Working Group 1 on Shape of Dose-Response Curve for Cancer Working	Simon Bouffler
11:45–12:30	Group 2 on Individual Radiation Sensitivity for Cancer	Mike Atkinson
<i>12:30-13:30 - Lunch</i>		
13:30–14:15	Working Group 3 on Non-Cancer Effects	Patrick Gourmelon
14:15–14:45	Working group 4 Infrastructure	Laure Sabatier
14:45–15:15	Working group 5 Education and Training	Andrea Ottolenghi
15:15–18:00 – MELODI-Conclusions and Closing Sessions		
15:15–16:00	Panel discussion: Low Dose Risk research in Europe and Next Steps in Setting Up MELODI	Simon Webster and Jacques Repussard Moderator: W. Weiss
<i>16:00–16:30 - Coffee and Tea Break</i>		
16:30–17:45	Panel discussion: Research Priorities Identified for Low Dose Risk Research and the Medium Term Road Map	D. Goodhead, Barrett N. Fountos, M. Nenoï S. Yamashita, Moderator: W. Weiss
17:45–18:00	Conclusions and Workshop Closing	Wolfgang Weiss

Annex 2

General Questions to Guide the Discussion in the Working Groups

Radiation risk assessment and radiation protection is faced with scientific uncertainty especially in the low dose region. A successful low dose research program should narrow these uncertainties.

What are the areas of greatest uncertainty in radiation research ?

What are the areas of greatest uncertainty in radiation protection ?

Which open questions need immediate attention, which can be answered later?

Which evidence should be given to results from studies in

- humans
- animals
- tissues and cells
- models ?

What is the population of interest (general population, workers, sensitive subpopulations etc.) ?

What are the endpoints of interest (adverse health effects, biological effects, molecular effects, predictive markers etc.) ?

What study design would you use to investigate the radiation effect on these endpoints when using an

- epidemiological
- biological
- molecular-epidemiological
- mechanistic
- interdisciplinary

approach ?

How should dosimetry be included in the investigation ?

In which areas is a need for further methodological development ?

In which areas is no need for further research ?

What kind of infrastructure is needed for

- further scientific research
- training
- education ?

From which scientific areas could beneficial input be sought ?

- stem cell research
- carcinogenesis and tumour therapy
- toxicology
- statistics
- bioinformatics
- astronomy
-

How would this benefit look like ?

How should an interaction be established ?