Scientific meeting of the Belgian Society for Radiation Protection

Emerging issues with regard to organ/tissue dose

Friday December 9, 2016

Brussel

Programme

13.00-14.00	General Assembly
14.00-14.30:	*Cognitive and cerebrovascular effects induced by low dose radiation (CEREBRAD)* Rafi Benotmane SCK•CEN
14.30-15.00	*Cardiovascular risks after exposure to ionizing radiation* An Aerts SCK•CEN
15.00-15.30:	Coffee break
15.30-16.00	*The thyroid: a radiosensitive organ* Hanane Derradji SCK•CEN
16.00-16.20:	*Low-dose ionizing radiation risk research: key issues* Patrick Smeesters UCL, CSS
16.20-17.00:	Final discussion, questions and remarks

Publication

The presentations of this meeting will be published in the Annals of the Belgian Society for Radiation Protection BVS/ABR.

*Dr. **Abderrafi Benotmane** obtained his PhD in Biomedical sciences in 1999 from the KULeuven in Belgium at the Center for Molecular and Vascular Biology 'CMVB' directed by Pr. Désiré Collen. After his PhD he joined the Radiobiology group at the Belgian Nuclear Research Center (SCK•CEN) for a post-doctoral fellow dealing with low dose effect of radiation, one of his duties was to introduce the molecular biology techniques to study the effect of radiation and to identify relevant biomarkers for exposure. In 2001 he obtains a permanent position and he took in charge the brain research with main interest to study the cellular and molecular changes in the brain after exposure to radiation during critical stages of development. In 2003 he set up the Genomic platform at SCK•CEN to assess genome wide gene expression. In 2011 he successfully obtained funding from the European Commission to coordinate the CEREBRAD project for ' Cognitive and Cerebrovascular Effects Induced by Low Dose Ionizing Radiation' involving 10 European partners and Ukraine. Dr Benotmane is involved in many societies for neuroscience, radiation research and protection in Europe and outside Europe. He is involved in the MELODI working group for infrastructures and up to 2014 was member of the board of the European Radiation Research Society. He supervised several PhD and master theses and is author and co-author of several publications about effect of low and moderate doses of radiation.*

Cognitive and Cerebrovascular Effects Induced by Low Dose Ionizing Radiation 'CEREBRAD' (Grant agreement: 295552)

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Epidemiological evidences about the occurrence of late cognitive and cerebrovascular diseases due to exposure to radiation early in life (*in utero* or during childhood) are scarce. Nevertheless, A-bomb survivor data indicate a linear dose-response curve with a threshold around 200 mGy. Thus, raising the concern regarding the uncertainty of low-dose radiation, which is in part due to the lack of sufficiently large cohorts, combined with a lack of understanding the underlying mechanisms. Moreover, the increasing use of radiation in medical diagnostics urges the need for appropriate research to define precisely the effect of low dose radiation on the brain. The FP7 CEREBRAD project for cognitive and cerebrovascular effects induced by low dose ionizing radiation (grant agreement n°295552), aimed thus to gather sufficient scientific evidence to increase the statistical power of epidemiological data. Moreover, the project aimed to explain the related cellular and molecular events modulated early after exposure and most probably responsible for late cognitive and cerebrovascular diseases. The main CEREBRAD findings are as follow:

I) Epidemiological evaluations of the risk of cerebrovascular disease following low dose exposures were based upon a cohort of 233 survivors of childhood cancer receiving radiation therapy before the age of 5 year, matched to an equal number of survivors not treated with radiation. The Excess of Odds Ratio (EOR) of stroke per Gy of average radiation dose to the cerebral arteries, was equal to EOR/Gy = 0.49 (95% CI: 0.22 to 1.17) in a linear model.

II) Cognitive impairments have been evaluated in a medical and in Chernobyl cohorts, in which exposure to radiation occurred either *in utero*, or during childhood below the age of one year, or at adult age in clean-up workers. Impairments appear to be age-dependent; in *in utero* exposed cohort, effects are observed below 0.1 Gy, in the medical cohort (exposure at childhood below the age of one year), impairments increased with increasing dose to the thyroid and cerebral hemispheres from thresholds of 0.12 Gy and 0.054 Gy, respectively. On the other hand, Cleanup workers demonstrated significant cognitive deficits when exposed to doses over 0,25 Gy.

III) The shape of the dose-response curve for cognitive impairments in animal models shows a linear dose-response curve with age-dependent sensitivity. In *in utero* exposed mice, subtle changes in behavior can still be observed with the low dose 0.1 Gy, while early postnatal exposure showed impairments starting from 0.3 Gy on. More importantly, postnatal co-exposure with environmental toxicants (such as MeHg, nicotine and PBDE) showed defects at a dose below 0.1 Gy. In all, our data indicate there might be no threshold below which no effects are observed, warranting thus further investigations.

VI) The cellular and molecular investigations revealed obvious effects of low-dose ionizing radiation 'LD-IR' on the brain at multiple levels. In general, we could observe a clear dose-dependent effect and could unveil different anomalies induced by the lowest X-ray dose studied (0.1 Gy) in terms of cognition, cell death and neurogenesis. Of interest, next to the administered dose, also the age at which exposure occurs strongly influences radiation effects, which are mostly exacerbated when irradiation is induced at earlier stages. finally, mechanisms acting at low doses are different from those at high doses, while, processing of the late response could in part be mastered through epigenetic events, requiring thus additional investigations.

Acknowledgements: CEREBRAD (Cognitive and Cerebrovascular Effects Induced by Low Dose Ionizing Radiation) project is financially supported by the European commission under the 7th EU framework programme, grant agreement n°295552.

***Dr. An Aerts** graduated as a Master in Bio-engineering Sciences at KULeuven in 2003. Subsequently, in 2007 she obtained a PhD at the same university at the Centre of Microbial and Plant Genetics, and worked here for 1 additional year as a postdoc associate. In 2008, she was hired as Senior Scientist in the Belgian Nuclear Research Center SCK•CEN in the Unit Radiobiology, Expert group Molecular and Cellular Biology, Institute for Environment, Health and Safety. Currently, Dr. Aerts coordinates two research lines: (i) Assessment of cardiovascular risks after exposure to ionizing radiation and (ii) preclinical investigations of radiopharmaceuticals. She guides 2 to 3 parallel PhD students and 2 to 3 MSc students each year on these topics. Research is embedded in SCK•CEN internal projects, as well as national projects or Tasks within European projects. Dr. Aerts is (co)author of near 30 journal articles and has delivered near 100 conference presentations. In addition, she is an active teaching member of the SCK•CEN Academy. Finally, Dr. Aerts is an appointed expert for the Belgian Superior Health Council, working group on ionizing radiation.*

Cardiovascular risks after exposure to low dose ionizing radiation: research at the Belgian Nuclear Research Institute SCK•CEN

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Although thought to be radioresistant in earlier days, the cardiovascular system is now recognized as being vulnerable to ionizing radiation. Epidemiological findings suggest that cardiovascular diseases may be a health risk associated with radiation exposure. However, below 0.5 Gy an increased risk cannot be evidenced by epidemiology alone, and a better understanding of the underlying biological and molecular mechanisms is needed.

At the Belgian Nuclear Research Centre SCK•CEN research is ongoing in the field of cardiovascular risks after exposure to low dose ionizing radiation. For our in vitro models, we use cells derived from human endothelium, the inner lining of the cardiovascular system playing a pivotal role in normal vascular functioning. Endothelial cells are also believed to be critical in radiation-related cardiovascular diseases. In our in vivo models tissue derived from the murine heart is used to perform tests. We study classical radiation responses like DNA damage and repair, cell cycle changes and apoptosis. In addition, we assess inflammation, mitochondrial dysfunction, senescence, and intercellular communication.

Our findings motivate further research on the shape of the dose-response and the dose rate effect for radiation-induced vascular disease in order to refine radiation protection. In addition, with our research we aim to contribute to the identification of potent countermeasures as well as a set of predictive biomarkers for radiation-induced cardiovascular disorders. As such we strive for a better life qualitiy for ionizing radiation exposed people.

Acknowledgements: This study was funded by the EU FP7 DoReMi (nr 249689), the EU FP7 Procardio project (nr 295823) and by the Federal Agency of Nuclear Control (FANC-AFCN, Belgium) (nr CO-90-13-3289-00). Rombouts C and Baselet B are recepients of a doctoral grant from SCK•CEN/Ghent University and SCK•CEN/Université Catholique de Louvain, respectively.

__Dr. Hanane Derradji__ graduated in 2003 at the Free University of Brussels (VUB) as a master in molecular biology. For her work in the field of developmental biology, more particularly on the consequences of in utero exposure to radiation she was granted a PhD in 2006 at the University of Ghent after which she joined SCK-CEN as a postdoctoral fellow to study thyroid cancer risks at low doses.
In her current position of senior scientist and leader of the thyroid research within the Unit of Radiobiology, she is involved in either funded or internal research projects concerning thyroid cancer following radiation exposure or the impact of combined stress factors like radiation and iodine deficiency on thyroid cells. She is co-author of more than 20 peer reviewed journal articles and is an active member of the SCK•CEN Academy giving courses in the context of the continuing professional development (CPD) sessions in radiation protection. Recently she became an appointed expert for the INSERM (Institut national de la santé et de la recherche médicale) working group on the health consequences of nuclear tests in the French Polynesia.

Thyroid cancer risk following exposure to ionizing radiation

Hanane Derradji [1]

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Thyroid cancer is one of the malignancies induced by radiation exposure, especially in children as shown by epidemiological studies performed after the Chernobyl accident, Hiroshima & Nagasaki bombing and the nuclear experimental testing in the Marshal islands and in the desert of Nevada.

Besides accidental or experimental radiation exposure, medical irradiation can also lead to the development of thyroid cancer, as reported by studies which monitored patients, especially children undergoing external radiation therapy for a variety of malignant or benign diseases. Indeed, many epidemiological studies have demonstrated that doses as low as 0.10 Gy or as high as 60 Gy can induce thyroid cancers (Shore RE, 1992). Most studies indicate that a linear dose response describes the data adequately and that tumor risk is higher in persons exposed during childhood. However, despite the fact that these studies have generated a rich knowledge on radiation induced thyroid cancer, they suffered insufficient data in individual studies.

Ron and colleagues have performed a pooled analysis of seven studies which included 120.000 people in total to address the issue of the risk of thyroid cancer after exposure to external radiation and have concluded that the thyroid gland in children has one of the highest risk coefficients and is the only tissue with convincing evidence for risk at about 0.10 Gy (Ron et al, 1995). Similarly, the childhood cancer survivor study which included 12.547 children has reported risk of secondary thyroid cancer after radiotherapy for a childhood cancer (Bhatti et al, 2010).

Regarding the risk of developing thyroid cancer following Computed Tomography (CT) examinations, the studies are currently underway to assess the incidence of cancer in large cohorts of children who received computed tomography scans but the available data seem to show that the risk is really small but not negligible (Mazonakis et al, 2006; Berrington de Gonzalez , 2011).

__Dr Patrick Smeesters__ is Doctor in medicine (Université Catholique de Louvain, UCL, 1977) and obtained a Master in Occupational medicine (Université Catholique de Louvain, 1980). Lecturer in the Faculty of Medicine of the Université Catholique de Louvain (UCL), he worked in the Department of radiological protection (SPRI) in the Ministry of social affairs, public health and environment until 2001 and later as radiological protection advisor in the Federal Agency for Nuclear Control (FANC) until his retirement in 2011. Among others, he has been member of the Committee of Radiological Protection and Public Health (CRPPH) of the Nuclear Energy Agency (NEA) of the OECD, and of the Radiation Safety Standards Committee (RASSC) of the IAEA. He was and is still member of the Belgian delegation in the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), member of the Scientific Committee of the MELODI platform and member of the Article 31 Group of experts (since 1989), where he chairs the working group « Research Implications on the Health Safety Standards » (RIHSS). Currently he is also member of the College of the Belgian Superior Health Council.

Low-dose ionizing radiation risk research: key issues

Patrick Smeesters

Recently, two reviews of priority key issues in low-dose radiation risk research were made. The first one comes from MELODI. MELODI (Multidisciplinary European Low Dose Initiative) is a European platform dedicated to low-dose ionizing radiation risk research, aiming to integrate national and European activities in this field and developing a regularly updated Strategic Research Agenda (SRA) and statements about priorities. The second one was elaborated by the Article 31 Working Party on Research Implications on Health and Safety Standards (WP RIHSS) and highlighted topics for research in support of radiological protection and implementation of Basic Safety Standards. MELODI highlighted individual susceptibility (including gender and age at exposure), biomarkers, target cells, dose inhomogeneity (including internal exposures), shape of the dose-effect relationship and finally epigenetic mechanisms, all topics covering also explicitly non-cancer diseases. RIHSS underlined non-cancer radiation-induced effects, combined exposures, chronic internal exposures, low dose effects of irradiation in utero, transgenerational mutagenesis and the need to develop new more risk-related dose concepts.

In fact there is a large coherence between these two reviews, both highlighting in particular the potential role of new mechanisms , such as epigenetic alterations (DNA-methylation for example). These cover radiation-induced (or other stressor-induced) effects without targeted DNA mutation but linked with genomic instability. They are also not linked with classical mechanisms of deterministic effects and are therefore falling outside the classical paradigm of radiation effects. A typical example is transgenerational mutagenesis. There is a need to explore the potential role of these epigenetic effects, particularly in non-cancer and hereditary diseases, and the relation with age at exposure (incl in utero) and environmental stress, including chronic internal exposures..This is the area where the uncertainties are the largest and at the same time for which the potential implications for radiation protection are the most striking, particularly in post-accidental situations. In this respect, it must be stessed that the continuation of the Chernobyl research programs, in particular a long term LSS-like follow up, is an ethical need. Indeed, even if the situation for conducting such studies is not ideal, it is the only possibility to study a large population exposed to protracted and/or chronic exposures of IR and showing a large inhomogeneity in the dose distribution. This issue will be central in any future nuclear accident. An important issue is that the scope of these programs should include exploring the possible role of accumulation of epigenetic effects , particularly in children chronically exposed by ingestion of caesium 137.