DoReMi Radiation Quality workshop

SCK-CEN Headquarters, Brussels. 9-10 July 2013

Summary of the points made during discussion

Context

The meeting centred around 18 lectures by invited experts from Europe and the US, including a representative from ICRP, followed by questions and discussion. The conclusions focused on:

1) What are the outstanding issues around the influence of radiation quality on the risk of adverse health effects from low dose ?
2) What are the priorities for short term research programmes addressing outstanding issues?
3) What are the priorities for long-term research programmes to address remaining outstanding issues?

The message from ICRP was that within the present formalism more detail on radiation weighting factors (and individual sensitivities etc) for different qualities of radiation will not affect the ICRP population-based radiation protection principles, used for setting dose limits, intervention limits etc. Apart from an obligation on the part of the ICRP to take new scientific developments into account at an appropriate time, there is no perceived need for greater precision. However, there is a growing call for individual risk assessment that should be based on the best risk prediction models available and this approach is already being taken for specific exposed groups. Research into the effects of radiation quality is in this category and should include individual radiosensitivity and biomarker stratification on normal tissue responses.

The workshop agreed that “Low dose” or “low dose rate” are terms that should not be strictly bounded by any limits, especially when considering different qualities where the dose volume is a key variable influencing dose. The future research should include doses and dose rates that are relevant for investigating mechanisms, sensitivity, and dose-response relationships that could potentially add to the capability to carry out personal radiation risk assessments at low doses and dose-rates.

Increasingly the need is being acknowledged for personal radiation risk assessments for patients receiving radiation treatments, imaging procedures or radiodiagnostics as this is a rapidly expanding genetically very heterogeneous population. In the context of Horizon 2020, Euratom appears to be becoming more aware of the issue of personalization with the sharper focus on Societal challenges.

Furthermore it was suggested that the particular differences in the pattern of energy deposition for different qualities of radiation through cells and tissues may provide a powerful tool to investigate biological responses to different types of damage. Here the comparative study of different radiation qualities will make a valuable contribution to understanding biological processes in the radiation response.

The need for directed research

There was extended discussion on the relevance of future investigations specifically focussing on the effects of radiation quality. There is a perception that the number of individuals in the public and in the work force exposed to radiation qualities other than low-LET radiation is small. The one case presented at the meeting where risk assessment in situations of very high LET radiation was critical (inter-planetary space travel) could not in any way justify an international research effort in addition to that undertaken by the various space agencies including the European Space agency. On the other hand, a better knowledge of radiation quality effects is important in medical applications such as breast cancer screening (possibly elevated RBE for low-energy X-rays), paediatric proton and other ion therapy (including scattered neutrons), and the increasing use of therapeutic internal alpha-particle emitters.. There are also on-going concerns about radon exposure which need to be addressed.

It was agreed that there was a critical need to formulate any research proposals in terms of a clear radiation protection question that would be addressed at the individual level.

Radiation quality as a cross-cutting issue

With the exception of one specific task in Workpackage 5 (WP5), it was clear from the presentations on DoReMi WP5 (Shape of the Dose-response curve), WP6 (Individual susceptibility) and 7 (non-cancer effects) that the majority of the research continues to exclusively use low LET radiation, and that any research tasks in DoReMi that incorporated more than one radiation quality were not the result of any concerted effort to study quality effects This suggests that radiation quality should have been treated as a stand-alone topic in itself (as was initially proposed by HLEG) with its own defined workplan and strategic leadership. (The same is probably true for the other two topics treated as “cross-cutting” in the DoReMi structure, but these were not the subject of this workshop.). The structure of 3 main topics and 3 cross-cutting topics in DoReMi has not been effective in addressing the issue of radiation quality. The investigation of mechanisms that respond differently to different radiation qualities (and therefore different spatiotemporal distributions of initial events) need to be investigated in their own right. They are also fundamental to our understanding of low doses where ultimately individual tracks of radiation need to be assessed.

Possible lines of research

It was agreed that any research leading to individual risk estimates taking account of radiation quality would need to have a direct “traceable” line to human data, and this essentially means molecular epidemiology on a suitable human cohort. So this will involve biomarkers which need to be defined.

At the other end of the timescale, since the difference in effect caused by different radiation qualities, is amongst others, the result of the clustering and correlation of initial events, modelling the physical interactions with all potential targets has a role to play. With increasing

sophistication of the representation of the different targets, it will be possible to characterise the distribution of damage in all of the functional macromolecules, along with the distribution of damage across a cell and within tissue, and to attempt to relate this to biological response.

There is rapid development in the technology available to investigate biological response. Massively parallel sequencing of DNA and RNA "next generation sequencing" holds promise, as does high throughput proteomics and metabolomics. There seems to be a developing trend for biological processes to be seen to be more and more complex as the investigations get more sophisticated. The holy grail of the single biomarker that uniquely characterises a process seems more remote than ever. Nevertheless, it is hoped that systems biology may provide a possible answer. Nevertheless there was a need to build this approach by adopting the more biologically relevant but more complex 3D tissue and culture model systems, in particular those where stem cells and other progenitor populations are present.

Animal models seem to be an essential link in the chain in following the progression from initial biological insult and perturbation to disease, although caution must always be exerted when extrapolating results from mouse models to man. Rats do not offer a viable alternative as they are many times more expensive sand molecular manipulation / probes are sadly lacking. Other than diabetes models the rat has not proven to offer any superiority to mouse for biomedical research.

On a more global level, and taking account of previous comments about the need for clear justification of the research, any project needs to be presented as either an integrated pathway that will address a clear question, or at the very minimum be recognisable as an essential step in such a pathway. This will be just as important as the quality of the science in each subtask.

Impediments to research

The presentation on DoReMi WP4 (Infrastructures) made it clear that there is no shortage of infrastructure for doing experiments in a range of different qualities of radiation within Europe. However it was pointed out that very few of the facilities are being used effectively by DoReMi partners. One of the reasons, of course, is that there is not much radiation quality research being done compared with research outside of DoReMi. It was also made very clear that considerable difficulties arise in performing radiobiological experiments on cells or animals at an outside facility, particularly at a large distance or in another country, so improving accessibility to infrastructures is important. The other point raised in conjunction with research on animals is the high (and increasing) cost. Most of the research uses mice, which have limitations in extrapolation to humans, mainly because they are the cheapest and have extensive genetic manipulation possibilities.

Conclusions

The meeting was designed to stimulate discussion by "putting all the main issues on the table and looking for solutions". The plan was to arrive at one or more concrete proposals for new research projects. In the event some key ideas were discussed but the discussion stayed at a more general level around some of the challenges and general strategy for moving forward. But the result was a very thorough working through the why and how. It was noted that a direct comparison of radiation quality could be added on to many existing projects with little additional effort or cost involved. It is our recommendation that future TRA versions include a more forcible demand that this be carried out under DoReMi funded projects.

The result of this work must now be translated into practical recommendations to be included in the MELODI Strategic Research Agenda, and the participants must digest the resulting brew and see what comes of it.