RISCRAD comments to HLEG reports

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We give here general comments focussed on endpoints that we found missing or poorly described.

Shape of dose response relationship

1. This topic should also include individual variability and should define which endpoints are studied
2. Research is needed on the factors that will influence the shape of dose response relationship?
    a. Influence of radiation quality
    b. Mixed fields interaction between radiation and other agents
3. Definition of the missing links between early and late endpoints, with cancer
    a. Better mechanistic understanding of processes giving the risk
    b. Define the critical steps contributing to cancer and markers of exposure
4. We need to study the problem on a multiscale level: assuming a system biol. approach: considering the the cell itself and within their environment (networks)

Tissue sensitivity for cancer

RISC RAD highlights that the choice of the models is crucial for this topic

1. Identification of cells that are important for health effects
    a. Where do the radionuclides go and to which cells after internal exposure
    b. Include (micro) environment and cell signalling
    c. Identification of "important cells" (e.g. stem cells?)
    d. Mechanisms of specific tissues like senescence/inflammation are poorly understood
    e. Include relation to genetic susceptibility.
2. Increase attention to human (3D) tissue models for experimental and theoretical studies and also the whole organisms when possible
    a. Comparison in vitro/in vivo (releted to next point)
    b. Optimise Wt for low dose: focus on human
    c. Always look for cohorts that are informative at low dose.
3. Search for preferred for instance, thyroid, breast leukemia, lung cancer
    a. Mouse models with predictive power for human: besides AML?
    b. Look for tissue reactions to radiation not already proved to be important for cancer.

Quality of radiation

1. Missing topics concerns the spatio temporal characteristics of the exposure and tof the iological response to radiations. Pulsed irradiation plus timing are not taken into account (especially for diagnosis) in the report..
    a. Dose rate fractionation and time related to single tracks.
    b. Risk dose and time in 3D.
    c. Newly developed sources of radiation.
2. Using WR and DDREF can be a big economical factor. Thus more study of radiation quality dependence of the dose response curve are needed

Indvidual variability :

RISC RAD welcomes the inclusion of the topic of individual variability in cancer risk and genetic susceptibility to cancer as a topic area in the HLEG consultation draft. Further, we point out that this topic was a major focus of RISC RAD.

1. Opportunities have been identified where epidemiological analyses can be productively linked to laboratory studies. Given the very wide range of genetic variants that exist in the human population that might impact on low dose risk, it is highly unlikely that sufficiently powered epidemiological studies will be conducted to assess the quantitative impact of all potential risk variants. Therefore combined epidemiological and animal model studies will be of use in identifying risk variants.
2. It was noted that one of the most pressing needs is to establish the range of human low dose radiation cancer susceptibility and the major factors that contribute to this. Twin studies could be highly beneficial in this regard.
3. Linkage of low dose risk studies with ongoing biobanking activities (eg the UK Biobank) could be highly productive. In experimental settings linkage to mouse mutagenesis programmes may be valuable. External linkages of this sort could be highly beneficial for future low dose risk work.
4. A very wide range of factors contribute to variation in risk, a full understanding, particularly in a quantitative fashion, will be very difficult to obtain.
5. We note that there are several ongoing radiation worker follow-up epidemiological studies ongoing in observed EU countries, the UK NRRW and Gazelle in France. There may be opportunities to obtain samples from such populations to assess exposures or disease risk that have not yet been established.
6. RISC RAD also welcomes the inclusion of non-cancer disease amongst the key topics that require further investigation. This is a wide ranging area covering several apparently disparate conditions that are likely to have distinct aetiologies.
7. One potentially promising alternative approach to that of considering individual conditions is to study different systemic responses to low dose radiation – eg of the immune systems inflammatory reactions.
8. Primary risk data for these conditions will come from epidemiological studies but in some cases it will be very difficult to establish unequivocal evidence of increased risk at low dose levels. This will be particularly the case for circulatory diseases when background, spontaneous incidences are very high. Therefore there is a strong need for parallel experimental and epidemiological approaches.
9. We agree that there is a need for improved animal and cellular models for use in studies of circulatory disease risk.
10. 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 and modulated by the interplay between “natural” aging of cell, tissue, organism and radiation induced damage

Education and training :

RISC-RAD welcomes the inclusion of education and training topics.

1. MELODI and the future NoE might take a role in convincing authorities to support radiation biology research. Keeping in mind that development of Nuclear Industry would require large number of experts in radiation biology, in some cases this expertise should be *re-create.* Future progression from graduate level to Ph.D., Post Doctoral and professor positions should be provided. Moreover radiobiological positions should be guaranteed by the state to ensure continuance of training and expertise, national agencies should be informed

2. Training should be attractive for prospective students. 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..
    a. There is a need for an audit of existing courses in Radiobiology-Epidemiolog-Radioprotection available in Europe
    b. Training should be planned in close contact with stakeholders
    c. Links with ESTRO should be developed and links between radiation biology and clinic should be developed
    d. Training courses in companies, which are dealing with radiation biology

Infrastructure

1. The first action might be to have an audit of large-scale irradiation facilities in Europe
    a. Low dose low dose rate protracted exposure animal irradiation facilities in Europe
    2. Support for existing microbeam irradiation facilities in Europe
    c. Preserving of Cs-137 facilities for radiobiological research
    d. Radon facilities should be maintained
2. A lot of tissue, cell lines and data banks exist, European audit is needed, provision of access need to be assured
    a. The formation of network of epidemiological cohorts of interest in Europe (i.e. cohort of people treated for benign conditions or rector workers) might improve the access to bioligical samples
3. The research infrastructures and platforms for analysis include also high resolution structure analysis and multidimensional imaging such as synchrotrons, ion microbeams, advanced spectroscopic techniques.

Networking actvities

1. Network projects related to radiation biology funded in Europe include satellite meetings on technological areas not directly related to radiation sciences
2. Meetings, short term exchange and involvement of young scientists is essential; some “meeting policy” needs to be developed
3. US (DOE Low dose programme, NASA) and Japanese research programmes should be involved; more interaction should be promoted and supported via travel/short term visits grants
4. Networking will increase transparency in radiation research
5. Networking with security and emergency preparedness programmes
6. Flexibility funds for networking needs to be allocated in future projects