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Draft report of

**High Level Expert Group
on
European Low Dose Risk Research**

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Executive summary

Both natural and man-made sources of ionising radiation contribute to human exposure and constitute a hazard for human health. Exposure of the population to natural radiation is to some extent unavoidable and medical use of radiation is now an indispensable part of modern healthcare. The exposure of workers, and to a smaller extent of the public, to low levels of radiation from nuclear energy production and other industrial uses of ionising radiation have become an integral part of industrialised society. These uses are heavily regulated. Radiation protection standards rely on current knowledge of the risks from radiation exposure. **Any over-, or under-, estimation of these risks could lead either to unnecessary restriction or to a lower level of health protection than intended.**

Although much is known about the quantitative effects of exposure to ionising radiation, considerable uncertainties and divergent views remain about the health effects at low doses. The importance of low dose risk research is now recognised globally. Outside of Europe, the US and Japan have established large programmes of research. Many of the larger Member States of the EU also have considerable research activities in low dose risk. However, beyond the EURATOM research programme, little has been done to integrate these programmes. There has been a decline in scientific and regulatory expertise in radiobiology and radiotoxicology during the last decades, but plans to establish new nuclear plants and the increasing application of ionising radiation in medicine now accentuate the need to revitalise the field and research capacity. All these aspects highlight the necessity to address these issues at a strategic level in Europe.

A European High Level Expert Group (HLEG) was formed to consider these issues. Membership comprised representatives of national funding bodies and the European Commission. They were assisted by experts from the research community to identify research priorities and training needs.

The objectives of the Group were:

- To formulate and agree the policy goals to be addressed by low dose risk research;
- To develop a strategic research agenda and road map for such research in Europe;
- To specify the essential elements of and next steps for establishing a sustainable operational framework for low dose risk research in Europe.

This report of the European High Level Expert Group has been prepared under the responsibility of those members representing funding bodies and the European Commission (see Term of Reference on the web). In preparing the report, input has been obtained from a broad range of expertise within the

research community (with expert members co-opted onto the HLEG), in particular for determining those research directions most likely to respond effectively to the policy questions established by the funding bodies. The responsibilities of the scientific experts were to provide input on scientific matters.

In order to address the above goals, the report

- identifies key policy issues;
- assesses the state of science and the main research challenges;
- proposes a European research strategy and a way forward for its implementation.

The over-arching policy questions addressed in this report are:

- How robust is the current system of radiation protection and risk assessment in the light of scientific uncertainties?
- How can it be improved?

The radiation protection system, in order to make it practicable, is underpinned by a number of value judgements and simplifying assumptions based on the existing scientific knowledge. The robustness of each of these value judgements or simplifying assumptions determines that of the protection system as a whole. It is pertinent, therefore, to address each of the key value judgements or simplifying assumptions separately.

The more important issues in this respect are:

- the shape of dose-response for cancer;
- tissue sensitivities for cancer induction;
- individual variability in cancer risk;
- the effects of radiation quality (type);
- risks from internal radiation exposure;
- risks of, and dose response relationships for, non-cancer diseases.

For each of these issues, the report provides a summary of the current state of knowledge and identifies the most promising future research directions.

The complex and multidisciplinary nature of these issues is such that their resolution can be achieved only through the integration of research at a European, or even international, level. The report therefore proposes the establishment of a **trans-national organisation** capable of ensuring an appropriate governance of research in this field, and a **scientific strategy** capable of structuring future research in the most effective way, taking into account available resources.

It is proposed to achieve these goals through the launch of a new initiative, which is described in this report as “Multidisciplinary European LOw Dose Initiative” (MELODI). Subject to further consultation, “MELODI” would aim, with a view to sustainable integration, to:

- Bring together the programmes of the various funding bodies and research organisations in Europe;
- Establish effective interfaces with stakeholders and the broader scientific and health community in Europe and beyond;
- Ensure the availability of key infrastructures;
- Establish an integrated approach for training and education, including knowledge management.

Increasingly rapid advances in biological and medical knowledge are providing new opportunities to achieve these goals.

The report is now open for public consultation. The group is inviting comments from a broad range of stakeholders (research community, regulatory bodies, industry, healthcare, NGOs, etc.). Comments will be duly considered by the HLEG in finalizing its report.

1. Introduction

Exposure of the population to natural radiation is to some extent unavoidable and medical exposure of the patient during diagnosis and therapy, and of population groups during screening, is now an indispensable part of modern medicine. The exposure of workers, and to a smaller extent of the public, to low levels of radiation from nuclear energy production and other industrial uses of ionising radiation have become an integral part of industrialised society. Any over-, or under-, estimation of the risks to health from ionising radiation could lead either to unnecessary restriction or to a lower level of health protection than intended.

Judgements on radiation protection standards in Europe and elsewhere are highly dependent upon a) scientific knowledge that is reviewed in cycles by national committees and by a committee of the United Nations (UNSCEAR¹) and b) the recommendations made by the International Commission on Radiological Protection (ICRP) that seek to take account of such scientific development. The acquisition of new scientific knowledge through research is therefore a crucial element in improving the protection of the public, radiation workers and medical patients from the adverse health effects of radiation. Although current radiation protection standards are generally judged to be acceptably robust there remains considerable scientific uncertainty particularly with regard to health risks at low doses and low dose rates. Consequent upon these uncertainties, the issue of low dose risk is a controversial in both scientific and political circles.

This report summarizes the current state of knowledge, the major elements of scientific uncertainty in the context of protection policy and risk assessment, and future research activities that have the greatest potential to address these uncertainties. In general these future research activities centre on questions relating to doses and biological effects from different types of radiation, the biological processes in cells/tissues that mediate the health effects of low dose radiation (principally, but not only, cancer), individual variability and direct assessment of health effects through epidemiological study of groups exposed to low doses. An additional question is how best to combine data from a range of research areas in order to formulate computational models within a more systematic framework for low dose radiation risk.

The answer to these questions requires integrated input from many scientific disciplines. Moreover, the over-arching policy question of the robustness of the current system of radiation protection and risk assessment, has to be broken down into specific scientific questions that can be answered by multidisciplinary research that takes into account the full breadth of the latest advances in

¹ United Nations Scientific Committee on Effects of Atomic Radiation

scientific knowledge and techniques. A global description of these questions is presented in the following subsections, under the headings:

1. shape of dose response relationship and tissue sensitivity for cancer;
2. individual variability in cancer risk and genetic susceptibility to cancer;
3. radiation quality² (type);
4. internal exposure risk;
5. risks of, and dose response relationships for, non-cancer diseases.

In each area, the scientific state of the art is presented, and issues are identified that require further investigation in order to answer the over-arching-policy questions.

Given the revival in the interest of some Governments in nuclear power generation and the ever increasing use of ionising radiation in diagnostic medicine in Europe and elsewhere in the developed world, it is essential to ensure the long-term maintenance and re-building of expertise, infrastructures and resources relating to radiation protection research. Accordingly, the report addresses scientific competence and training and the elements of research infrastructure that are necessary to sustain future work.

The report also describes the key elements of a proposed research strategy for low dose risk research. This will required to go beyond the expression of key research needs and challenges as described above. To achieve success it will be essential to have mechanisms for the specification and periodic updating of priorities for research, for ensuring the provision of long-term funding for focussed research projects and for ensuring the availability of key infrastructures. The representatives from the funding bodies³ and the European Commission participating in HLEG consider it necessary to establish a sustainable governance structure, at European level, in order to consolidate, implement, and review as necessary over time, such an agreed research strategy.

² Radiation quality refers not only to radiations of different type (such as gamma rays and alpha particles) but also to other properties of the radiation (such as its energy or ionisation density) that can influence its biological effectiveness.

³ For simplicity 'representatives from the funding bodies' is used in this report to describe the members of the HLEG who represent the six national funding (or regulatory) bodies with a significant programme/activities, or with a policy interest, in low dose risk research or of national institutes with a substantial research programme in this area (see Terms of Reference: www.hleg.de/tor.pdf).

2. Key policy issues for ionising radiation risk management in a European context

The over-arching policy questions addressed in this report are: How robust is the current system of radiation protection and risk assessment, given its uncertainties? How can it be improved for delivering intended levels of protection of the population from occupational, environmental and medical exposures to ionising radiation?

Judgement on the shape of the dose-response relationship for cancer risk at low doses (say <100 mGy or 100 mSv whole body) and/or low dose rates for adverse health effects is a critical issue for radiation protection policy. This judgement determines the assessments of risk for practical low-dose exposures of the public and workers and it is a critical component of the current system of radiation protection applied throughout Europe and the world (UNSCEAR 2000; CERRIE 2004; French Academy 2005; NRC 2006; ICRP 2007). For largely pragmatic reasons, the linear non-threshold (LNT) model describing the relationship between dose and the appearance of radiation-induced cancer (and hereditary effects) has been applied for many years in the development of radiation protection policy. Under this model, there is no dose-threshold for induction of effects and each increment of dose in the low-dose region is assumed to produce a directly proportionate increment in biological and/or health effect.

With appropriate weighting, the doses and effects arising from different sources, different radiation qualities and in different tissues may be summed. The LNT model is therefore a critical element in the current ICRP system of radiation protection (ICRP 2007), which rests on the use of two dosimetric quantities, equivalent dose and effective dose.

This system does not assume a 'safe/no-risk' level of exposure but rather embodies the philosophy of maintaining all exposure 'as low as reasonably achievable' (ALARA). Recent reviews and recommendations from UNSCEAR (2000), NRC (2006) and ICRP (2007) have, on the balance of scientific evidence, favoured the use of the LNT model. Other bodies, including the French Academy (2005) have come to different conclusions, in particular that the LNT model may overestimate the carcinogenic effects of low doses. There is, however, wide agreement that DNA damage response processes are likely to play an important role in radiation-associated cancer risk and that a variety of less well understood epigenetic factors and non-targeted effects may also be involved. Until there is a comprehensive biological understanding of carcinogenesis in general, identification and precise quantification of the particular roles of radiation remain elusive, particularly at low doses.

The radiation protection system, in order to make it practicable, is underpinned by a number of value judgements and/or simplifying assumptions of the existing scientific knowledge. The robustness of each of these value judgements or

simplifying assumptions determines that of the protection system as a whole. In addressing the over-arching question it is pertinent, therefore, to address each of the key value judgements or simplifying assumptions separately. The more important issues where such judgements/assumptions have been exercised are shown in Figure 1 and comprise:

- the shape of dose-response for cancer;
- tissue sensitivities for cancer induction;
- individual variability in cancer risk;
- the effects of radiation quality (type);
- risks from internal radiation exposure;
- risks of, and dose response relationships for, non-cancer diseases.

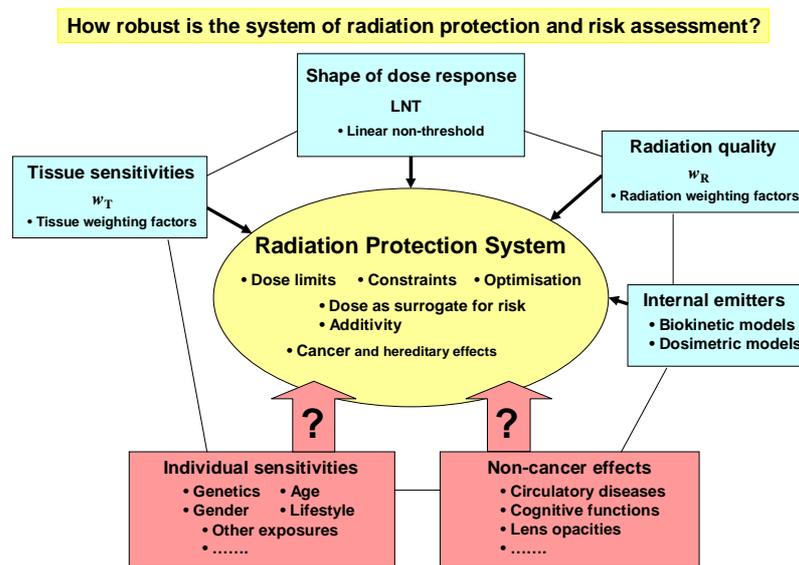


Figure 1: The main issues where judgements are made in the current system of radiation protection. The four upper boxes denote judgements that fall directly within the main ICRP dosimetric system, while the two lower boxes include issues that are at present included only to a relatively minor degree.

Inevitably, there are interactions or inter-dependencies between some of these aspects but, to the extent practicable, each is addressed separately (with cross references where appropriate), except that the two topics, "shape of dose response" and "tissue sensitivity", are addressed together because of their close relationship.

The nature of the value judgements or simplifying assumptions made in respect of each of the above issues in the protection system are described in Section 3 in relation to the available scientific knowledge as an indicator of their robustness.

Areas where the scientific evidence (or at least significant parts of it) may depart substantially from the value judgements or simplifying assumptions (or where major differences of view exist within the scientific community on the issue) are identified. Indications are given of future research directions that currently have the greatest potential to resolve these differences and enhance the robustness of the protection system overall.

The overarching policy questions therefore lead to a number of sub-questions concerned with the robustness of the value judgements or simplifying assumptions exercised on each of the issues shown in Fig 1. Each of these is addressed in turn in the following Section.

3. State of science and main research challenges

For each of the sub-questions, a brief summary is provided below of the current state of knowledge, the relevant policy issues and the most promising future research directions to address the questions, illustrated at the end by an indicative time-course diagram.

3.1 Shape of dose-response relationship and tissue sensitivity for cancer

As stated above, the shapes of the dose-response relationship at low doses and low dose rates for radiation-induced health effects, particularly cancer, are critical judgements for radiation protection policy and risk assessment. In brief, four basic model options on low dose response tend to be considered following exposure of the whole body or of individual tissues (Fig 2): i) linear-no-threshold, ii) linear but with a zero-effect interval below a given threshold dose, iii) supra-linear (hypersensitivity), or (iv) more complex bi-modal relationships (including beneficial health effects or hormesis at low doses). (UNSCEAR 2000; CERRIE 2004; NRC 2006; French Academy 2005; ICRP 2007).

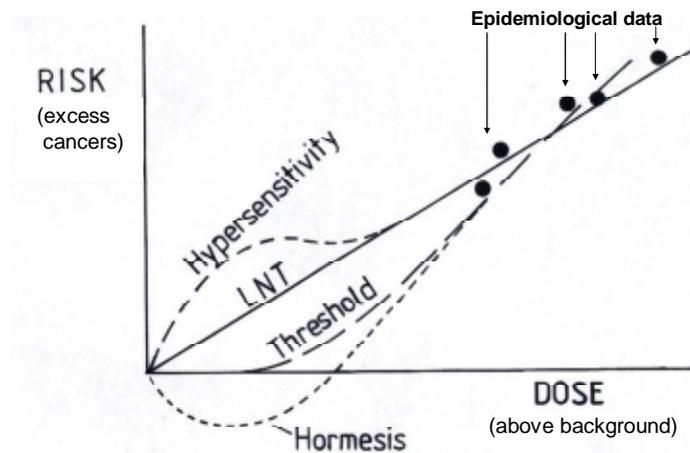


Figure 2: Low-dose risk extrapolation: diagrammatic representation of model options commonly discussed for dose-response relationships at low dose and low dose rates. Additional deviations in the shape are likely to occur at higher doses.

Many factors have been identified that can influence the shape or the steepness of the dose-response relationship. These include the type of ionising radiation and the way that it is delivered in time and space, the particular tissues of the body that are exposed and differences between individuals (in genetic characteristics and in lifestyles). While the main low-dose risk is currently assessed to be from cancer induction and, to a lesser extent hereditary effects, some non-cancer effects may also be of concern even at low doses.

Judgements on the validity of dose-response models are frequently questioned – the common criticisms raised include:

- Over-interpretation of single epidemiological data sets or even single data points on a dose response;
- Insufficient attention given to potential confounding factors and biases in epidemiological data;
- Insufficient attention given to the statistical power of some studies;
- Generalisation of results from atypical or limited experimental models;
- Insufficient understanding of low-dose radiobiology.

It is accepted that there is much uncertainty on the shape of the dose-response for cancer derived from epidemiological studies below doses of ~100 mGy (or ~100 mSv of whole-body low-LET⁴ radiation) and on the cellular/tissue

⁴ Low linear energy transfer (i.e. sparsely ionising)

mechanisms that determine the response, including the potential role of non-targeted processes.

The low dose response debate noted above has tended to centre on external low-LET radiations where the dose response for many biological effects tends to have a greater-than-linear component at acute higher doses. On account of this shape, it is currently assumed for radiation protection purposes that the slope of the response at low doses and low dose rates is reduced by a factor two compared to high doses and dose rates. As LET increases, the dose response tends to linearity throughout the dose range (e.g. for alpha particles and fission neutrons). This feature has been associated in part with the induction by high-LET⁵ particles of more complex DNA lesions that are more prone to DNA mis-repair and to the larger dose delivered to each individual cell traversed by a high-LET particle (see also Radiation Quality).

For radionuclides within the body, particularly alpha emitters and other very short-ranged radiations, the localisation of the nuclide in tissues or tissue sub-regions can create difficulties in the interpretation of dose-response data (see also Internal Exposure Risk). Such difficulties may be associated with nuclide biokinetics and/or target cell traversal probabilities and energy deposition in relatively small tissue volumes. For many tissues the key features of cell biology, e.g. target cell identity and location, are not well understood. The possible existence and the location of targets with characteristics of stem cells is a major factor in judgements on alpha-particle induced tumours in some tissues.

It is established that different tissues (or organs) of the body have different sensitivities for the induction of cancer by radiation. This is reflected in the use of tissue weighting factors in the current system of radiation protection (ICRP 2007). The biological bases of these recognised differences, e.g. between myeloid and lymphoid tissues or between different solid tissues, are not well understood and current judgements are largely based upon empirical epidemiological observations after relatively high dose acute exposures to low-LET radiation. Epidemiological studies of sufficient power should be able to yield more information on these tissue sensitivities and the potential for modification by dose, dose-rate, radiation type, gender and age.

In general, there is a need to continue epidemiological studies of low-dose responses, in different tissues, and to combine these with experimental studies. Further experimental approaches need to be developed and utilized in order to understand better the biological mechanisms that underpin the responses. Mechanistic studies should be closely coupled with computational approaches that specifically incorporate biological processes in models of low-dose response. A systems biology approach is needed that will combine quantitative experimental data and mathematical modelling of critical biological processes in the radiation response. Optimally, such an approach would involve experiments

⁵ High linear energy transfer (i.e. densely ionising)

performed at low doses at different scales (cell, tissue, organ, organism and population). This strategy would be expected to deliver predictive models of the behaviour of the complex systems to radiation, allowing a better understanding of the risks to health from exposure at low doses and low dose rates, and from different radiation qualities. A critical stage in the development of a systems approach is the cooperation between the fundamental radiobiological research and mathematical-modelling communities.

Shape of Dose-Response Relationships and Tissue Sensitivity for cancer

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

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

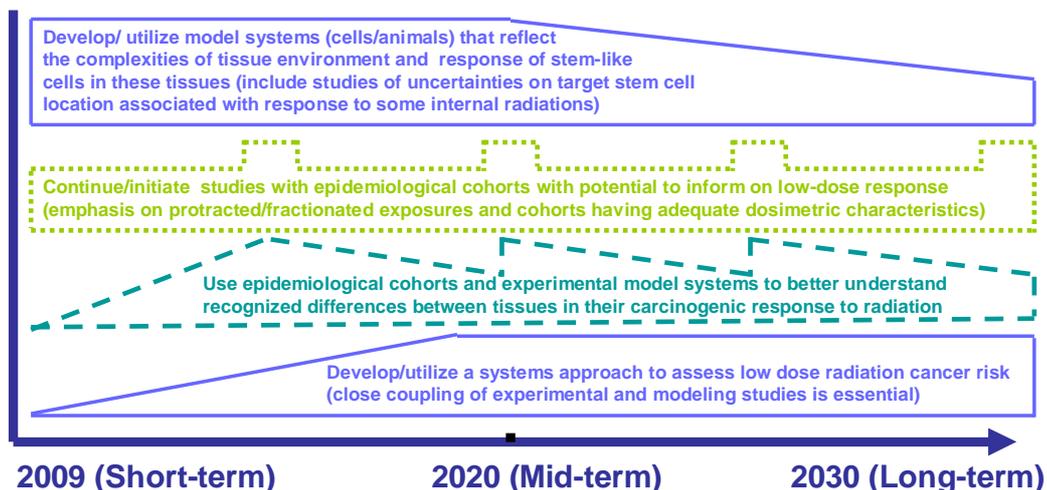


Figure 3: Indicative research directions to address issues on the shape of dose response relationship and tissue sensitivities for cancer. In figures 3-7, the boxes indicate potential research effort in the short, medium and long term, with some depiction of time dependence such as periodic increases in activity when new epidemiological cohorts are set up or when follow-up analyses take place on existing cohorts. Solid boxes denote combined experimental and modelling studies, dashed-line boxes denote combined experimental and epidemiological studies and dotted-line boxes denote epidemiological studies.

3.2 Individual variability in cancer risk and genetic susceptibility to cancer

Dose limits applied in radiation protection have been set to protect an “average individual”, based on studies of risks (mostly cancer) seen in large population groups following exposure to radiation, such as the A-bomb survivors in Japan. For cancer induction, it is well established that there are differences in radiation sensitivity between individuals (and population subgroups), depending on their gender, age, genetic make-up, lifestyle such as smoking, and exposures to other agents. In general, however, although these differences are recognised, they are not specifically accounted for in the setting of dose limits for planning purposes in radiation protection practice, apart from very few special situations (e.g for the embryo and foetus). In principle, the setting of dose constraints can take account of individual variability in radiation response, but this is rarely possible in practice. At present there is insufficient information to establish how large these various differences in sensitivity may be between individuals or between groups of individuals and their consequent influence on risk estimates at low dose. Variations between individuals are also relevant contributing factors in respect of the other topics discussed in Shape of Dose Response and Tissue Sensitivity, above, and Radiation Quality, Internal Exposure Risk and Non-cancer Effects, below.

Differences in radiation sensitivity between individuals, or groups, raise the ethical and policy question as to whether some individuals, or groups, are inadequately protected by the present system and regulations. Should different dose limits or constraints be set for men and women, for different ethnic or age groups or should additional lifestyle risk factors be taken into account? If some individuals are at much greater risk because of their genetic make-up, how should their safety, but also their individual rights in employment or public activities or as patients, be protected? To what extent should it be policy to test and identify such individuals, or to design specific medical procedures to take account of their individual characteristics? The current radiation protection system may, in due course, need to be refined to encompass individual variations in a more general way or to include special cases if these differences are substantial or affect a significant fraction of the population.

In order to address these policy questions it is necessary to obtain better scientific information on the extent of the variations in sensitivity in the population, both in the sizes of the variations and also in the proportions of the population that are affected. Therefore, research is needed to identify the factors that affect individual sensitivity to radiation risk and to obtain realistic estimates of how large the differences may be in extreme cases and also the spread of sensitivities in average population groups. Epidemiology is the most direct way to estimate human risks. However, because low-dose risks are small and difficult to detect, additional approaches are also needed. In order to study genetic effects, including functional polymorphisms, and epigenetic effects that could modulate radiation risks, epidemiological studies with sufficient statistical power

must be enhanced by combining with molecular characterisations of the individuals and supplemented with laboratory studies aimed at identifying the underlying mechanisms.

Individual Variability

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

Relevance: protection of particular subgroups of population

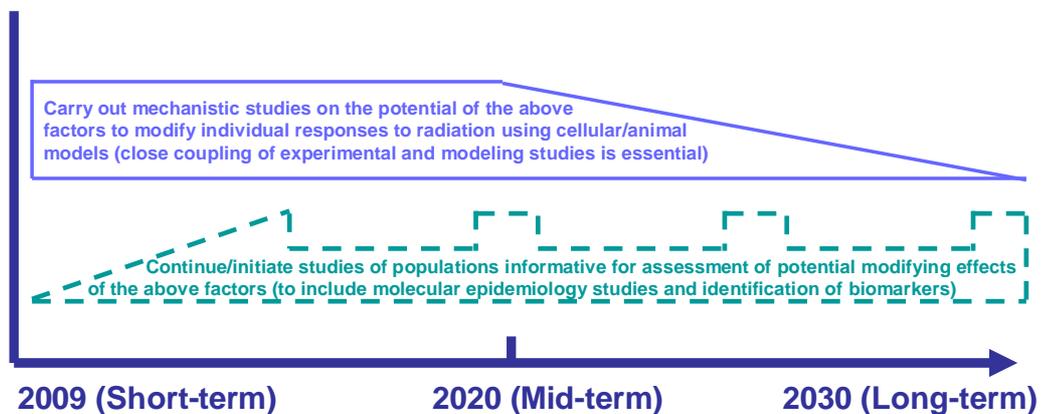


Figure 4: Indicative research directions to address issues of individual variability and genetic susceptibility to cancer.

3.3 Radiation Quality (Type)

A wide variety of radiation types are present in environmental, occupational and medical exposures. It is well established that, on the basis of equal *absorbed dose*, some densely ionising (high-LET) radiations are considerably more effective than sparsely ionising radiations (low-LET, such as gamma-rays) in leading to biological changes, including the induction of cancer. Qualitative and quantitative differences between the biological effects arise mainly from the spatial (and temporal) energy deposition properties of the different radiation types, at the nanometer, micrometer and all higher levels. There is, however, very little human epidemiological information on which to base quantitative judgements on their relative effectiveness for inducing cancer or other effects. What information does exist is not wholly consistent.

In the current radiation protection system, a simplifying assumption is made that the relative effectiveness of each radiation type is represented by a specified radiation weighting factor (w_R), which is used to convert the physical *absorbed dose* in a tissue into the *equivalent dose*. The values of radiation weighting factor have been specified by the ICRP on its judgement, based mainly on laboratory studies of carcinogenesis and life shortening in rodents and selected short-term cellular effects *in vitro*. There are, however, limited epidemiological data that inform on the carcinogenic effects of alpha particles in some tissues. In one instance (i.e. radon and its decay products) the epidemiological data are sufficient to enable regulatory limits to be based directly on exposure concentrations, without the use of weighting factors.

The same radiation weighting factors are, for simplicity, used irrespective of tissue (see also Shape of Dose Response above), dose rate, mode and heterogeneity of exposure with internal emitters (see also Internal Exposure Risk below), individual sensitivities (see also Individual Variability above) or other variables – even when there is scientific evidence to the contrary. Heterogeneity of exposure at the levels of the DNA, cells and tissues are particularly important considerations in this context and the possible influence of non-DNA-targeted effects is a further important complication.

The scope for epidemiology to provide clear answers to these issues (apart from radon and a few other special cases) is limited due to lack of cohorts with sufficient statistical power, exposure uncertainties and the usually mixed nature of the radiation types. Therefore, specific strategies are needed for the assessment of the risk of low-dose, high-LET radiation. However, it is very important to continue and/or initiate well designed epidemiological studies of relevant populations that can provide significant information. Mechanistic understanding is required of the processes involved in radiation carcinogenesis generally, and in non cancer diseases (see also Non-Cancer Effects), and of the impact of radiation quality on key aspects, starting from track structure and physical interactions with various biological “targets”. A critical question is how

radiation quality affects the initial damage (DNA and non-DNA) and its time evolution (considering both faithful repair and mis-repair processes), the intra- and intercellular signalling, and in general non-DNA-targeted effects. A deeper understanding is necessary of the relevance of clustered DNA damage from a single track, in inducing chromosome aberrations, mutations and carcinogenesis. Also the possible role of dose-rate needs to be understood better, together with mixed field effects (including possible synergistic and adaptive phenomena).

Deeper investigation is still needed of the mechanisms that govern the possible different shapes of dose-effect curves and their specific dependence on radiation quality. This need applies both to cancer and to non-cancer risks. A systems biology approach for these radiation effects is advisable, with coordinated experimental, modelling and epidemiological studies to encompass the key processes from the initial radiation tracks that define the radiation quality through to the final health risks. Consideration also needs to be given to how radiation quality influences epigenetic phenomena and the occurrence of genomic instability.

Radiation Quality (Type)

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

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

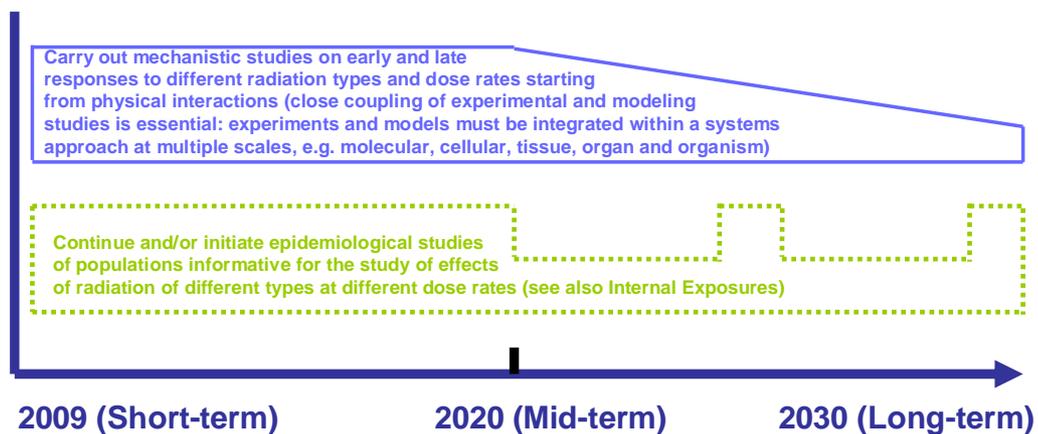


Figure 5: Indicative research directions to address issues of radiation quality (type)

3.4 Internal exposure risks

It is currently assumed for radiation protection that ionising radiation from internal and external sources gives rise to similar effects on tissue. While external irradiation usually subjects tissues to a reasonably uniform irradiation, this is often not the case for internally-deposited radiation sources. For short-ranged emissions, such as alpha particles and Auger electrons⁶, the microscopic location of radionuclides within tissues is particularly important in relation to the cells at risk and the tissue structures. The situation is further complicated by differences in radiation quality (see above). Even at the level of whole tissues or major tissue components, estimation of average doses (or dose coefficients) from intakes of radionuclides requires highly complex biokinetic and dosimetric model calculations. These can be relatively accurate for some well-characterised and practically relevant situations such as in the nuclear power industry, but for others the uncertainty range can extend over orders of magnitude. Comparisons of risks derived from the ICRP dosimetric approach with those obtained from direct epidemiological observations in the few available situations, indicate that the discrepancies can vary from about a factor 2 in some cases to 10 or more in others.

Limits on intakes of internal emitters from the environment are currently regulated on the basis of their dose coefficients, calculated according to the ICRP methodology for effective dose. No explicit account is taken of questions on the appropriateness of the use of standard w_R and w_T values for these inhomogeneous internal emitters. Generally similar methods are used for the dosimetry of internal emitters in medical practice, which includes an increasing variety of radiopharmaceutical compounds for specific targeting in tissues; particularly in this case, there is insufficient awareness of the large uncertainties in some of the dose coefficients utilised.

Epidemiological studies of particular groups with reliable exposure/dosimetric information could provide further quantification of effects (both cancer and non-cancer) from internally-deposited radionuclides. These could include patients from diagnostic investigations and therapeutic treatments (e.g. iodine-131 and radionuclides labelled onto monoclonal antibodies), as well as well-characterised cohorts of workers and the public with substantial exposures to internal emitters incurred, in particular, during the early stages of the development of nuclear weapons (e.g. tritium and nuclides of strontium, caesium, uranium, plutonium). Experimental studies, particularly using in vivo animal models, are required to improve understanding of the mechanisms of health effects from heterogeneously deposited radionuclides in the body

⁶ Low-energy electrons emitted from atoms after some types of radioactive decay,

and to improve biokinetic and dosimetric models for their assessment.

Internal Exposure

Objective: To better quantify the risk estimates from internal exposure

Relevance: robustness of systems of protection for intake of radioactive materials

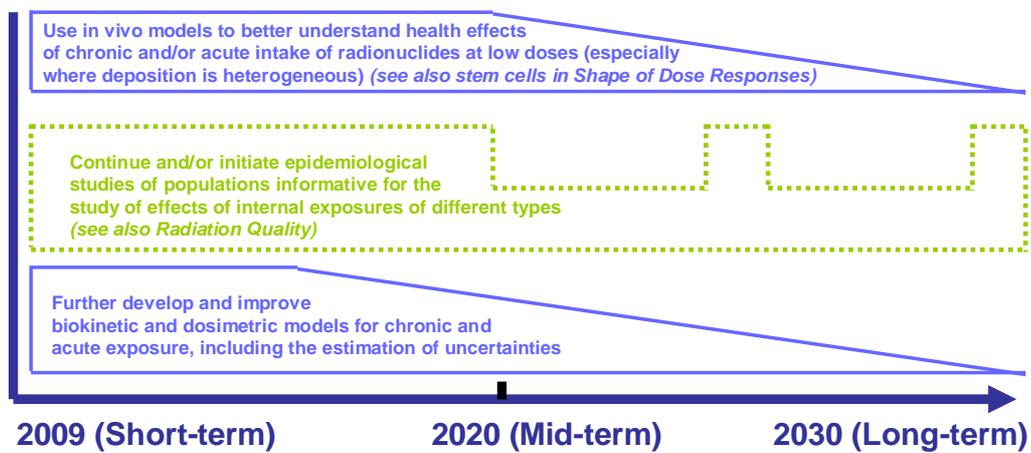


Figure 6: Indicative research directions to address issues of internal exposure risks.

3.5 Non-cancer effects

The current system of radiation protection is based primarily on protection against the risk of cancer from low doses of radiation. A small additional allowance is made for possible hereditary detriment. It is well established that moderate to high doses of radiation can increase the occurrence also of a variety of non-cancer effects in exposed individuals, but for radiation protection purposes it has generally been assumed that there is a threshold of dose below which no significant non-cancer effects (apart from hereditary disease) arise. Recent studies have, however, called into question this assumption, particularly in respect of circulatory diseases (i.e. heart disease and strokes), effects on cognitive function following radiation exposure in infancy and occurrence of opacities in the lens of the eye (cataract) (UNSCEAR 2008a). In each case epidemiological studies have suggested the possibility that these effects may arise after exposure to much lower doses than previously thought and possibly within the range of low doses encountered in the use of radiation in industry and medicine. The mechanisms behind these non-cancer effects are not well understood and they need to be investigated, including the potential roles of non-targeted effects (UNSCEAR 2008b).

For their recent recommendations, the ICRP judged that the data available for these non-cancer diseases do not allow for their inclusion in the estimation of detriment following low radiation doses (ICRP 2008). If a linear no-threshold response were to apply (or be assumed to apply) to circulatory disease, however, then on the basis of the present epidemiology of the A-bomb survivors this risk factor may be of sufficient magnitude to require explicit incorporation into the radiation protection system, on a comparable basis to that for cancer. This could imply changes to dose limits and constraints, but also structural changes to tissue and radiation weighting factors and other aspects. Exposures in infancy and possible effects on the developing brain need further investigation, particularly in the context of medical exposures.

Well-controlled epidemiological approaches will continue to be essential in addressing each of these areas. However, new more-suitable animal models also need to be developed for mechanistic studies of circulatory effects at low doses and for effects on learning and cognitive functions. Better understanding is also needed of the extent to which some biological modifications observed in animals exposed chronically to low levels of radionuclide contamination (eg, uranium, caesium nuclides) could lead to clinical effects.

Although judgements on heritable risks following gonadal dose are relatively well developed, it remains important to keep the topic under review and to retain scientific competence to undertake further studies if new issues are revealed.

Non-Cancer Effects

Objective: To better understand the mechanisms of and quantify the risks for non-cancer health effects (in particular lens opacities, cardio- and cerebro-vascular diseases, impaired cognitive function) resulting from exposure to low and protracted doses

Relevance: contribution of non-cancer diseases to radiation risk, and its implications for radiation protection systems

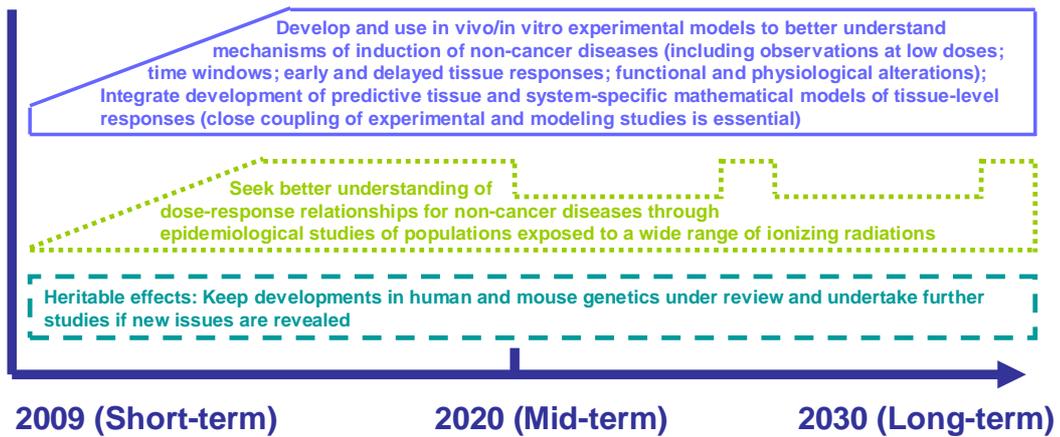


Figure 7: Indicative research directions to address issues on risks from non-cancer effects

4. Proposed European research strategy

A broad consensus exists within the HLEG on the policy issues to be addressed and the directions of future research that currently offer the best prospects for resolving these issues (see Chapter 3). This consensus provides a sound conceptual basis on which to proceed but, alone, it is not sufficient. It needs to be complemented by more strategic and practical considerations, in particular how to translate the concept into practice in the light of a number of important impediments to its realisation. Many difficulties lie ahead, not least because of the complexity of the issues, of the large uncertainties that need to be overcome, and of the very limited convergence so far achieved between national research strategies and programmes, notwithstanding the efforts in this direction of the European Research Framework Programmes. The establishment of the following two elements will be critical in terms of making tangible progress:

- A **trans-national structure** capable of ensuring appropriate governance of research in this field, in the pursuit of a long term shared vision:

- bringing together the programmes of the various funding bodies and research organisations into a coherent and optimized ensemble, thus ensuring long term research funding in accordance with an agreed strategic research agenda (SRA);
- interfacing with the many stakeholders, in particular regulatory bodies and the broader scientific community;
- overseeing investments in key infrastructures, as well as knowledge management, training and education;
- ensuring the consistency of research methodologies.

For this purpose, it is proposed to take an initiative, which we have called the **Multidisciplinary European Low Dose Initiative (“MELODI”)**. Subject to further consultations, such a concept could take the shape of a new platform, with a structure similar to those proposed in the Commission’s research policies⁷.

- A **scientific strategy** in order to structure the research programmes in the most effective way, taking into account available resources. This strategy would constitute the backbone of the SRA, progressively bringing together otherwise separate actors, research programmes, and scientific communities, facilitating linkage where needed between disciplines, and facilitating investment into areas of high risk research. Much of the research will be of an applied nature and clearly targeted towards resolving the key policy issues set out in the report. More basic research will, however, be an essential component of any low dose risk programme given the nature of the challenges to be faced and the timescales required for the resolution of some of them, i.e., in some areas knowledge accumulation would be the only way to proceed at present. This type

⁷ Consideration could also be given to a Joint Programming Initiative.

of research would to some extent include high-risk/high-gain (potential) research in order to test new ideas which might be at the margin of the current state of knowledge.

4.1 The “MELODI” initiative

“MELODI” would sustainably associate funding bodies and research organisations in Europe with significant programmes in low dose risk research with the aim to integrate future research. The representatives of the six national funding bodies participating in the HLEG are committed to launch an initiative, such as “MELODI”, subject to further consultation. Appropriate arrangements will be made within MELODI to involve any research organisation that is willing and able to contribute to its goals. These would include those who can contribute to specific areas of research and especially those who can bring other pertinent perspectives and expertise to the low dose field. “MELODI” would actively engage with all potential contributors from the wider scientific community and devise mechanisms for their inclusion. MELODI would be developed in a step by step process. Initially, MELODI would focus on the means to achieve a fully integrated and sustainable approach to low dose risk research in Europe and of the related governance structure. In addition, a more detailed road map would be developed to address the priorities identified in the SRA to provide a framework for better direction and integration of future research.

An example of a possible governance structure is illustrated in Figure 8, taking after the model of an already existing Platform. The main participants in the platform would be national funding bodies and research organisations (i.e., national institutes, universities, etc) with significant low dose risk research activities. Effective links would also need to be established with key stakeholders, in particular regulatory bodies and users of radiation and radioactive material in industry and medicine who will be the ultimate clients for this research.

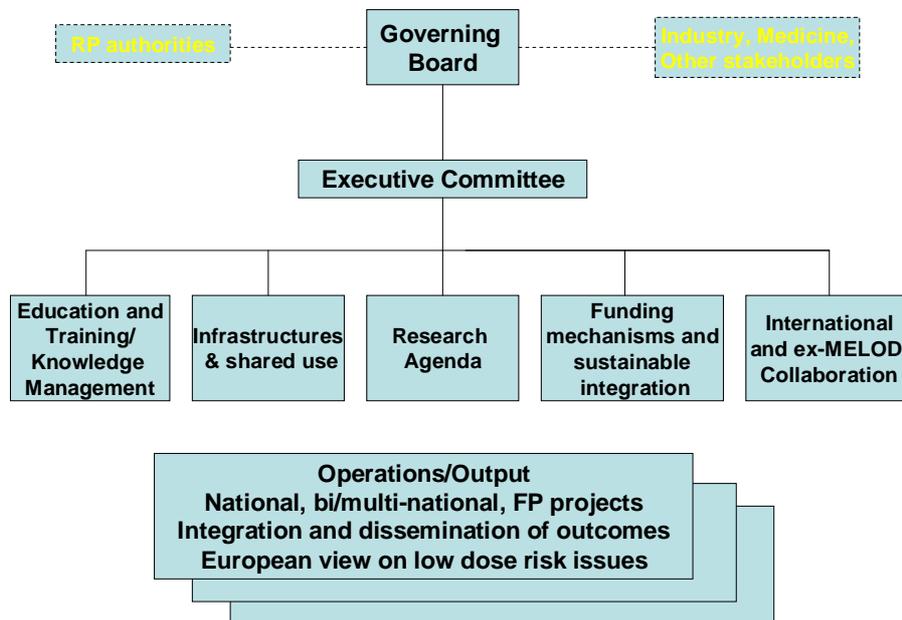


Figure 8: Possible governance structure for “MELODI”

4.1.1 The need for a structure such as “MELODI”

Many of the larger Members States of the EU have significant research activities on Low Dose Risk Research and a few have dedicated programmes. Up to now there has been little effort or commitment to integrate these national activities/programmes. “MELODI” would better integrate these programmes and activities and make better use of limited resources and exploit synergies for future work. Given the nature, scale and importance of the challenges to be addressed in low dose risk research and the competition for scarce resources, effective integrated collaboration at a European, if not international level, is long overdue.

Current understanding and quantification of risk at low doses is limited by the uncertainties of the available scientific methods and by a lack of understanding of the basic biological mechanisms. This situation can only be improved by a long term commitment of all scientific disciplines involved, a shared view on the roles of these disciplines within a research strategy and a common vision among the research community.

Integration of low dose risk research at the European level would strengthen the European position in further developing radiation protection standards. This could for example be achieved by major periodic reviews of the knowledge on risks of radiation at low doses – based on epidemiological and mechanistic studies and

the development of scientific views on major emerging scientific or policy issues related to low dose risk.

4.1.2 Interaction with stakeholders

The very nature of the policy questions to be answered by low dose risk research and the complexity of the scientific issues to be addressed requires a continuous dialogue with all stakeholders involved, e.g. the society and the public authorities responsible for protection as well as those using radioactive substances or ionising radiation in industry or medicine. One of the aims of such a dialogue is to increase awareness of the current knowledge of low dose risks with the ultimate goal of further developing institutional trust and a safety culture at all levels of operation. One aspect of such a dialogue is to provide feedback on the practical needs and questions arising during the application of ionising radiation in everyday life to researchers, and vice-versa. Another potentially more important consideration is to raise awareness among users and producers of radioactive material and/or ionising radiation in industry and medicine of the need for, and importance of, low dose risk research and for them to make a more significant contribution to its funding.

4.1.3 Interaction with the broader scientific and health community

A comprehensive and systematic understanding of the biological processes that lead to cancer, and other relevant diseases, and also the identification and quantification of the particular roles played by radiation in the processes can only be achieved within the context of the broad advances in biological and medical knowledge through basic and applied research. This requires an intensive scientific exchange with disciplines outside the classical areas of radiobiology, nuclear physics, radioecology, and (molecular) epidemiology, such as with cancer research, genetics and biomedical research more generally. Current understanding and quantification of risk at low doses can only be improved by a long term commitment of all scientific disciplines involved, a shared view on the roles of these disciplines within a research strategy and a common vision among the research community at national and European level and beyond. "MELODI" would facilitate the establishment of effective, timely and sustainable links with the broader biological research communities, in particular to take advantage of emerging developments elsewhere.

4.1.4 Research infrastructures

Research infrastructures are essential for low dose risk research. The types of facilities required are diverse. They include laboratory infrastructures such as large accelerator facilities, dedicated animal facilities, databases or tissue banks, and arrangements for long term access to trans-national cohorts for epidemiological studies and for their maintenance.

One of the early priorities of “MELODI” would be to establish an inventory of European infrastructures and future needs in each of the above areas in order to achieve the SRA goals.

Radiation facilities

Existing infrastructures will have to be reviewed and, where necessary, improved. Sufficient human resources must be allocated. Very few facilities offer the full range of equipment required for radiobiology experiments; modernization and maintenance need to be evaluated for those facilities involved in low dose risk research projects.

Some facilities, although unique in Europe, are “pseudo-dormant” such as Razès (radon Inhalation) and are at high risk of being dismantled in the coming years. It is necessary to identify the issues that need to be addressed in respect of provision (including dosimetry and radiobiological/animal facilities), modernization, maintenance, sustainability (medium and long term) and accessibility of facilities.

The need for new infrastructures required for European low dose research (such as for chronic low dose rate exposure and microbeams) needs to be assessed along with how these infrastructures might be provided and used jointly by overseas partners (Chalk River, Canada; IES, Japan) or how these would have to be implemented in Europe, to maximise the future impact of research in this field.

Data bases and tissue banks

Irradiation experiments generate large sets of biological samples and data that are gathered in tissue banks and databases. Indeed, many of them exist although they are rather dispersed, heterogeneous and frequently dormant. Optimal utilisation of the banks and access to data and material would need a survey of what currently exists, characterisation of the quality of the samples, validation of their storage conditions and accessibility to European scientists. Large networking effort will permit the identification of the “missing links” and maximisation of the potential usefulness of European databases and samples banks.

Platforms for analysis

Many infrastructures are required for analysis such as platforms of high-throughput cell biology, genotyping and genetics, gene expression, animal phenotyping, microscopy and imaging of living cells and organisms, proteomics and computing centres. Limiting factors include their proximity to radiation facilities, their accessibility and their time response.

Trans-national cohorts

Over recent decades, much effort has been invested in the constitution of (often) trans-national epidemiological cohorts of populations (uranium miners, nuclear

workers, medically exposed groups, residential radon exposures, etc.) potentially informative for low dose risk research. Additional cohorts are also being identified (patients with substantial paediatric diagnostic exposures) and collaborative international studies are being carried out on other non-EU cohorts of particular interest for low dose rate research (e.g. Mayak workers, Techa river cohort, Chernobyl liquidators).

Having invested in the constitution, dose assessment and follow-up of these cohorts, it is essential to maximise their informativeness and therefore the return on these investments. In this context a survey of existing cohorts should be conducted, the information collected and documented, their informativeness evaluated, and data storage conditions and availability to European researchers be assessed. In addition mechanisms need to be set-up to ensure their continued availability for research, including database management and periodic updates of follow-up in the foreseeable future. Where necessary, harmonisation of the collected data and of the methods for collecting them needs to be strengthened, so as to improve the statistical power of epidemiological studies by interlinking them more easily.

4.1.5 Education and training

Many European member states have lost key competences and are no longer capable of independently retaining their current research activities in radiation sciences, with implications for effectively fulfilling operational and policy needs and obligations.

Programmes aiming at knowledge management across generations have to be designed in a way that they achieve sustainable results. In this respect several aspects have to be considered. One is that the underlying scientific programmes have to address questions that are attractive to both young scientists and faculties of universities or to the management of research organizations. In the long term such programmes cannot be successful unless they do provide job opportunities to young scientists. Given the current situation, sustainability of such programmes can only be achieved by a long-term commitment of funding bodies.

“MELODI” would respond effectively to these needs and aim at establishing an integrated approach to education and training (E&T) in radiation research in Europe. Particular consideration will be given to the better integration of research and teaching at Universities and at non-university research organisations. Existing elements of ongoing E&T activities such as the European MSc course should be strengthened, making it Bologna⁸ compliant. International networking of education and training programmes would be beneficial. It would not only ease

⁸ The Bologna Process is the process of creating the European Higher Education Area (EHEA) and is based on cooperation between ministries, higher education institutions, students and staff from 46 countries, with the participation of international organisations.

the burden of researchers engaged in education and training but would also broaden the scientific background of the training programmes and contribute to increasing the mobility of the trainees. Graduate school(s) of radiation sciences would to some degree alleviate the lack of sufficient geographically situated experts. One option would be a virtual European school, with an exchange of students between host institutes; the alternative would be a centralized European Graduate School with input from seconded experts.

4.1.6 SRA funding and operational management

Initially the funding and operational management of the activities of "MELODI" would be based on the existing arrangements, resources and responsibilities of the partners of "MELODI". Following the establishment of "MELODI", a critical inventory of ongoing and planned low dose research projects including the identification of potential synergies for deeper collaboration/ integration would be established. Key elements of such an assessment are the identification of the inventory of existing infrastructures and of education and training as well as future needs. Based on such an inventory, a strategy for better integrating the research, infrastructures and other activities would be developed. This would include elements of shared responsibilities for setting research priorities at a European level as well as mechanisms for shared funding of short, medium and long term projects. In addition, mechanisms would need to be established for the collaboration/interaction between the research programme of "MELODI" and non-European programmes and European organisations that are not members of the initiative:

- Regular, i.e., yearly review of the structural and planning arrangements of the initiative, to adjust to emerging needs;
- Strategies for education and training and knowledge management as well as for infrastructures and their shared use;
- Coordination of national/multinational calls for research projects best able to address/resolve the policy issues.

Performance indicators would be established at the outset to measure progress in relation to sustainable integration, which would be a *sine qua non* for "MELODI".

Budgetary questions have only briefly been addressed by the HLEG. The indicative cost, over a 20 year period, of an integrated European low dose research programme with good prospects for resolving the identified policy issues is judged to be of the order of one billion Euro.

4.2 Scientific strategy

It is unlikely that research aiming at the better understanding of the basic mechanisms of radiation risk and quantification of health risks at low doses will

be successful unless the main funding and research organizations commit themselves to fund and implement well-structured programmes over an extended period of time. A shared long term vision, not only of objectives but also of scientific strategy, is therefore needed. Four key concepts have been identified that should be incorporated into the scientific strategy for a multi-disciplinary low dose initiative to become viable:

- **Holistic approach:** Because of the many interrelations which exist between the various policy issues or research objectives, future research programmes should adopt a holistic approach. Seeking the active collaboration of many different disciplines and actively reaching out to the wider community of advanced biology research will be critical. In particular there is a need to move away from or rise above the more traditional “organ pipe” structure where specialists of a given area are, *de facto*, in charge of defining their own research objectives and related actions.
- **Periodic review of objectives:** Given the complexity of the policy issues to be resolved, the SRA will need to span a relatively long period, say twenty years. During this time, adjustments to the research strategy will need to be kept under continuous review and adjustments made at intervals. It is essential that such reviews provide adequate information to evaluate the ongoing contribution of the research to the robustness of the radiation protection systems (i.e., the key policy issues). This should be done in the context of the evolving needs of society and the end users of research results and of the broader advances in biomedical science.
- **Dissemination of research outcomes and interaction with users:** A considered strategy and appropriate mechanisms would need to be put in place to ensure effective dialogue with key stakeholders, in particular regulatory bodies and users of radiation and radioactive material in industry and medicine. As end users of the research outcomes, their needs will continue to be influential in the scope and content of the programme.
- **Ensuring that key prerequisites are met:** Beyond the availability of adequate infrastructures, funding, and research personnel, the SRA will identify some “barriers” or “impediments” that must be overcome before further progress can be made. The programming and funding system to be set up under “MELODI” would need to be conceived and implemented so as to ensure that, where necessary, resources will be directed to “barrier solving” before “barrier dependant” programmes are initiated.

4.2.1 Holistic approach

The SRA will aim to overcome one of the major impediments to making effective progress in ongoing and recent research in this area, i.e., the failure to fully integrate the many disciplines involved within a coherent vision and programme, in particular between the experimental and theoretical scientific communities. The SRA will engineer programmes which bring together mechanistic studies, modelling (at multi scale levels whenever appropriate), epidemiology, dosimetry, etc. The programmes will take on board the most recent paradigms developed in radiobiology (such as non-targeted effects), and in fundamental biology (systems biology, carcinogenesis), and solicit the most recent investigative techniques (tracer biology, track analysis, microdosimetry). This will require, *inter alia*, the development of closer links between the radiobiology and epidemiology communities and other disciplines involved in fundamental biology.

Figure 9 provides a schematic representation of the suggested ambition of “MELODI” to accelerate the understanding and better quantification of low dose risks (or reduction in their uncertainties) over a 20 year period.

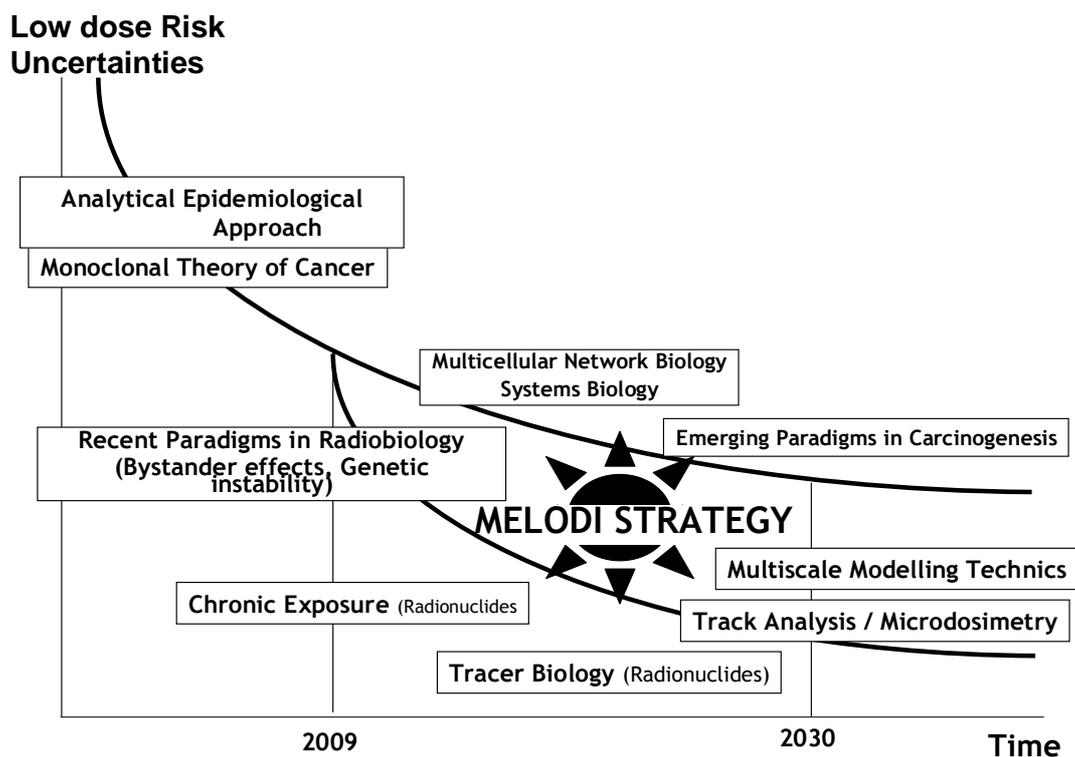


Figure 9: A new holistic approach to accelerate over 20 years the reduction of uncertainties in the understanding of low dose risks

4. 2. 2 Periodic review of objectives and dissemination of outcomes

In addition to the continuous review that will be put in place to ensure the SRA remains fully responsive in addressing policy issues, emerging needs and scientific progress, periodic review and dissemination meetings would be organized under the framework of “MELODI”. Fully open to all the concerned R&D community, the radiation protection community and to other stakeholders, these meetings should result in an assessment of the progress in implementing the SRA, and of the perspective for strengthening, at the operational and policy levels, the radiation protection system. Such strengthening could result either from validation of existing radiation protection policy or practice, thereby reinforcing the societal robustness of the system, or from identifying the need or desirability for change in order to reflect new scientific findings. Such a process would enhance Europe's position in the further development of radiation protection policy and practice internationally.

4.2.3 Ensuring that key prerequisites are met

The proposed holistic approach to future low dose risk R&D will only be successful if there is a full and shared commitment to multidisciplinary research carried out in an operationally effective manner. This can be best illustrated through three examples:

- Advanced multiscale in vitro and animal models reflecting radiation dose/effect at low doses and low dose rates (chronic exposure) should be developed in such a way that they can relate to the most advanced research on the phenomena of induction of cancer and non cancer diseases potentially associated to radiation exposure. This will require the association of dosimetrists and radiobiologists with research teams involved in fundamental biology.
- Integrated studies, associating theoretical and experimental modelling should become a preferred approach. This will also lead to closer cooperation between research teams working in the different disciplines, including epidemiologists. It requires, however, a change from current practice in defining the R&D projects, as illustrated in the initial SRA outline.
- Systematic efforts should be made to increase the statistical power of epidemiological information. This objective may be pursued through the further integration of existing cohorts into multinational well harmonized instruments which will be able to reliably capture information needed to feed the above mentioned models. Thus, while cohorts will continue *per se* to offer valuable information, particularly for the radiation protection community, epidemiology projects should also be designed to contribute directly to research programmes of wider scope.

4.2.4 SRA roadmap outline

It is obviously premature, in the framework of the HLEG, to establish a fully blown definitive SRA for the next 20 years. However, in order for all stakeholders to appreciate the potential extent of “MELODI”, figures 3 to 7 in Chapter 3 have been shaped in such a way as to give an initial representation of the research directions that are expected to be most productive over the short, medium and long term, and to indicate the possible dynamics of such programmes over time, subject to further consultations.

An important initial effort would be needed within “MELODI” in order to quantify the financial resources needed in the different areas over 20 years. It would be necessary to take into account the likely duration of the programmes, and the sizes of the research teams. The costs of modernizing and operating key infrastructures would have also to be included. Detailed programming would have to be established once the overall SRA approach has been validated, and this would in turn lead to a more precise assessment of funding needs over time. These programmes would be conceived so as to embody the “holistic approach”, to identify in each area the key deliverables to be expected, for the first 5 year period, and to allocate funding adequately.

The implementation of such a coherent process at a European level, in the framework of a sustainable structure such as “MELODI”, would undoubtedly consolidate European research at the best level of international excellence, making this challenging and difficult field of low dose risks from ionising radiation an attractive proposition for researchers worldwide.

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