Contribution to the reflections of HLEG on the research strategy in the field of low doses of ionizing radiation

Tubiana M, Averbeck D, Masse R, Valleron AJ, Le Guenn B, Foray N, Aurengo A.
French Academy of Medicine – French Academy of Sciences

Nov 30 2008

The co-authors of the French Academies of medicine and science report on the effects of low doses of ionizing radiation (IR)[1] have taken note, with satisfaction and great interest, of the HLEG[2] work and wish to make a contribution to this topic of particular importance in terms of knowledge advancement and from a societal point of view.

The objectives of radiation protection are on the one hand to increase knowledge on the health effects of IR, especially in the field of carcinogenesis[3], on the other hand to propose recommendations and regulations based on scientific data in order to protect people exposed to IR for occupational, medical or environmental reasons.

During the past fifteen years the paradigms on which these two goals were based have been controversial regarding low doses[4], for several reasons:

- The number of individuals that would be needed to assess risks of doses below 100 mSv exceeds by far the size of the largest surveys already performed or achievable. Therefore, estimates currently available for these doses are based on an assumption of identity and similar effectiveness of cell and tissue defense mechanisms against low and high doses. This assumption makes it possible to quantify the effects of low doses using data obtained at 10 to 100 times greater doses, but advances in biological research have shown that this assumption is not plausible.
- Research on animals is difficult to extrapolate to humans[5]. Moreover, these results are incompatible with former ideas on radiation-induced carcinogenesis, especially, because a practical threshold is observed in almost all experiments and because hormetic effects are observed in about 40% of the studies identified[6].
- The defense mechanisms against IR are extremely complex[7], and far from the simplistic concepts prevailing two decades ago. These mechanisms are different against low and high doses; they involve cellular, tissular and immunological levels in a network of interrelations which must be studied. The assumption that any given dose, even the lowest possible, can be carcinogenic is not consistent with available scientific data.
- There is not one but different relationships between dose and cancer risk depending on the nature of radiation, dose rate and dose fractionation, the tissue concerned, as well as genetic and other as yet unknown factors to be discovered.

Although the old paradigms are controversial, we currently do not have a coherent and validated vision of low-dose radiocarcinogenesis which could be able to replace them. A strong research effort must therefore be conducted, using a holistic approach integrating genomic and transcriptomic technologies, microdosimetric approaches, networks of genes, tissues, mechanisms related to cancer promotion and regulation of epigenetic effects.

---

[1] Dose-effect relationships and estimation of the carcinogenic effects of low doses of ionizing radiation.
French Academies of medicine and of sciences. February 2005.
http://www.academie-medecine.fr/detailPublication.cfm?idRub=26&idLigne=260

[2] High Level Expert Group : http://www.hleg.de/

[3] These advances have an impact far beyond radiation protection issues.

[4] We define here as low doses doses below 100 mGy.

[5] Rodents are very different from humans in terms of sequences and in terms of the regulation of genes involved in radiation responses ; their genes are often limited in cell cycle control and DNA repair.

[6] Calabrese EJ, Baldwin LA 2003 Ann. Rev. Pharmaco Toxicol. l 43 :175-197.
Duport P. Int J Low Radiation 2003 ;1 :120-131.

[7] Given the significant proportion of the genome devoted to DNA repair, this complexity could be of the same magnitude as that of the whole metabolism.

This ambitious program could focus on five priorities:

1. Assessing the existence and the magnitude of radiation-induced cancer risks brought about by current medical procedures; this corresponds to a regulatory requirement for risk-benefit analysis of examinations involving low doses. Possibly repetitive irradiation with varying time intervals could affect children, newborn or possibly foetus. It should be kept in mind, however, that the only cases of cancer caused by radiodiagnostic examinations are related to clinical indications outdated for half a century.
2. Assessing the risk of second cancer arising from exposed regions outside the target radiation field during radiation therapy to optimize the exposure ballistics and timing.
3. Assessing the risk of most prevalent environmental exposures, in particular radon which concerns several European countries including France, and for which the threshold of radiation risk is controversial.
4. Assessing the risk of industrial and occupational exposures, consisting of internal or external low-dose exposures, repeated for several decades.
5. Quantifying the risk of public exposure resulting from
   - industrial activities, in particular from nuclear waste, which pose the problem of alpha emitter impact;
   - terrorist acts, for example a “dirty bomb”, for which an accurate assessment of the radiological long term risk is essential to avoid phenomena such as panic.

It would be unrealistic to expect direct and rapid answers to all these questions, but we can define short term objectives.

1. To conduct an evaluation of the evidence provided by epidemiological studies already performed on low dose effects, by examining in particular:
   - if the low dose range is studied without preconceived ideas, for example avoiding an *a priori* assumption of a linear no threshold relationship;
   - if the uncertainties of the exposures have been studied and taken into account in the statistical analysis;
   - if confounding factors have been quantified and taken into account.

   Such an analysis, which requires access to baseline data, would allow to better understand radiation risks and to explain the contradictions within or between studies, and to establish guidelines for future epidemiological studies.
2. To accumulate enough knowledge on the molecular, cellular, tissular and immunological mechanisms, involved in radiocarcinogenesis in order to propose reliable exposure risk assessments consistent with *in vitro* and *in vivo* data. This requires:
   - to develop experiments allowing to validate at the level of tissues, organs and whole body the results obtained on cell cultures. This pertains to the mechanisms of defense against low doses[8] and to the involvement of epigenetic effects.
   - To characterize radiation damages induced in various cellular components[9] using recent analytical detection methods in order to determine their frequency, persistence, pathways of elimination and biological significance depending on the nature of ionizing radiation. This could lead to the use of such damages as biomarkers of IR exposure.
   - To strengthen the analysis of radiation-induced transcriptomic, proteomic and metabolomic changes in connection with long-term health risks such as cancer and non-cancerous diseases, genetic and epigenetic alterations, inheritance. The relationship between transcriptomic and

[8] e. g. signalling, adaptive response, modulation of intercellular signals, repair or misrepair, apoptosis, cell survival and immunosurveillance.

[9] especially DNA double strand breaks and locally multiply damaged sites (LMDS), epigenetic effects, damage to proteins, lipids and intra-and intercellular signaling systems.

proteomic data and long-term genotoxic effects of IR are not yet well understood. We need new insights on hypersensitivity at low doses and on the metabolic networks involved in radiation-induced carcinogenesis. The role of epigenetic factors, chromatin structure and regulatory mechanisms[10], the influence of signaling on cell differentiation and proliferation or IR effects on intercellular signalling should be considered.

- To improve our knowledge on promotion and signaling which play a key role in carcinogenesis, as important as or even more important than mutations. As highlighted by recent studies[11] the promotional effect of RI is only expressed in specific conditions and above a certain dose, indicating a threshold effect.
- To study the conditions of the additivity of low but recurrent exposures depending on the dose, dose rate, interval between exposures and nature of the residual effects. Such studies could be conducted on animals and, prospectively, on diagnostic or therapeutic medical exposures, whose conditions can assessed accurately without ethical problems.
- To initiate a special effort on the health effects and the mechanisms involved in the case of internal contamination, as the present epidemiological data are not consistent.

3. To conduct prospective studies on second cancers after radiotherapy (over 100,000 cases a year in the world[12]), with the dual purpose of optimizing treatments in order to reduce the incidence of these second cancers and extending our knowledge on radiation-induced carcinogenesis. When the necessary dosimetric data are available, one patient provides information on the carcinogenic effect from a few tens of mGy (the lowest doses received at the most distant region from the tumor) to a few tens of Gy (dose to the target volume). The delay for the occurrence of second cancers, the influence of age, sex, individual susceptibility factors, cumulative dose, dose per session, interval between sessions and radiation dose rate should be studied. The case of hyperfractionated radiation[13] should be reviewed, particularly in view of the theoretical reduction of second cancer that it could provide.
4. To identify, if they do exist, specific molecular signatures of radiation-induced cancers (and not just the markers of IR exposure), which could not yet be confirmatively identified, despite numerous studies. Such signatures, coupled with the search for possible genetic or epigenetic markers in individuals may allow molecular epidemiological studies on low dose radiation effects.

In February 2005, the French Academies of Medicine and of Sciences published a report on the effects of low doses. Epidemiological knowledge (and its limitations) and recent results from basic research in terms of radiation-induced carcinogenesis were presented. In this context we welcome the integrated approach proposed by the European HLEG which raises great hope.

Epidemiology, biology and research projects should be integrated. We feel that the French research community is ready to actively contribute to this European endeavour.

---

[10] such as the methylation of cytosine in human cancers during the evolution of preneoplastic lesions to invasive cancer.

[11] R. A. Weinberg. The biology of cancer. Taylor & Francis, New York, 2007.

[12] Currently, about seven million cancer patients are treated each year by radiotherapy, two million of them survive more than a decade ; 10% of them will develop a second cancer. The number of these is estimated to be approximately 200 00 cases per year, i.e. 100 to 1 000 greater than those allocated to all other causes.

[13] Two sessions of 1.1 Gy at 6 or 8-hour intervals, instead of one session of 2 Gy.