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Review

Progress in low dose health risk research
Novel effects and new concepts in low dose radiobiology

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ABSTRACT

People are more often exposed to low as opposed to high doses of ionising radiation (IR). Knowledge on the health risks associated with exposures to ionising radiation above 100 mGy is quite well established, while lower dose risks are inferred from higher level exposure information (ICRP). The health risk assessments are mainly based on epidemiological data derived from the atomic bombing of Hiroshima and Nagasaki, medical exposure studies and follow-up studies after nuclear accidents. For the estimation of long-term stochastic radiation health effects (such as cancer) and radiation protection purposes, a linear non-threshold (LNT) model is applied. However, the general validity of the LNT hypothesis for extrapolations from effects of high to low doses (< 100 mGy) and low dose-rates (< 6 mGy/h) has been questioned as epidemiological studies are statistically limited at low doses and unable to evaluate low dose and low dose-rate health risks (UNSCEAR). Thus, uncertainties on health risks need to be clarified with the help of mechanistic studies.

The European Network of Excellence DoReMi (2010–2016) was designed to address some of the existing uncertainties and to identify research lines that are likely to be most informative for low dose risk assessment. The present review reports the results obtained from studies addressing the induction of cancer and non-cancer effects by low dose IR as well as on individual radiation sensitivity. It is shown that low dose and low dose-rate effects are the result of complex network responses including genetic, epigenetic, metabolic and immunological regulation. Evidence is provided for the existence of nonlinear biological responses in the low and medium dose range as well as effects other than the classical DNA damage. Such effects may have a bearing on the quantitative and qualitative judgements on health effects induced by low dose radiations.

1. Introduction

For many years, radiation research has been at the origin of important discoveries and knowledge on the biological mechanisms operating in living systems, such as genetic effects induced by external agents and DNA repair.

However, despite decades of research on the effects of ionising radiation, considerable uncertainties still remain on the health effects of low doses (i.e. those defined as 100 mGy) and low dose-rates (i.e. those defined as less than 6 mGy/h [1–3]), and some scientific conclusions on the effects induced by low doses of ionising radiation turned out to be contradictory [4,5]. On the basis of the available scientific literature, BEIR supported the LNT extrapolation for risk of cancer, even at low doses, whereas the French Academy concluded that there are non-linearities in low dose responses that may need to be taken into account. The European Commission asked a group of high level experts ('High Level and Expert Group,' HLEG) to help to clarify the subject. After a thorough analysis of available data on low dose radiation effects, the HLEG came up with the conclusion that more research on the mechanisms involved in low dose and low dose-rate radiation responses would be essential to complement epidemiological studies that were limited by low statistical power at low doses and low dose-rates [6].

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Such research would help to elaborate concepts and paradigms. The HLEG recommended the establishment of the transnational research platform MELODI (2010) ('Multidisciplinary European Low Dose Risk Research Initiative') that would be capable of ensuring an appropriate governance of research in this field [7], and a scientific strategy capable of structuring future research in the most effective way, taking into account the resources.

Following the HLEG recommendation of 2009 the European Network of Excellence, DoReMi was launched [8]. DoReMi (2010–2015) consisted of a European Research project with specific working packages dedicated to the establishment of a short term strategic research agenda and in accord with this research work at low doses (< 100 mGy) and low dose-rates (0.1 mG/h). In parallel, the MELODI association was set up in 2010. It consisted of a consortium of leading European research institutions with long term interests in low dose radiation research and radiation protection. In the following years, the MELODI platform developed further into an independent body initiating and coordinating low dose research activities in Europe. The common goal of DoReMi and MELODI was the promotion of low dose health risk research in Europe, the reduction of existing uncertainties in radiation risk assessment and the improvement of radiation protection [9].

As proposed by the HLEG, the DoReMi project focused on two main questions:

1. How robust is the system of radiation protection and health risk assessment, in particular, at low doses and dose-rates?
2. How can it be improved?

Judgements on radiation protection standards in Europe and elsewhere are highly dependent upon a) scientific knowledge that is regularly reviewed by national committees and by a committee of the United Nations (UNSCEAR) 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 radiation protection standards for the public, radiation workers and medical patients. 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/or low dose-rates. Consequent upon these uncertainties, the issue of low-dose risk is controversial in both scientific and political debate. Research on epidemiology as well as mechanisms of radiation action at low doses can reduce uncertainties and help evolve common concepts.

Exposure of the population to natural radiation is unavoidable. Additionally, medical exposure of the patient during diagnosis and therapy, and of population groups during medical screening programs, is now an indispensable and increasing part of modern medicine, and the annual cumulated doses from medical exposure exceed nowadays those from natural sources in some countries. The exposure of workers and, to a very much smaller extent of the public, to low levels of radiation from nuclear energy production and from industrial uses of ionising radiation is part of the life in industrialised societies. Any over-, or underestimation of the risks to health from ionising radiation could lead either to unnecessary restriction of the beneficial uses of radiation or to a lower level of health protection than intended. Despite regular human exposure to natural radioactivity (e.g., radon in homes), from cosmic radiation during long-distance flights, from many medical diagnostic exposures (CT scans, radiography, use of radionuclides as tracers in medicine, etc.), the social questioning has focused more on possible exposures from radioactive waste disposal (from industrial or medical uses), radioactive contamination as a consequence from past radiation accidents (Chernobyl, Fukushima etc.) or atomic bomb tests.

In addition to cancer, further uncertainties in low dose health risks are brought about by the tissue reactions and non-cancer health effects such as cataracts, dysfunctions of the central nervous system and circulatory diseases [10]. For example, although it is well established that high-dose ionising radiation like radiotherapy causes cardiovascular diseases, the evidence for long-term risk of cardiovascular disease is weak after lower doses (< 0.5 Gy). However, evidence is emerging that doses under 0.5 Gy may also increase long-term risk of cardiovascular disease [11,12]. The main scientific questions to be answered concern molecular mechanisms that relate to the perturbations and damage induced by low (< 100 mGy) and medium (< 1 Gy) doses and low dose-rates < 6 mGy/h) of ionising radiation causing short and/or long-term modifications of normal biological functions, e.g., metabolic alterations and onset of pathologies (cancers and non-cancer effects). Here, the uncertainties include the actual low dose responses, the effects of radiation quality and dose inhomogeneities, and the deregulation of cellular pathways and normal metabolism, and cell and tissue (organs) specific and individual responses.

The over-arching policy question of the robustness of the current system of radiation protection and risk assessment was broken down by the HLEG into specific scientific questions that can only be answered by multidisciplinary research that takes into account the full breadth of the latest advances in scientific knowledge and techniques [6]. A global description of these questions was presented, under the headings:

- Shape of dose response relationship and tissue sensitivity for cancer;
- Individual variability in cancer risk and genetic susceptibility to cancer;
- Radiation quality (type);
- Internal exposure risk;
- Risks of and dose response relationships for non-cancer effects (and sensitivity to non-cancer effects).

DoReMi addressed each of these questions with research programmes on the shape of the dose response relationship, individual sensitivities, and non-cancer effects. Because radiation quality and internal radiation exposure have implications for each of the other research areas, they were treated as cross-cutting topics within the three programmes. In order to support the research effort, DoReMi also supported education and training and development of radiation research infrastructures [8].

As discussed below, the results obtained during the DoReMi project highlighted the evolution of new radiobiological concepts and paradigms and opened new research lines with an important bearing on current radiation protection issues.

2. Results obtained

At the time DoReMi Network of Excellence was launched in 2010; fundamental studies on low dose effects were relatively rare. A vast majority of studies reported in the literature addressed doses well above 1 Gy. A common perception was that at low doses 'there was nothing to see', and low dose effects were expected to be small and extremely challenging to detect. Furthermore, the effects most frequently studied were related to DNA damage and IR responses [13]. While highly relevant for the induction of cancer and hereditary effects, this line of research is not likely to shed much light on the mechanisms underlying non-cancer effects that are of growing interest to the radiation research community [14,15]. Low dose research constituted a great scientific challenge because of the lack of sensitive methods to detect and reliably quantify relevant biological effects in the low dose range. Because of the lack of studies addressing low doses effects and the mechanisms involved, DoReMi first launched a number of feasibility studies that paved the way for wider ranging and more detailed hypothesis driven research activities.

According to the existing uncertainties in radiation protection, the research was as much as possible centred on effects and mechanisms of action of low doses and low dose-rates and around 9 questions (as