# Response on consultation of the draft report of HLEG on European Low Dose Risk research

November 29, 2008

This response represents the combined views of the research teams at **Institute of cellular and molecular radiation biology (CEA / Life Science Division), France**.

## A - General comments

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

The key question about this grant proposal is the appropriate definition of low doses. First, what is the scientific background that defines low doses. Are low doses the doses that define the frontiers between a measurable biological effect and nothing? If so, it will be very complicated to define these doses as they will depend on the tissue or the animal studied. The first issue is thus to develop a very large epidemiological study that will linked doses received to possible pathological effects. If and only if these studies indicate that low doses are associated to pathological effects, then biological studied aimed at understanding the molecular and cellular mechanisms that underlie these effects can start.

The characterization of tissue sensitivity and individual variability will also be helped by murine models and primary cells that might be an alternative tool to simulate an epidemiological study and to definite the potent effects of low doses. One of the first steps in such study is the construction of a bibliographic database that will collect data published on low doses effects on whole organism (mice, rat, etc...) and on primary cell cultures in order to define any possible phenotypic alterations. This database will include all the elements on the exposition, the genetic background of the animal model used and all the experimental background of the study and will generate few primary questions that are lacking in the document.

Finally, another important issue is the genetic background used to study the effects of low doses. Mutations or polymorphisms that affect the expression of genes involved in the cellular responses to exogenous and/or endogenous stresses might be directly associated to low doses responses and thus studies that aimed at the definition of the genetics events that regulate normal cellular homeostasis are of highest importance in this proposal.

Contamination with low doses of radioactive materials is largely absent from this proposal and the word radiotoxicology is not mentioned even though the problem of internal contamination is explicitly stated. Furthermore, validation of biokinetics models that evaluate the

biological risk after contamination is not clearly stated in this proposal. This is an important gap that needs to be filled. Contamination with radioactive materials is linked to pollution and might become a real societal issue with the development of civil nuclear energy and the use of injected radioactive materials in medicine. Finally, contamination with low doses results in biological effects that cannot be evidenced with low doses irradiation.

## 3. State of science and main research challenges

### About non carcinogenic effects

Potential consequences of low doses on human fertility are not mentioned, whereas the incidence of low fertility and sterility is increasing. Low doses exposition may represent a risk factor, as well as low doses combined to chemical. It will be interesting to analyze consequences of low doses combined with the chemicals abnormally present in the blood of the few European deputies tested 2 years ago! Finally, transgenerational effects linked to epigenetic reprogrammation of the germinal cells and caused by exposure of pregnant mice to chemicals should be studied in the case of irradiation or combined action of irradiation and chemical exposure.

## 4. Proposed European research strategy

### About MELODI initiative

MELODI initiative and the HLEG report that is now proposed for discussion to the scientific community have to be supported if and only if they maintain European and national funding for radiobiology. The main concern however is on the implementation of the project. A coordination of the projects at the European level is an obvious requirement to avoid redundancy. However without specific funding for hiring new researchers it will be hard to attract into the field already established groups, at least in the basic science aspects. As proposed, MELODI has a risk of becoming yet another consulting organism, the real impact of it depending on the political and economic situation of the different countries. For example, it is highly unlikely that in the present context, in particular in France, specific funding will be allowed without diminishing other research programmes.

**About Interaction with the broader scientific and health community**

Apart from all the restrictions previously indicated and going through the report, it does indeed cover the main issues related to research in radiobiology. The need of epidemiological studies is obvious but as stated almost in every chapter, basic research on the mechanistic aspects is also required. However, there are concerns on relative weights of epidemiology and mechanistic aspects indicated in the draft report. HLEG document proposes to mainly develop epidemiological and mathematical modelling studies on low dose risk. Important items like “radiation and stem cells” are only explicitly mentioned in figure 3. Although the epidemiological approach is of highest importance in the field of low doses, experimental/fundamental researches that will get insights into the cellular and molecular mechanisms activated after irradiation (by high and low doses) have to be funded as they will define a network of cellular and molecular responses to stress that can be use to define phenotypes useful for epidemiology.

# B - Added comments

## Page 6 : 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.
Cancer patients are exposed to low doses (few tens of mGy) during imaging for diagnostic and treatment-planning processes (IMRT technology) purpose before exposure to a large dose (for instance, a fractionated exposure of 50Gy with daily fraction of 2Gy in the case of breast cancer treatment). The possible consequence of a synergistic or an adaptive effect needs to be taken into account.
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 (UNSCEAR[1]) 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 scientific knowledge and techniques.

[1] United Nations Scientific Committee on Effects of Atomic Radiation

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

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-LET[5] particles of more complex DNA lesions that are more prone to DNA misrepair 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 subregions 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).
For many tissues, the key features of cell biology, e.g. target cells identity and location, are not well understood. The possible location of targets with characteristics of stem cells or progenitors is a major factor that must be taken into account to characterize the carcinogenic risk after radiation exposure.
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)

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must be enhanced by combining with molecular characterisations of the individuals and supplemented with laboratory studies aimed at identifying the underlying mechanisms.
It is necessary to develop studies from single cell to new 3D models for human cells. Furthermore, due to the discrepancy between animal and human responses, 3D human models are more relevant to human carcinogenesis than animal models. New human models of carcinogenesis are now available that should be relevant to study low doses late effects.

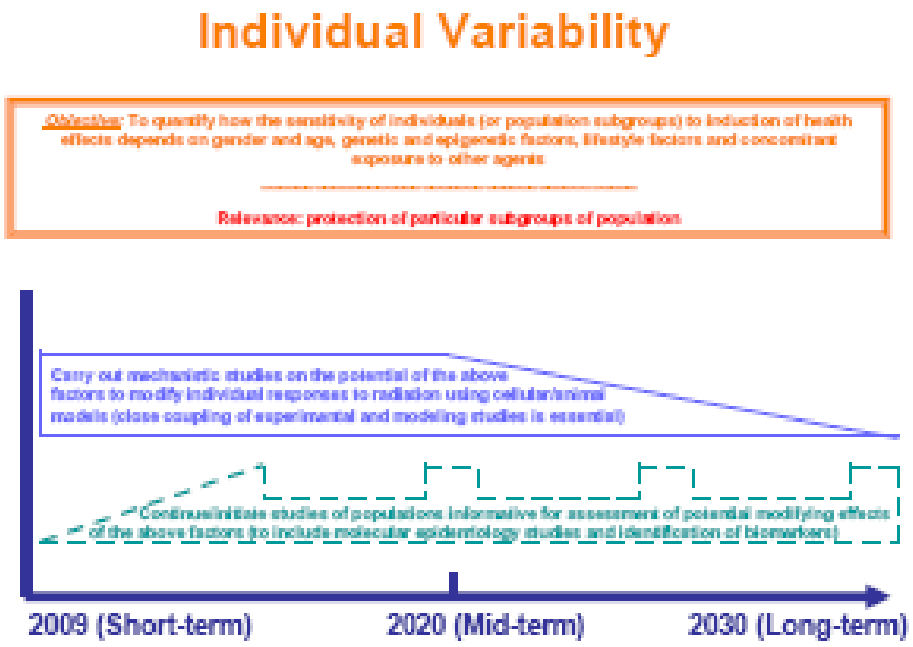


**Figure 4:** Indicative research directions to address issues of individual variability and genetic susceptibility to cancer.

Individual radiosensitivity can also rely on the ability to transmit radiation-induced damage to cell progeny. The transmission of radiation-induced damage could be age-dependent.

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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.
Further insights have to include the interplay between "natural" aging of cell, tissue, organism and radiation induced damage. 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 the transmission of radiation-induced damage to the progeny of irradiated or bystander affected cell including epigenetic phenomena and ~~the occurrence of~~ genomic instability.

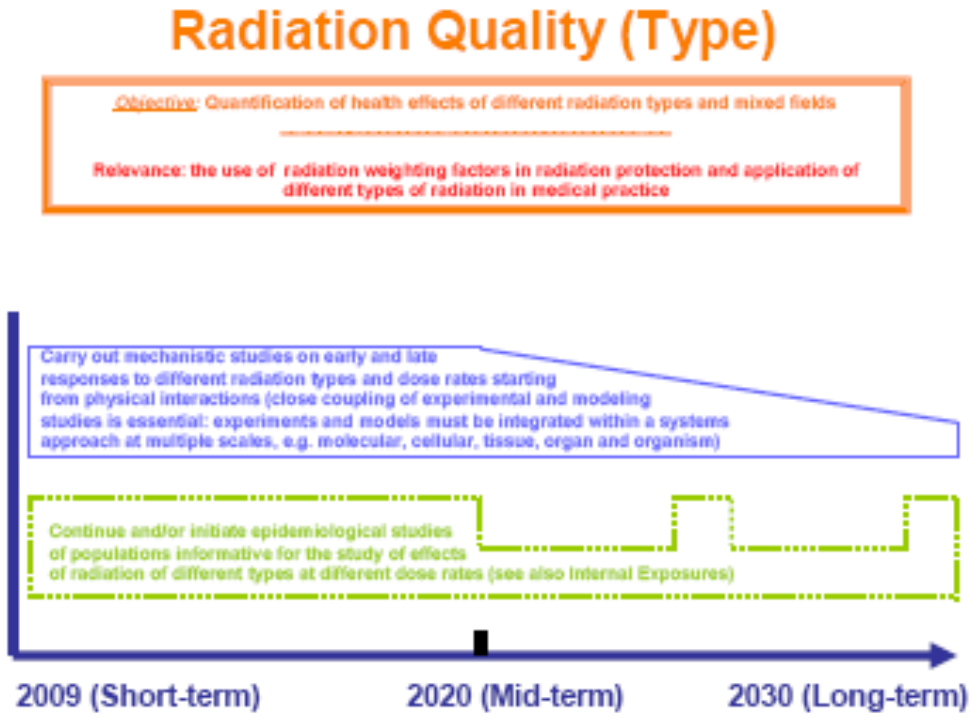


**Figure 5:** Indicative research directions to address issues of radiation quality (type)

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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 highthroughput cell biology, genotyping and genetics, gene expression, animal phenotyping, microscopy and imaging of living cells and organisms, proteomics and computing centres, facilities for high resolution structure analysis and multidimensional imaging such as synchrotrons, ion microbeams, advanced spectroscopic techniques. 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. Attractiveness of the field might be increased and a multistep approach has to be implemented from Summer schools to master, PhD and post-doctoral European programmes. 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 Bologna[8] 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.

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### 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 is misleading and potentially counterproductive. On the one hand it is quite vague by putting an axis covering more than 20 years combined with topics way too specific as "Monoclonal theory of cancer". A background of basic research in different subjects should be maintained all along with, at different times, specific questions about more applied aspects, in particular technical ones like dosimetry, toxicology of radionuclides (tissue distribution, half life etc..) modelling and of course cohort building and the subsequent epidemiological studies among others.

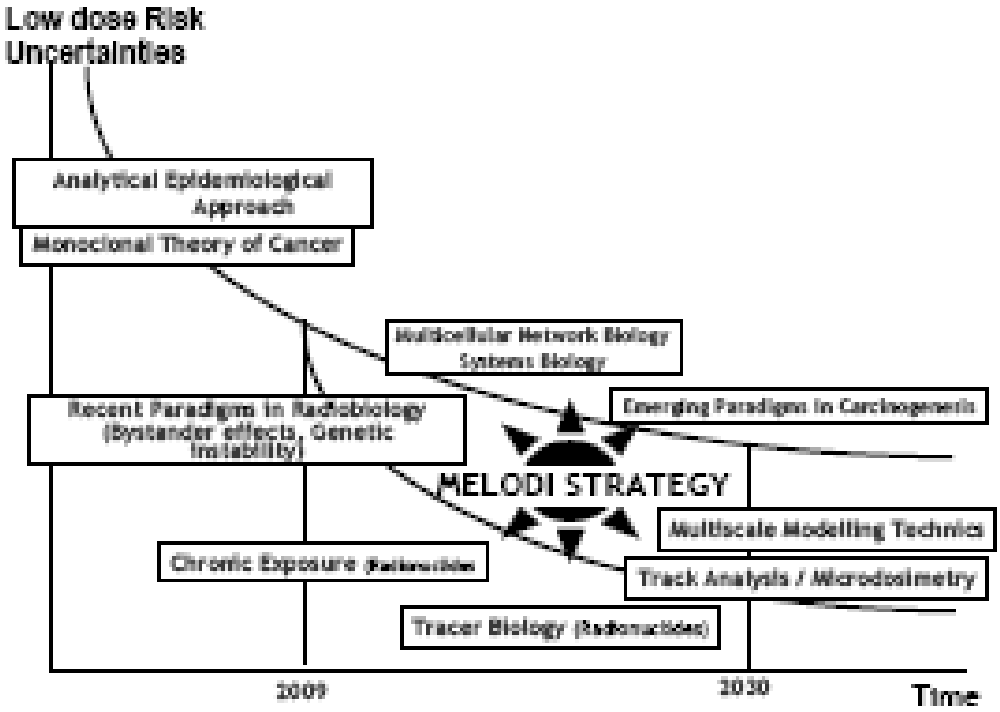


**Figure 9:** A new holistic approach to accelerate over 20 years the reduction of uncertainties in the understanding of low dose risks