MELUSYN response to
High Level Expert Group on European Low Dose Risk Research
Draft report (HLEG document)

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On behalf of the MELUSYN network, France

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Founded in 2005, MELUSYN network federates more than one hundred French experts coming from physical, chemical, biological, medical institutes and private companies around two innovative fields: synchrotron radiation based biomedical imaging and spatio-temporal radiation biology. This scientific network favours forum for multidisciplinary discussions and the development of trans-disciplinary research projects. MELUSYN network organizes regularly working groups, thematic workshops and international conferences (ESF-EMBO research conference in 2009, www.esf.org/conferences/09287*) on innovative advances for biomedical applications (new emerging concepts for radiation biology and radiation therapies, micro-imaging for medical diagnosis).*

A. General comments

- MELUSYN network highly appreciates the initiative of the HLEG, and supports its generic conclusions on the interest to provide a methodology for enhancing and coordinating the European research in radiation biology.

- MELYSUN welcomes the initiative named MELODI and supports an efficient timely structure for multi-disciplinary synergies, including physical, chemical, biological and medical sciences.

- Risk-concern may be different considering on one hand exposure from human activities using or generating ionising radiation, and on the other hand medical exposure. For public exposure and occupational exposure, limitation of dose received is regulated, and ensures that the level of risk is acceptable. That's why general rules, like LNT, have been developed.
As far as medical exposure is concerned, the value considered by the physician is the risk/benefit ratio for the health of the patient. No limitation of doses can be applied. Each patient has his own history, genetic background ... and has to be treated as an individual. Hence the protection of the public and the worker is of the responsibility of the regulator whilst the protection of the patient is mainly the responsibility of medical practitioners.

- In order to go further into the discussion, members of MELUSYN have provided some comments, listed below. MELUSYN wishes to highlight *two key issues*, which will be of the utmost importance in the future: *the spatio-temporal considerations in the study of ionizing radiation effects, and the necessity to carry out experiments on human cells (from single cells to 3D tissue), particularly in the low dose range, as animal models are often irrelevant. In this context, some methods based upon in situ microdialysis, combining nanodosimetry systems and biomarkers, allows monitoring of physiopathological processes at the cellular level in vivo.*

Moreover, MELUSYN proposes to modify the HLEG document, so that a better balance between epidemiological studies and experimental/fundamental studies appears in the proposal. From a general point of view, MELUSYN agrees more with the figure contents (Fig.3 to 7) than with the text of the document.

B. Specific comments

- In the **introduction** (**page 5 § 1**), we suggest adding the following sentence, stressing on forthcoming public health issues: “Emerging public health issues, involving large population, include medical diagnosis (For example, in France in 2002, **about 60** millions of radiodiagnostic exams have been performed), imaging tools, radon, security screening…”

- (**page 5 § 3**) We suggest adding the following sentence: “The way by which the dose is delivered in time and space is a key issue, and has to be addressed in the future research programs, integrating approaches of the physical and chemical processes occurring after an irradiation as well as the new concepts to be developed (for instance, repetitive medical imaging, low doses delivered in high dose peaks for workers near advance pulsed radiation sources - estimated dose peak).”

- Regarding the **definition of radiation quality** (see the **footnote page 6**), a clarification seems useful for continuous and pulsed sources: indeed, a radiation energy represents a physical parameter, not a property. Moreover, an ionization density triggered by a radiation-matter interaction is not a property but a consequence of physico-chemical processes.

Moreover, the 1D parameter LET seems more and more inadequate to define the radiation quality of specific radiation sources. Regarding numerous new pulsed radiation sources such as synchrotrons, table-top laser systems, particle accelerators (X or gamma rays, relativistic particles and ions), new concepts would include time-dependent energetic fluence profile, peak dose delivery, energy radial distribution functions, spatio-temporal dose rate profiles. These parameters are essential to clearly understand the early consequences of radiation-living matter interactions at the nanometer, micrometer scales (temporal and spatial approaches) and to estimate risks at more integrated levels.

- In **figure 2** (**page 10**), numerical values should be given on the X, Y axis (for instance, is it 100 mSv for the lowest experimental point?)

- This figure reports an inadequate unified approach which mixes risk management (extrapolation of epidemiological data for the LNT at low doses) and experimental results from biology (hormesis, hypersensitivity).

- The wording “above background” on the X axis may be misinterpreted (we suggest to delete it): a background dose would not be responsible for a risk. Furthermore, in epidemiological studies, a dosimeter used to estimate the dose may include part of the background radiation in its indication.

- What does mean, in the legend “Additional deviations in the shape are likely to occur at higher doses.”? At high doses (> few Gy), the problem of stochastic effects is no more relevant (and therefore the LNT), as severe deterministic effects may occur.

- (**page 13 § 1**) May be you could check if the current definition of dose constraint from ICRP allows taking into account individual variability in radiation response.

In ICRP 103, published in 2007, the dose constraint is defined as “A prospective and source-related restriction on the individual dose from a source, which provides a basic level of protection for the most highly exposed individuals from a source, and serves as an upper bound on the dose in optimisation of protection for that source. For occupational exposures, the dose constraint is a value of individual dose used to limit the range of options considered in the process of optimisation. For public exposure, the dose constraint is an upper bound on the annual doses that members of the public should receive from the planned operation of any controlled source.”

- (**page 13 § 2**) It must be paid attention to the UNESCO statement on genetic testing:

International declaration on human genetic data (2003): “every effort should be made to ensure that human genetic data and human proteomic data are not used for purposes that discriminate in a way

that it is intended to infringe, or has the effect of infringing human rights, fundamental freedoms or human dignity of an individual or for purposes that lead to the stigmatization of an individual, a family, a group or communities".

- (**Page 11, § 3 and 4**) We suggest modifying the comment on stem cells, as it is a major issue for all types of tumours; it must not be restricted to alpha-particle induced tumours:
  - Move the present sentences from paragraph 3 to 4 and modify: "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 is a major factor that must be taken into account to characterize the carcinogenic risk after radiation exposure. "
  - Delete the "s": radiation.

- Regarding **radiation facilities in the world** (**page 24**), some advanced technological developments raising new radiation protection issues should be considered. The consequences of the development of pulsed radiation sources, generating ionising radiation at very high dose rates, with low averaged doses, haven't been investigated so far. Researches on the metrology of these new domains as well as on their health effects have to be carried out simultaneously to the technical developments producing such fields.

In the part devoted to **research infrastructures and platforms for analysis** (**page 25**), several European recognized facilities including synchrotrons, table-top laser sources, free electron lasers, ion microbeams, advanced spectroscopic techniques; high resolution structure analysis and multidimensional imaging should be mentioned.

C. Other comments

- **Page 5 – end of §3**: "formulate computational models within a more systematic framework for low dose radiation risk."
  Comment: Melysun suggests adding:
  "Due to the discrepancy between animal and human responses to low doses, it is necessary to develop relevant models for human cells starting from single cells **up to new** 3D models of human **carcinogenesis**."

- **Page 5 – § 4**: "The answer to these questions requires integrated input from many scientific disciplines."
  Comment: add "from medical to physical science, including biology, chemistry and mathematics".

- **Page 5 – § 1**: "have become an integral part of industrialised society."
  Comment: Melusyn suggests adding the following:
  "About occupational exposure, a rising issue concerns the development of facilities such as advance pulsed radiation sources."

- **Page 7, § 2**: "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."
  Comment: The LNT has been defined for the management of risk of stochastic effects from ionizing radiation, not for modelling of biological effects.

- **Page 8: figure 1**
  Comment: add "hereditary effects" in the list of non-cancer effects.

- **Page 11 - § 2**: "This feature has been associated in part with the induction by high- LET particles of more complex DNA lesions"
  Add "and collective reactions such as bystander effects".

- **Page 11 – 12**: “Optimally, such an approach would involve experiments performed at low doses at different scales (cell, tissue, organ, organism and population).
  Comments:
  - Replace “scales (cell,” by “levels(molecules, cells,”
  - Do you mean experiments on populations or epidemiological studies?

- **Page 12, § 1**: “A critical stage in the development of a systems approach is the cooperation between the fundamental radiobiological research and mathematical-modelling communities.”
  Comment: replace “the cooperation between the fundamental radiobiological research and mathematical-modelling communities” by “a multidisciplinary approach, including physics, chemistry, fundamental radiobiological research and mathematical-modelling communities.”

- **Page 14, end of § 1**: “with laboratory studies aimed at identifying the underlying mechanisms.”
  Comment: Melusyn suggest adding:
  “In addition, experimental studies from single cells to 3D models are necessary to answer these questions.

- **Page 16, end of § 1**: “in inducing chromosome aberrations, mutations and carcinogenesis.”
  Comment: Add “Further insights have to include premature aging of cell tissue organism and its interplay with future exposure.”

- **Page 16, end of § 1**:“(including possible synergistic and adaptive phenomena)”
  Comment: To be replaced and complemented by “(including molecular recombination, and possible **synergistic and adaptive** phenomena). For example a small dose delivered by repetitive imaging before radiotherapy treatment may modify the response of the tumor to the therapeutic dose.”

- **Page 16, § 2**: Replace “Deeper investigation is still needed of the mechanisms” by “Deeper investigation of the mechanisms is still needed”

- **Page 16, end of § 2**: Modify the last sentence as indicated “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 genomic instability. Individual radiosensitivity can modulate the biological response to irradiation according to radiation characteristics.

- **Page 19, § 3** : “circulatory effects”
  Comment: “Circulatory” or “cardiovascular”? During the first "Science and Values in radiation protection" workshop, held in Helsinki in 2008, this was discussed and a decision was made.Page 26, line 1

- **Page 26,line 1**:
  Comment: after “medically exposed groups”, add “(both from diagnosis and therapy)”

- **Page 26, end of § 1**:
  Comment: In order to strengthen on results in the low dose range, add “Very large cohorts should be necessary to carry out epidemiological studies in the low dose range, corresponding to significant fractions of the European population”.

Page 26, § 3: Attractiveness of the field has to be reinforced by a multistep approach, from Summer school dedicated to undergraduates to post-doctoral programmes.

- At Master level, the already existing international Master programmes, such as SERP Chem (www.serp-chem.eu), focused on the applications of radiations and coordinated by different European countries, should be the first step to propose new education training in the field of the radioprotection.