

## Joint research towards a better radiation protection—highlights of the Fifth MELODI Workshop

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## Memorandum

# Joint research towards a better radiation protection—highlights of the Fifth MELODI Workshop

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## Abstract

MELODI is the European platform dedicated to low-dose radiation risk research. From 7 October through 10 October 2013 the Fifth MELODI Workshop took place in Brussels, Belgium. The workshop offered the opportunity to 221 unique participants originating from 22 countries worldwide to update their knowledge and discuss radiation research issues through 118 oral and 44 poster presentations. In addition, the MELODI 2013 workshop was reaching out to the broader radiation protection community, rather than only the low-dose community, with contributions from the fields of radioecology, emergency and recovery preparedness, and dosimetry. In this review, we summarise the major scientific conclusions of the workshop, which are important to keep the MELODI strategic research agenda up-to-

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date and which will serve to establish a joint radiation protection research roadmap for the future.

**Keywords:** multidisciplinary european low dose initiative (MELODI), Fifth MELODI Workshop 2013, ionising radiation, radiation protection, EURADOS, NERIS and ALLIANCE, integrated research

(Some figures may appear in colour only in the online journal)

## 1. Introduction

MELODI, acronym for Multidisciplinary European Low Dose Initiative, is a European Platform dedicated to low-dose radiation risk research ([www.melodi-online.eu](http://www.melodi-online.eu)). MELODI was founded in 2010 as a registered association with 15 members. Today, MELODI includes 30 members from 16 European countries. The purpose of MELODI is (i) to propose research and training priorities for Europe in its fields of competence, (ii) to seek the views of stakeholders on the priorities for research, keep them informed on progress made, and contribute to the dissemination of knowledge, and (iii) to interface with international partners (like WHO, IAEA, ICRP, UNSCEAR). With this in mind, the Strategic Research Agenda (SRA) of MELODI is developed. The SRA is regularly updated based on the outcomes of the yearly MELODI workshops, and is available for consultation and comment on the MELODI website. To ensure an open and transparent discussion and development of the SRA, MELODI solicits contributions from a large number of institutions and stakeholders.

The Fifth International MELODI Workshop was organised by SCK•CEN, the Belgian Nuclear Research Centre, from 7 October through 10 October 2013 in Brussels ([www.melodi2013.org](http://www.melodi2013.org)). The workshop offered a unique opportunity to the 221 participants originating from 22 countries worldwide and representing various universities, research institutes and organisations, regulatory bodies, service providers, or national and international stakeholder organisations, to update their knowledge and discuss low-dose radiation research issues, as well as to be involved in the MELODI low-dose research platform. In addition, the MELODI 2013 workshop was reaching out to the broader radiation protection community, rather than only the low-dose community, with contributions from the fields of radioecology, emergency and recovery preparedness, and dosimetry. A total of 118 oral presentations were given and 44 posters were presented. Abstracts, and oral or poster presentations are available at the workshop website ([www.melodi2013.org/en/Presentations](http://www.melodi2013.org/en/Presentations)).

During this particular MELODI 2013 workshop, plenary sessions focused on topics in which significant breakthrough progress had been made over the past few years, whilst three thematic sessions running in parallel were devoted to more specific research topics related to radiobiology, dosimetry, epidemiology, radiotherapy (RT), radioecology, emergency planning and other fields of low-dose risk research. The parallel sessions were rounded off by discussions which served to keep the SRA up-to-date and to further implement it into the various low-dose research groups throughout Europe. MELODI also aims to recognise talented and promising young scientists (under 35 years old) who have already contributed greatly to low-dose research. Therefore, for the second time, an annual MELODI award was granted during the workshop. In their MELODI award presentation, awardees Anna Acheva (Radiation and Nuclear Safety Authority, STUK, Finland) and Luca Mariotti (University of Pavia, Italy) presented their work about '3D skin and lung epithelial models for radiation biology studies', and 'Systems radiation biology to model non-linear effects', respectively.

This paper summarises the major scientific findings presented during the MELODI Workshop 2013. Here, we refer to the workshop speakers as well as to the selected recent publications highlighting the topics under discussion during the workshop.

## 2. SRA and priorities of MELODI, ALLIANCE, NERIS and EURADOS

The MELODI workshop 2013 in Brussels was the first reaching out to the broader Radiation Protection Community rather than only to the low-dose community. In this session, the four radiation protection associations, MELODI ([www.melodi-online.eu](http://www.melodi-online.eu)), EURADOS ([www.eurados.org](http://www.eurados.org)), NERIS ([www.eu-neris.net](http://www.eu-neris.net)) and ALLIANCE ([www.er-alliance.org](http://www.er-alliance.org)) presented their latest versions of their respective SRA. The aim of the presentations was to foster integration and find interfaces for further collaboration between the research planned within the four organisations.

Radiation protection covers the fields of (1) radioecology (within ALLIANCE), (2) emergency and recovery preparedness (within NERIS), (3) research on the effect of low-dose ionising radiation (from environmental, accidental and medical origin) to humans (within MELODI) and (4) dosimetry (within EURADOS). The expertise needed in these fields rely on a broad range of scientific disciplines. Some of these disciplines are needed in two or more of the radiation protection fields. For example, genetics is a discipline needed in radioecology and low-dose research, or, meteorology is a vital discipline in radioecology and emergency preparedness. An in-depth analysis reveals numerous interfaces between the different radiation protection fields. To increase synergy, it is important to initiate joint efforts to map the respective expertise, the complementarities and the common challenges. MELODI, EURADOS, NERIS and ALLIANCE all acknowledged and appreciated the workshop initiative to bring these fields together and present/discuss their research areas in order to foster further collaboration/integration.

### 2.1. Further developments in June 2014

In the meantime, the four radiation protection associations have signed a Memorandum of Understanding to collaborate on radiation protection research. The first step was to establish a Joint Radiation Protection Research Roadmap Committee, in order to better coordinate their respective SRAs and priority roadmaps that would ensure completeness and complementarity. The aim is to establish a common radiation protection research roadmap, to be updated and made publicly available on a yearly basis, setting out coherent priorities for the whole field of radiation protection research. The four associations will also set up joint working groups in order to elaborate a joint vision in areas of common concern, for the benefit of the European radiation protection research.

As a first joint action, the radiation protection associations have established a list of research priorities in which the expertise of at least two of the radiation protection associations is needed to achieve the objectives. This list has recently been published as a part of an electronic survey ([www.melodi-online.eu/operra\\_eSurvey.html](http://www.melodi-online.eu/operra_eSurvey.html)) launched in the framework of the EU FP7 OPERRA project. Responses are expected from the four RP communities and their respective stakeholders. The answers to the survey part on synergistic research priorities will be available and presented at the next MELODI workshop, to be held in Barcelona, Spain (7–9 October 2014).

## 3. Fukushima accident: emergency, dosimetry, environment and health

The UNSCEAR Fukushima report was summarised by Jean-René Jourdain (French Institute for Radiological Protection and Nuclear Safety, IRSN, France) [1]. After the Fukushima

accident of 11 March 2011, Japan, other member states of the United Nations, and international organisations made available to the UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation) extensive data for its assessment, regarding the radiation levels and deposition of radioactive materials in every prefecture in Japan as well as the radionuclide concentrations in foodstuffs, and public and workers exposures. Many of these data were provided by official Japanese governmental agencies and were published in peer-reviewed scientific journals. Furthermore, 25 other UN Member States provided information on request. Additional relevant data were made available by other international organisations. Several non-governmental organisations also made data available that were considered in the assessment. The quality of these data (data sets, reports, journal articles and so on) was evaluated in terms of their usefulness for the assessment.

Limited uncertainty/sensitivity studies have been conducted, as appropriate, to underpin the UNSCEAR's qualitative statements of its confidence in its conclusions. In addition UNSCEAR deployed five working groups to perform quantitative assessments of doses received to the public and emergency workers, and made a judgment on their reliability. Initially, the publication of the UNSCEAR's report was expected on 8 October 2013. However, due to the time required to take into account late comments from some UN delegations, the report was not released at the time of the Workshop (published April 2014 and available on [www.unscear.org](http://www.unscear.org)). The report discusses the course of the accident, the release of radioactive material into the environment, dose assessment, health implications, and radiation exposures and effects on nonhuman biota.

Richard Wakeford (University of Manchester, UK) commented the WHO (World Health Organisation) Fukushima reports [2, 3] (both reports are freely available on [www.who.org](http://www.who.org)). Following the releases of radioactive materials into the environment from the Fukushima Daiichi Nuclear Power Station in March 2011, WHO initiated a study of the possible health risks resulting from the releases. The study has two parts: an estimate of the radiation doses received during the first year after the accident, and the health risks arising from these doses.

For two highly exposed locations in the Fukushima Prefecture, effective doses during the first year after the accident were assessed to be in the range 10–50 mSv, of which organ dose to the thyroid accounted for 10–100 mSv (and for infants, the estimated thyroid dose was in the range 100–200 mSv). Doses elsewhere were less than this, generally much less. The WHO report points out that for a child aged 10 years living in most affected areas, 57% of the cumulative effective dose (mainly from ground deposition) and 79% of the cumulative thyroid dose (mainly from inhalation) were received during the first month after the accident.

On the basis of these dose estimates, the health consequences were evaluated. Both excess relative risks and excess absolute risks were calculated on the basis of recently developed risk models. For the population with highest assessed doses, the additional lifetime risk of cancer is about 1% (of which approximately 0.5% is due to thyroid cancer). The group with highest risk consists of females who were infants at the time of exposure. The given estimates are for the highest exposed areas, and subsequently the estimated excess risk is lower for other age groups and locations. For emergency workers, about one-third received thyroid doses that, for the youngest workers, could increase the risk of thyroid cancer by about 20%. The proportional increase of leukaemia for the youngest workers is estimated to be less than 1%.

Thyroid cancer is one of the major health concerns after the accident in the Fukushima Daiichi Nuclear Power Station. Ultrasonography surveys are being performed for persons residing in the Fukushima Prefecture at the time of the accident with an age of up to 18 years, as was explained by Peter Jacob (Helmholtz Zentrum München, HMGU, Germany). The prevalence of thyroid cancer was estimated to be 0.034% (95% confidence interval (CI):

0.009–0.085%). Compared to the incidence rate in Japan in 2007, the ultrasonography survey is predicted to increase baseline thyroid cancer incidence by a factor of 7.2 (95% CI: 3.7; 10.7). Under the condition of continued screening, thyroid cancer during the first 50 years after the accident is predicted to be detected for about 2% of the screened population. The prediction of radiation-related thyroid cancer in the screened population of the Fukushima prefecture has a large uncertainty with best estimates of the average risk of 0.1–0.3%, depending on average dose.

Johan Camps (Belgian Nuclear Research Centre, SCK•CEN, Belgium) provided details concerning the response of SCK•CEN to the Fukushima nuclear accident in the context of the protection of Belgian citizens. As a research organisation, SCK•CEN is a partner of the authorities related to emergency planning and response. The response was organised *ad hoc* because the Belgian nuclear emergency plan was not declared. The challenges in the response included (i) an early radiological impact assessment for advice for Belgians in Japan with little and uncertain information: this showed the importance of including uncertainties in assessments and combining atmospheric dispersion modelling efforts with monitoring data, (ii) mobile and laboratory measurements of people returning from Japan: first persons measured resulted in more qualitative information of the impact on the locations the persons stayed. Although only limited contaminations were found, this campaign showed to be very important for re-assuring the worried travellers, (iii) increased surveillance of the Belgian territory (air concentration, grass, milk): the clearly measurable but trivial exposures made communication about the effect of the accident on the Belgian territory a challenge, (iv) many questions related to imported goods: this illustrated the need for a better preparedness related to contaminated goods. In this context a NERIS (European Platform on preparedness for nuclear and radiological emergency response and recovery, [www.eu-neris.net](http://www.eu-neris.net)) working group and a work package in the FP7 PREPARE project were set up.

A study by cytogenetic analysis of 12 restoration workers in the aftermath of the Fukushima Daiichi Nuclear Power Station accident was presented by Yumiko Suto (National Institute of Radiological Sciences, NIRS, Japan). Two methods were used to examine the blood samples of the 12 workers. Dicentric chromosome assay (DCA) showed for none of the workers values exceeding the dose limit of 300 mGy (at 95% upper confidence limit), which is lower than the lower limit level of medical triage for acute radiation syndrome which is 1 Gy. These results confirm the fact that no acute radiation syndromes were observed among the workers examined and the obtained values are in good agreement with physically estimated doses by personal dosimeters. Fluorescence *in situ* hybridisation (FISH), more especially multiplex and three-colour FISH, was used for translocation analysis. The results suggest that the frequency of translocations is considered to be 1.5 times higher in the workers compared to an unexposed control group. Based on this experience the need for improved cytogenetic research strategies adopted for mass-casualty management was reconsidered.

Yutaka Hamaoka (Keio University, Japan) presented preliminary results of an analysis of radiation dose and occurrence of thyroid nodules using data from 14 cities and villages. More specifically a relationship was made between the number of thyroid nodules and the radiation dose. The radiation dose used was based on available data on radiation level within cities and villages. A conjecture 'If a nodule was caused by radiation, taking into account the slow growth of thyroid nodules, the number of smaller nodules would correlate with radiation dose rather than that of larger nodules' is supported by thyroid dose estimates made by WHO and NIRS on Fukushima external doses. Although the sample size was limited, the robustness of the results was confirmed. The results might indicate an early warning for future incidence of thyroid cancer. Follow-up is necessary.

#### 4. Transgenerational effects induced by radiation

Transgenerational instability can be defined as a genome-wide phenomenon affecting the frequency of chromosome aberrations and gene mutations in the next-generation offspring. The thematic issues debated for transgenerational effects covered both paternal and maternal transmission of genomic instability in mice. The first experimental evidence of increased germ-line mutation rates in the first and second generation of unexposed offspring of neutron-irradiated male mice was obtained in the CBA/H mouse strain [4]. The effects of strain specificity and high and low linear energy transfer (LET) exposure on germ-line mutation rates in the first and second generation progeny of irradiated males were addressed by Yuri Dubrova (University of Leicester, UK). The data revealed elevated ESTR (Expanded Simple Tandem Repeat) mutation in both generations of all of the three inbred strains (CBA/H, C57BL/6, BALAB/c) tested and that either high or low LET irradiation resulted in an increase in germ-line mutation rates in both generations [5]. Other irradiation criteria can influence the paternal transmission of genomic instability in mice. In this regard, the dose and dose rate effects were discussed. The data presented showed that acute  $\gamma$ -radiations (50 and 100 cGy) of the male parents increased evenly the frequencies of ESTR mutations in the brain and in the germ line of their progeny. Unlike, high dose acute radiation, acute irradiation at lower doses (10–25 cGy) and low-dose-rate exposure to 100 cGy did not affect stability of the next-generation offspring. From these data, it appears that the manifestation of transgenerational instability is triggered by a threshold dose of acute paternal irradiation [6].

Maternal transmission of genomic instability was discussed during this session after the presentation given by Paul Jacquet (SCK•CEN, Belgium). Transgenerational effects and congenital malformations were investigated after moderate x-irradiation (0.2 and 0.4 Gy) of two mouse strain (ICR and CF1) embryos during the pre-implantation stage (1-cell embryo). In both ICR and CF1 mouse strains, irradiation of female zygotes did not result in an increase in the frequency of malformations nor to the increase of chromosomal instability in the next-generation embryos. Overall, these results suggest that, at the moderate doses used, the very few developmental defects observed after X-irradiation of female zygotes of these two sensitive mouse strains should not be transmitted to the next generation [7].

Overall, transgenerational instability is attributed to the presence of a persistent subset of endogenous DNA lesions and to the epigenetic changes affecting the expression of a subset of genes, involved in rhythmic process and regulation of transcription. From the results of the mouse studies, it would appear that maternal or paternal irradiation with low doses and low-dose-rate irradiation do not destabilise the genome of the offspring while irradiation of the male parent with acute high doses does. Despite the latter finding in mice, experimental evidence for transgenerational instability in humans remains highly controversial especially when comparing the transgenerational effects in children from fathers exposed to post-Chernobyl radioactive contamination or from cancer RT survivors. Nevertheless, the risk for transgenerational instability in humans cannot be completely excluded as only a few generations have been observed. Moreover, lack of human evidence does not mean evidence of lack of effect as was stressed by Patrick Smeesters (Federal Agency for Nuclear Control, FANC, Belgium).

#### 5. Mixed toxicity between radiation and other substances

The session on mixed exposure started with a general overview talk of Nele Horemans (SCK•CEN, Belgium) defining what is meant by mixed exposure conditions and what approaches could be used to estimate possible interacting effects from different compounds.

In our environment, mammals (including humans) are exposed to various types of ionising radiation and both persistent and non-persistent toxic chemicals. This area of research certainly deserves more interest to understand the combined effect of radiation and environmental toxicants; it would also inform us about the effect of confounding factors rendering the epidemiological data from radiation-exposed cohorts in some situations less conclusive for the radiation effect. Most scientists today acknowledge that in natural situations organisms are generally exposed to multiple stressors either simultaneously or at different times during their lifespan. In general, however, most experimental studies assess effects of stressors including low-dose radiation in controlled single contaminant conditions. Moreover, for some mixed exposure experiments results or possible interactions are sometimes misinterpreted [8]. Hence, a key question to assess the risk of low-dose gamma exposure is to know whether interacting effects might occur when humans or nonhuman biota are exposed to several stressors. The presentation focused on the different mathematical models that can be used for the prediction of combined effects based on the known individual effects, namely concentration addition (CA) and independent action (IA) [9]. After this more general overview, four specific presentations dealing with different aspects of exposure to radiation in a mixed contaminant set-up were presented.

RT can come with a secondary cost such as possible gonadal dysfunction or DNA damage in germ cells during spermatogenesis or oogenesis leading to meiosis malfunction, abortions or hereditary effects. A study on radiation-induced genome instability and possible induction of transgenerational effects was given by Aurora Ruiz-Herrera (Autonomous University of Barcelona, UAB, Spain). Foetal offspring of x-ray exposed female rats (5 Gy, acute dose) were evaluated. In addition the possible interaction between pre-treatment with x-rays on the action of the chemical mutagen aphidicolin was studied. Cytogenetic analysis showed a statistical increase in the frequency of chromosomal breaks and aberrant metaphases in the F1 foetal somatic cells from F0 exposed mothers to irradiation. This study concluded that the x-ray treatment resulted in transgenerational chromosomal instability. Moreover, this genome instability was enhanced by the secondary stressor aphidicolin as indicated by the increased induction of chromosomal damage.

Eeva Salminen (STUK, Finland) dealt with RT given together with other chemical agents. In her presentation, an overview was given of the advantages and disadvantages of a combination of RT and chemotherapy. In most cancer treatments, both therapies are combined resulting in lesser dose of both and a higher survival rate for the patient. Advantages and disadvantages of the timing of the two treatments (sequential, concomitant or intermittent) were discussed indicating, as could be expected, that concomitant application of chemo- and radiotherapy is the most toxic. In this situation additional growth factors are often applied to reduce the dose effects on non-cancer cells. Further research in this area will not only result in less toxic and more specific drugs for chemotherapy but also in fine-tuning of the dose and timing of the chemo- and radiotherapy. Finally, some attention was given to the possible beneficiary effects of the use of drugs that would reduce DNA damage in combination with the RT [10, 11].

The presentation given by Sonia Buratovic, on behalf of Per Eriksson (Uppsala University, Sweden), dealt with the possible changes in habituation and altered cognitive function in adult mice due to exposure to gamma radiation or nicotine or a combination of both during a critical period of neonatal brain development. Exposure to gamma radiation (0.2 Gy with a dose rate of  $0.07 \text{ Gy min}^{-1}$ ) and/or nicotine ( $66 \mu\text{g kg}^{-1}$ ) was given at one to three successive days starting at postnatal day 10. Subsequently, two-month old adult mice were scored for spontaneous behaviour in a novel home environment. Additionally, neurotoxic susceptibility to nicotine was tested by additional exposure of the adult animals to nicotine. Their data indicate that

interactive effects between gamma irradiation and nicotine during prenatal brain development exist and can lead to enhanced behavioural aberrations and increased susceptibility to nicotine at adulthood. In addition, it was suggested that the cholinergic system is involved in the increased radiation susceptibility upon mixed gamma radiation and nicotine exposure during neonatal brain development. Together, these data provide evidence on the confounding effect of smoking in radiation-exposed epidemiological cohorts.

As explained during her presentation, the objective of Ann-Karin Olsen's research (Norwegian Institute of Public Health, NIPH, Norway) is to investigate the genotoxic and reproductive effects of low-dose-rate gamma exposure in combination with a varying selenium (Se) level in mice. Mice deficient in the repair of oxidised DNA (8-oxoguanine DNA glycosylase, *Ogg1*) were used in addition to control mice. The *Ogg1* model was used to mimic repair characteristics of human germ cells as this differs between humans and rodents in this respect [12]. Selenium intake which is sub-optimal in many regions of the world is essential for the optimal function of antioxidative selenoproteins enzymes (such as glutathione peroxidase), a number of enzymes known to play an important role in hormonal activation (like thioredoxin reductases) and in the functioning of sperm. Mice were exposed to an average gamma dose rate of  $1.63 \text{ mGy h}^{-1}$  during 45 d resulting in a total dose of 1.71 Gy. Gamma exposure resulted in higher DNA damage levels (as evidenced by the Comet assay), induced clastogenic effects (such as increased micronuclei) and increased gene mutation rates (as measured by *Pig-a* mutation). However gamma-induced effects were irrespective of the Se status or the *Ogg1*-genotype showing that selenium does not seem to play a role in gamma-induced toxicity.

## 6. Radiation effects on wildlife

Traditionally radiation protection has focused on the protection of humans. The past decades however have been marked by a growing awareness that levels of radiation that are considered safe to humans may not always result in no harm to wildlife and/or ecosystems [13, 14]. A short introduction of this session was given by Tom Hinton (IRSN, France). It was said that for the development of a framework for deriving protection criteria for nonhuman biota there is an urging need for more environmental relevant data and for a better mechanistic understanding of radiation-induced effects. After the introduction four specialised talks from different research areas were given.

A critical view on the realism and scientific value of acute lab-based ecotoxicological tests for risk assessment as well as the setting and evaluation of radiation protection standards was given in the presentation of Nele Horemans (SCK•CEN, Belgium). An introduction was given on the approach. A species sensitivity distribution (SSD) led to a generic no-effect dose rate for wildlife of  $10 \mu\text{Gy h}^{-1}$  that currently can be used in environmental radiation protection to screen out situations of no concern [15]. The basic information that is put in to this SSD, are effect concentrations or effect dose rates (ECx or EDRx) derived from individual dose–response curves. However, as the amount of effects for nonhuman biota is limited, it is not evident to make specific SSDs for specific exposure scenarios such as chronic exposure compared to acute exposure or separate lab from field experiments. Using the OECD (Organisation for Economic Cooperation and Development) guidelines for a growth inhibition test for *Lemna minor* [16], some of the drawbacks of the use of ecotoxicological tests were presented. As such it was shown that the derived ECx/EDRx values are highly dependent on the endpoint chosen (*Lemna* frond area, number of fronds, fresh weight, dry weight), the growth conditions (e.g. nutrient medium), as well as the experimental set-up (e.g. duration of the test). As an example the effective dose rate resulting in 50% growth inhibition (EDR50) of *Lemna* plants

shifted from 900 to 270 mGy h<sup>-1</sup> when the plants were given an extra 7 d recovery after the exposure to gamma irradiation. This lower EDR50 value suggests a higher sensitivity and a lack of DNA damage repair in the plants during the recovery period. In conclusion, it was indicated that an increased data collection especially in environmental relevant situations is needed to lead to more scientific robust bench marks for radioprotection for nonhuman biota.

Christelle Adam-Guillermin (IRSN, France) presented the preliminary results of the project FREEBIRD (that stands for Fukushima Radiation Exposure and Effects in Bird populations) that aims at studying effects of radiation originating from the Fukushima accident on bird populations in the 100 km zone around the Daiichi nuclear power plant. As indicated by Adam-Guillermin the strength and innovative character of this project find their origin in the multidisciplinary nature of the approach in which behavioural ecology, toxicological responses on the physiology and the reproductive success of the birds are studied and integrated with a dosimetry as accurate as possible for wildlife. During the Workshop, the set-up and first sampling campaign of the project were introduced. Although only preliminary results were available at the time of the meeting, already high interspecies differences could be found. As such it was shown that internal exposure levels in frogs were much higher than in birds probably due to differences in living habit between these animals. Based on the preliminary dose estimation, including internal and external doses, it was indicated that frogs are exposed to dose rates above the safe threshold of 10 μGy h<sup>-1</sup> [15].

In order to investigate if modulation of radiation at background levels can modify the response of organisms to genotoxic agents there is a need to have experimental conditions with different radiation environments. As presented by Maria Antonella Taboccini (National Institute of Health, ISS, Italy) the underground 'Gran Sasso National' Laboratory (LGNS) of the Italian National Institute of Nuclear Physics offers the possibility to have near-zero background radiation levels. As such in this facility the cosmic ray and neutron flux are up to six orders of magnitude lower than at the surface. Yeast cells, grown for 120 generations in this low background radiation environment and subsequently exposed to different genotoxic agents, had higher frequency of recombination in the LGNS compared to a reference culture [17]. Further studies have been carried out on higher eukaryotic cell cultures (V79 Chinese hamster lung fibroblasts, TK6 lymphoblasts and A11 mouse cell line) for long exposure conditions to reach comparable number of generations as the yeast cells. In general the experiments with the different eukaryotic lines confirmed that cells cultured in reduced environmental radiation conditions were less tolerant to radiation-induced DNA damage and less efficient in scavenging reactive oxygen species [18–20]. Future experiments will include *in vivo* studies.

## 7. Non-cancer effects induced by radiation

### 7.1. Radiation exposure of the eye lens and cataract risk

Increased risk of cataract after radiation exposure to the eyes has been investigated in many epidemiological studies, as explained by Roy Shore (Radiation Effects Research Foundation, RERF, Japan). The cohorts consisted, besides others, of A-bomb survivors, children receiving radium plaques, residents of radium contaminated buildings, children from Ukraine after Chernobyl, Chernobyl clean-up workers, US radiologic technologists, and astronauts [21, 22]. All studies found significant relative risks (RR) of 1.2–1.6 per 1 Gy, except for the medical technologist studies, which reported a non-significant RR of 2.5–3.0 per 1 Gy. In terms of radiation protection, thresholds for cataract between 0.1 and 0.7 Gy have been reported.

Although these studies all reported excess risks of lens opacities, the results were nevertheless based on different methods regarding lens opacity classifications and assessment of known risk factors of cataract. Another point of concern was dosimetry, as almost all studies have substantial dose uncertainties. Therefore, results of all these studies are difficult to compare or combine [23].

A harmonised large cohort (multi-national) epidemiological study on the risk of lens opacities from low-dose radiation could prove to be a very valuable study. Based on limitations of similar past studies, several thoughts need to be considered. Some past studies had only crude adjustment or matching for age at examination. As age is clearly an important variable with regard to lens opacity prevalence, it needs to be carefully listed. Also other known risk factors of cataract need to be assessed and taken into account during risk analysis. More difficult to handle is the issue of selection bias. Indeed, low participation rates can induce both uncertainty and possible bias. It should therefore be considered also how one can define and obtain a comparable unexposed group and also get a high participation rate among them. The most difficult of all is how to reconstruct the doses to the eyes with a good degree of precision and accuracy. In this regard, the ELDO project (acronym for European epidemiological study of radiation-induced cataracts in interventional radiologists and cardiologists) was set up to combine epidemiology and dosimetry to study radiation-induced lens opacities among interventional cardiologists, as explained by Lara Struelens (SCK•CEN, Belgium). The objective of this European project was to develop the methodology on how a European epidemiological study on radiation-induced risk for cataract for interventional cardiologists should be conducted, including as well the retrospective assessment of eye lens doses. A European initiative has recently started to perform such an epidemiological study by recruiting interventional cardiologists in several European countries following the same protocol to be able to carefully evaluate on the pooled European cohort the linearity/non-linearity of the dose–response relationship on cataract. This will have important implications with regard to occupational and patient dose limits.

Further actions should also help answering the following questions. (i) What is the dose threshold, if any, and risk after highly fractionated or protracted exposure since there is a lack of dose–response data for such scenarios? (ii) How frequently do radiation-associated small posterior sub capsular opacities progress to become vision-impairing cataracts? (iii) Does radiation multiply or only add to the effects of other cataract risk factors? (iv) What biological mechanisms mediate the development of radiation cataracts at lower doses?

## 7.2. Radiation-induced cognitive and cerebrovascular effects

The cognitive and cerebrovascular effects in humans after exposure to ionising radiation were addressed by Rafi Benotmane (SCK•CEN, Belgium). The received doses and the stages of development of the brain are the major determinants for cognitive disease occurrence at later age. The main evidence is provided from epidemiological studies (A-bomb survivors, Ukraine residents) indicating an increase in development disorders, neurological disorders and strokes [24, 25]. Several neurological diseases have been shown to be the result of defect in gene regulation during a critical period of brain development [26, 27], thus molecular studies can contribute in identifying specific signatures of disease occurrence. Biological understanding of the actions of radiation can be used to improve evaluations of health risks at low doses. Improved understanding of the mechanisms per se will not eliminate the uncertainty, but can help to reduce the risk-related uncertainties and thereby increase confidence in low-dose risk estimates [28].

A strategy towards future research was proposed in the following research areas: the effect of radiation quality, the study of delayed effects by setting up long-term studies, the role of epigenetics in long-term effects at disease occurrence, and to apply modern systems biology

techniques to evaluate non-cancer effects, combined exposure to radiation and other environmental pollutants, the combined efforts from epidemiology and radiobiology to launch molecular epidemiology, to evaluate the validity of LNT (linear non-threshold) assumption for non-cancer effects.

So far we have scarce evidence about the occurrence of cognitive disabilities following exposure to different radiation qualities. Most studies were devoted to acute external gamma and internal irradiation to confirm the observations of cognitive and cerebrovascular effects from the A-bomb survivors, Chernobyl and cancer survivors. More effort should be devoted to study the effect of high LET and heavy ions irradiation, as well as chronic exposure at different dose rates. On the other hand, most of the studies on the effect of radiation have focused for many years on the direct effect, few hours to days after exposure, although epidemiological data tell us that cognitive diseases may occur many years after exposure. Animal studies should mimic the human situations of disease presentation; by setting long-term studies (several weeks to months after exposure) we could better relate early events with late disease occurrence. This long-term setting would help to identify the epigenetic processes occurring between the early events and late disease presentation, as such epigenetic events involved in gene regulation (micro RNA, long non-coding RNA, CpG methylation, acetylation) can be identified, which will help in building a systems biology approach. In this context, the recent advances in molecular omics technologies such as next-generation sequencing and spectroscopy for transcriptomic, proteomic, methylomic and metabolomic changes start to provide useful data to identify the molecular fingerprints. It is therefore expected that data analysis and integration will play a major role in identifying the metabolic pathways and regulatory networks involved in the setting of long-term cognitive and cerebrovascular effects.

A first step towards the above explained systemic approach is achieved within the EU FP7 project CEREBRAD (Cognitive and Cerebrovascular effects induced by low-dose ionising radiation) (Grant Agreement No 295552). Health risk assessments at low radiation doses can contribute to understand the related mechanisms, and thus reducing the uncertainty at low doses. Animal studies could help to understand such mechanisms and are being performed within CEREBRAD. The consortium investigates the behavioural effects as well as molecular, cellular and tissue changes at early (days) and late (months) time points. Molecular mechanistic studies are supported by the proteomic and genomic information collected in different brain regions. Advanced bioinformatics will allow integration of the data at different levels in order to understand the biology of the system. In addition, CEREBRAD studies epidemiological data from several cohorts in order to increase the statistical power regarding radiation-induced cognitive and cerebrovascular effects, such as (1) cohorts of children having received RT to treat different types of cancer or haemangioma and having received low to moderate doses in the brain, and (2) a cohort of Ukrainian clean-up workers including *in utero* exposed individuals.

Finally, in order to confirm part of the genetic and epigenetic changes identified in animal studies, appropriate epidemiology cohorts are required to launch real molecular epidemiology for biomarker testing and validation. A lot of effort should be devoted to increase the statistical power of epidemiological data for cognitive and cerebrovascular diseases and using appropriate mathematical modelling, is the only way to validate the LNT model for cognitive non-cancer effects.

### 7.3. Cardiovascular risks associated with radiation

Because the effect of RT on the subsequent risk of ischemic heart disease is uncertain, a population-based case–control study was conducted of major coronary events in breast cancer patients who underwent RT between 1958 and 2001 [29]. The results were presented by

Sarah Darby (Oxford University, UK). From the RT chart of each patient the mean radiation doses to the whole heart and to the left anterior descending coronary artery were estimated. The average mean dose to the whole heart was 4.9 Gy and the dose–response relationship for major coronary events increased linearly with the mean dose to the heart by 7.4% per Gy, with no apparent threshold. The increase began a few years after exposure, and continued till the end of the observation period. The data was stratified by several other risk factors, and women with pre-existing cardiac risk factors showed greater absolute increases in risk from RT. Nevertheless RT can treat a lot of breast cancer patients with usually higher mortality rates compared to no RT. However, it is needed to balance absolute benefit from RT and absolute risk. Further studies are needed e.g. to seek for early detection of cardiovascular disorders after breast cancer RT with the possibility for early treatment and prevention. This may be achieved by exploring modern techniques like strain rate imaging and the integration of predictive molecular markers.

Although several studies have confirmed the damaging effect of ionising radiation on the myocardium and on the cardiac endothelial structure and function, the molecular mechanisms behind this damage are not yet elucidated. In her presentation, Soile Tapio (HMGU, Germany) explained how her group investigated radiation-induced changes in the cardiac proteome [30]. To this end, C57BL/6 mice were irradiated at the level of the heart with x-ray doses of 8 and 16 Gy at the age of 8 weeks and sacrificed 16 weeks later. Radiation-induced changes in the cardiac proteome were quantified using the isotope coded protein label (ICPL) method followed by mass spectrometry and suitable software packages for data mining, including STRING ([string-db.org](http://string-db.org)) and INGENUITY ([www.ingenuity.com](http://www.ingenuity.com)). Significant alterations were observed in proteins involved in lipid metabolism and oxidative phosphorylation. Ionising radiation markedly changed the phosphorylation and ubiquitination status of peroxisome proliferator-activated receptor alpha (PPAR alpha), a transcriptional regulator of lipid metabolism in heart tissue, which has recently received great attention in the development of cardiovascular disease. This was reflected as decreased expression of its target genes involved in energy metabolism and mitochondrial respiratory chain confirming the proteomics data. This study suggests that persistent alteration of cardiac metabolism due to impaired PPAR alpha activity contributes to the heart pathology after radiation.

Since the endothelium, the inner lining of the blood vessels in the entire cardiovascular system, plays a crucial role in normal cardiovascular functioning, endothelial cells have become a standard in cardiovascular *in vitro* research. Therefore, the cellular and molecular mechanisms underlying the cardiovascular risks after low-dose irradiation were studied using primary human umbilical vein endothelial cells (HUVEC) and its immortalised derivative the EA.hy926 cell line, as was presented by An Aerts (SCK•CEN, Belgium). Subtle, but significant increases in DNA double-strand breaks (DSB) were observed in HUVEC and EA.hy926 30 min after low-dose irradiation (0.05 Gy). Compared to high dose irradiation (2 Gy), relatively more DSB/Gy were formed after low dose. Also, a dose-dependent increase in apoptotic cells was observed, down to 0.5 Gy in HUVEC and 0.1 Gy in EA.hy926 cells. Furthermore, radiation induced significantly more apoptosis in EA.hy926 compared to HUVEC. As such, it was demonstrated for the first time that acute low doses of x-rays induce DNA damage and apoptosis in endothelial cells. Furthermore, the results point to a higher radiosensitivity of EA.hy926 cells compared to HUVEC, which should be taken into account using these cells as models studying the endothelium radiation response [31]. In addition, the effects in HUVEC cells after chronic low-dose-rate radiation (1.4 and 4.1 mGy h<sup>-1</sup>) during one, three or six weeks were investigated (FP7 DoReMi project). To gain more insight into the underlying signalling pathways of the biological effects of this exposure, gene expression changes were analysed using microarray technology [32]. The obtained data were analysed in a dual

approach, combining single gene expression analysis and Gene Set Enrichment Analysis. An early stress response was observed after one week of exposure to  $4.1 \text{ mGy h}^{-1}$ , which was replaced by a more inflammation-related expression profile after three weeks and onwards. This early stress response may have triggered the radiation-induced premature senescence in HUVEC exposed to  $4.1 \text{ mGy h}^{-1}$ , as was observed by the consortium by assessing proliferation rates,  $\beta$ -galactosidase levels, and performing proteomic studies [33, 34]. Further analysis of the microarray data pointed to the involvement of insulin-like growth factor binding protein 5 (IGFBP5) signalling in radiation-induced premature senescence.

## 8. Use of high-throughput technologies in radiation biology

With the ever increasing technological power, more and more high-throughput technologies are being applied in the field of radiation biology. Several of these methods were presented during the workshop. Regarding transcriptomics, microarrays seem to be still the preferred method for genome-wide gene expression screenings, although it is expected that also next-generation sequencing will soon enter the field. Grainne Manning (Public Health England, PHE, UK) investigated the dose–response curve of the gene expression response to low-dose radiation exposure (5–100 mGy) of human blood using predicted markers from the ATM/p53 pathway [35]. Gene expression was analysed by quantitative PCR, at different time points (2 h, 24 h) after radiation and showed that early changes were quite modest with only three genes *FDXR*, *CDKN1A* and *BBC3* showing a linear response. After 24 h, nine out of 13 tested genes produced a linear response, although for most of these the individual variability in the response between donors was quite high. Some of the donors had a consistent higher or lower response than others at different doses, suggesting that gene responses may also be useful as markers for individual radiosensitivity.

Continuing on the issue of gene expression biomarkers for low-dose exposure, Gaëtan Gruel (IRSN, France) commented on the results from Manning, which showed no significant modulation of gene expression below doses of 20–50 mGy. One of the problems at these doses is that only a small fraction of the cells will effectively produce a radiation-induced DNA DSB, so that any effect related to DSB repair becomes highly diluted among the entire cell population. He therefore irradiated (5–500 mGy) human blood and extracted CD4-positive cells to evaluate gene expression changes at different time points post-irradiation (150, 300, 450, 600 min) using microarrays [36]. He identified two main clusters of genes; the first cluster represented genes with a linear, dose-dependent expression profile. Most of these genes were known targets of p53 and some of them showed significant differences even at a dose of 10 mGy. The second cluster consisted of genes which were modulated at the same level at all doses. For these genes, no link to p53 could be found, but many of them seemed to play a role in mitochondrial function and were enriched in binding sites for transcription factors involved in mitochondrial function, biosynthesis and replication. So, high-throughput technologies may provide additional information about the molecular effects at very low doses, but must be validated in order to definitively conclude about the biological impact of very low dose exposure.

A third presentation about the transcriptional response to radiation was given by Rodolfo Negri (Sapienza Università di Roma, Italy). He first provided an overview of recent literature, showing that the transcriptional response to ionising radiation is strongly cell type-dependent. Going further on previous work [37], he showed results from a meta-analysis of 208 different radiation conditions (doses, time points, cell types, tissues, etc), from which a signature of 34 genes was identified which were modulated above 1.5-fold in at least 30% of the conditions.

Of these, CDKN1A, involved in cell cycle arrest and apoptosis, was found to be the most general radiation-induced gene, whereas negatively modulated genes were enriched in mitotic cell cycle regulation. Some of these data can be found on a public database of radiation-responsive genes, containing data from 180 different experiments in human, mouse and rat [38]. Because of the cell- and tissue-specific differences in the radiation response, Negri proposed that future research should more focus on the tissue level to identify sensors, signalling molecules and effectors for the tissue radiation response. He further discussed the role of leptin, an adipose-derived hormone which is induced in the epidermis and adipocytes both after irradiation and during wound healing [39].

In an attempt to unravel the mechanisms induced after exposure to low doses of ionising radiation, Houssein El Saghire and colleagues (SCK•CEN, Belgium) also used transcriptomic analyses (microarrays) and different bioinformatics approaches. Whole blood samples collected from healthy donors, x-irradiated *in vitro* with low (0.05 Gy) or high (1 Gy) doses, revealed two distinct dose-dependent profiles. In contrast to high doses, they found that a low dose of 0.05 Gy showed higher statistical ranking of immune-related pathways that are mainly involved in the response to and/or secretion of growth factors, chemokines and cytokines. However, at 1 Gy the response was dominated by classical radiation response genes activated by the tumour suppressor *TP53*, and involved in apoptosis, DNA damage and repair pathways [40]. They confirmed similar low-dose specific responses *in vivo* in a cohort of prostate cancer patients undergoing intensity modulated radiotherapy (IMRT). These patients receive a high RT dose targeted at the level of the tumour but the rest of the normal tissues receive low doses [41].

### 8.1. Epigenetics in radiation biology

Another type of expression data was presented by Natasa Anastasov (HMGU, Germany), who discussed the effect of radiation on the expression of long non-coding RNAs (lncRNA) and microRNAs (miRNA) which are known to play a role in epigenetic mechanisms. Over the past few years, several lncRNAs and miRNAs have been shown to be regulated in response to DNA damage [42] and to be involved in DSB repair [43]. Anastasov therefore proposed that they could also be used as prognostic biomarkers for cancer RT survival and individual sensitivity. She presented the example of miR-21, of which the expression in primary breast cancer correlates inversely with metastasis-free survival [44, 45]. miR-21 is induced in a human ductal breast epithelial tumour cell line, T47D, after radiation exposure (5 Gy), and its inhibition reduces cell proliferation after irradiation by increasing cell death [44]. Whether these miRNA genes can also be applied to the lower dose range needs to be further investigated.

Another presentation regarding radiation epigenetics was that of Chris Talbot (University of Leicester, UK) who addressed the role of DNA methyltransferases (DNMTs) in radiation-induced genomic instability. DNMTs regulate DNA methylation, in which DNMT3a and -b are responsible for *de novo* methylation whereas DNMT1 methylates the newly formed DNA strand during DNA synthesis. Besides this, DNMT1 also plays a role in DNA repair and gene expression. Talbot and co-workers used cell lines with different DNMT status and investigated radiation-induced genome stability, DNA methylation, DNA damage and clonogenic survival [46]. The results of these experiments showed that there was no simple relationship between DNA methylation levels and survival rates, although DNMT1 and DNMT3a/b knockouts did abrogate radiation-induced mutagenesis. However, rescuing the DNA methylation levels in these knockouts, did not rescue the radiation effects, suggesting a more complex relationship between DNMTs and mutagenesis, possibly related to their effects on DNA repair.

## 8.2. Radiogenomics

Radiogenomics, i.e. the study of genetic variations in relation to individual differences in the radiation response, is an important field in clinical radiation research. One of the aims of this field, as presented by Hubert Thierens (University of Ghent, Belgium), is to identify predictive biomarkers for radiation toxicity in patients undergoing RT treatment in order to better design interventional protocols to reduce possible side effects from therapy. Thierens provided an overview of different studies in which single nucleotide polymorphisms (SNP) were identified that could be associated with side effects resulting from RT treatments for various cancers. For prostate cancer treatment, a polymorphism in the TGF- $\beta$ 1 gene was identified, which was significantly associated with the development of acute nocturia (the complaint of an individual to wake at night for voiding) after radiation treatment [47]. In head and neck cancer patients suffering from acute dysphagia (difficulty in swallowing) following RT, a SNP was found in the base excision repair gene XRCC1 that could potentially predict an increased risk of dysphagia, although the final predictive model was considered to be too weak to be clinically implemented [48]. Finally for acute oesophagitis after lung cancer RT, a multicomponent predictive model was designed which included clinical parameters, treatment parameters and four genetic polymorphisms (in the EGFR, ENG, TRAF3 and ITGB2 genes). This model had a high sensitivity of 84% which therefore could allow clinical application [49], demonstrating the importance of the radiogenomics research field.

## 8.3. Systems biology

One of the purposes of systems radiation biology is to integrate data from different levels, in order to provide a holistic view of the effects of radiation at the level of a higher entity, be it the cell, the tissue or, ultimately, the organism as a whole. Leon Mullenders (Leiden University Medical Center LUMC, The Netherlands) presented such an approach, in which data from transcriptomics (mRNA and miRNA), functional genomics and phosphoproteomics from cisplatin-treated mouse embryonic stem cells were integrated to generate a model for the DNA damage signalling and biological effects of DNA damage in these cells. This showed a large overlap of affected pathways at the level of mRNA and phosphoproteins, but also an overrepresentation of networks related to differentiation and activation of a Wnt-mediated pathway which counteracts apoptosis. This latter was proposed to be in balance with the p53-regulated apoptotic pathway, to tune the final outcome of the DNA damage response [50].

Unravelling the radiation response of stem cells is of pivotal importance to better understand the development of radiation-induced cancers, but also the sensitivity to cancer therapy. Peggy Sotiropoulou (Free University of Brussels, ULB, Belgium) presented a multidisciplinary approach to assess the response and the sensitivity of four different types of skin epidermal stem cells to radiation-induced DNA damage. Whereas bulge stem cells and interfollicular epidermis progenitors seem very resistant, the sebaceous gland stem cells are sensitive, and interfollicular epidermis stem cells are extremely sensitive to radiation-induced apoptosis [51]. The reason for these differences in sensitivity of stem cells originating from the same tissue is the activation of different mechanisms in response to radiation with a particular role for the DNA repair gene *Brca1* [52]. These mechanisms can even be different in the same cell type, depending on the activation stage of the cell, or on the type of DNA damage, which further demonstrates the complexity of the DNA damage response. This also shows that, in order to fully understand the effects of radiation at the level of the organism, or even the tissue, as proposed by Rodolfo Negri, it is important to first establish these phenomena at the cellular level.

## 9. Advanced cancer therapy

Part of the MELODI workshop focused on advanced RT techniques which are used for cancer treatment. During the last decades, innovative techniques have been introduced including IMRT (intensity modulated radiation therapy) with photons and particle therapy with protons or ions. Compared to conventional RT, these advanced techniques lead to a reduction in the dose delivered to the surrounding healthy tissue. However, compared to IMRT, particle beams have superior physical (better ballistic accuracy) and biological properties (especially for heavy ions) resulting in an even more accurate and efficient irradiation of the tumour, thereby sparing the surrounding healthy tissues and thus leading to a lower integral dose to the patient [53].

Short- and long-term side effects following RT are strongly related to the amount of dose deposited to the healthy tissue surrounding the tumour. In this context, the generation of secondary neutrons after IMRT photon or particle treatment is of particular concern [54]. This session focused on ongoing studies in this field.

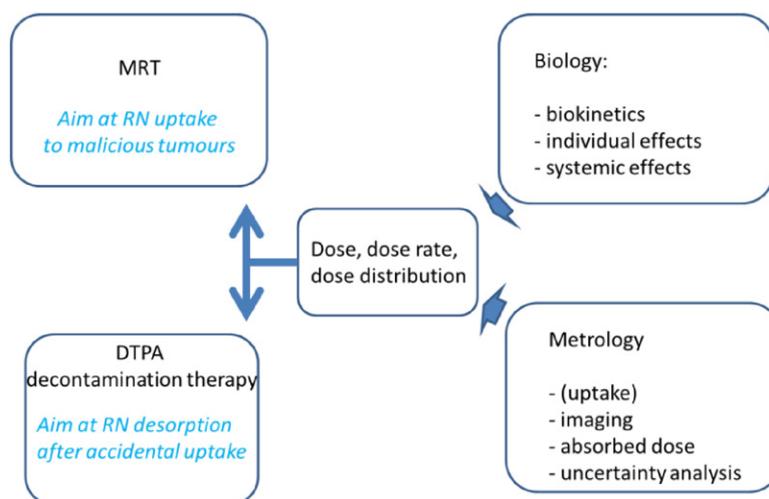
As presented by Liliana Stolarczyk (Institute of Nuclear Physics, PAN, Poland), characterisation of the radiation field outside the planned target volume is the first step for estimating health risks. A comparison between the results from previous dosimetric studies on secondary radiation and their contribution to the absorbed dose and equivalent dose for different RT technologies with the results obtained by the EURADOS Working group 9 'Radiation Protection Dosimetry in Medicine' were presented and discussed. These show that both passive and active proton and ion therapies result in a lower effective secondary radiation dose compared to IMRT and conventional RT. These data can be useful for further estimation of RT induced health risks. However, one must be aware that estimating the health risks from neutrons is complicated and depends on the neutron dose and energy. Therefore, at this moment, it is very difficult to obtain these risk data where the neutron energy is confined to a narrow spectrum. Moreover, the occurrence of risk events in the low-dose range is extremely low resulting in poor statistics.

The EU FP7 ANDANTE project which evaluates the risk of secondary cancer development from neutrons, was presented by Andrea Ottolenghi (University of Pavia, Italy). This project involves a multidisciplinary approach including physics, stem cell radiobiology and epidemiology in order to further clarify secondary neutrons risks in RT. Progress on characterising the exposure beams, initial radiobiological experiments with stem cells, and the data collection for the epidemiological studies were reviewed.

Next to secondary cancer formation, metastasis is another potential long-term risk that can occur after RT. Annelies Suetens (SCK•CEN, Belgium) presented results about the difference in the impact of carbon ions and x-irradiation on the expression levels of motility-related genes in human prostate cancer (PC3) cells. These data indicated that in PC3 cells, expression levels of several motility genes (CCDC88A, ROCK1, FN1, MYH9) were much more down-regulated after carbon ion exposure compared to x-irradiation [55]. Given the current lack of epidemiological data of long-term health risks after particle therapy, it was emphasised that basic radiobiological research is needed and can help to further understand underlying biological mechanisms in order to reduce radiation risk uncertainties in this field.

## 10. Radiopharmaceuticals, RT and decontamination techniques

In the session radiopharmaceuticals and RT, the link between radiation protection and molecular radiotherapy (MRT), also called targeted radiotherapy (TRT) or nuclear medicine therapy (NMT), was emphasised. MRT covers therapies with for example iodine radionuclides, or radionuclides attached to carrier molecules like peptides. In addition, the link was made



**Figure 1.** Set of expertise needed to better understand MRT and decontamination therapy. In case of decontamination, the situation is even more difficult than in the case of MRT, as the activity intake is usually unknown. Biokinetic models do not apply once the decontamination agent is administered. MRT: molecular radiotherapy; RN: radionuclide; DTPA: diethylene triamine pentaacetic acid.

with decontamination techniques aiming at desorption of radionuclides such as plutonium and actinides ingested due to an accident. The technique is based on administering chelating agents such as DTPA (diethylene triamine pentaacetic acid) to remove the ingested radionuclides through natural excretion pathways. During the session it was shown that largely analogous expertise is needed to understand and improve the radioprotection aspects of both MRT and DTPA decontamination therapy. In figure 1 it is shown how biology and metrology lay on the basis of determining the dosimetry, which is a key factor from a radiation protection point of view in both MRT and contamination techniques.

Vere Smyth (National Physical Laboratory, UK) focused during his presentation on dosimetry and metrology (<http://projects.npl.co.uk/metromrt/>). The absorbed dose, the dose rate and the dose distribution need to be determined accurately. Indeed, the same administered activity in case of MRT can result in a different absorbed dose with a factor of 100. Metrology should help to better assess which method(s) will deliver the most accurate doses. Moreover, the more accurate the dose, the less patients will be needed in clinical studies. However, it is important to note that differences due to individual effects can never be avoided. Concerning the determination of the MRT biokinetics, quantitative imaging plays a key role. A better quantification of the activity administered, the imaging, the biokinetics and detection of inhomogeneities are important to upgrade the protocols of MRT.

Bastian Breustedt (Karlsruhe Institute of Technology, Germany) elaborated more on the importance of biokinetic models in his presentation. The development of biokinetic models must consider which physiological processes are important for the specific situation and which tissues are of interest. In case of DTPA decontamination therapy, the activity ingested due to an accident is in general unknown. In addition, for unintended radionuclide uptake, the biokinetics are only available through reference models like the ones published in the International Commission on Radiological Protection (ICRP) 30 report [56–59] for the alimentary tract, ICRP 66 [60] for the respiratory tract, and ICRP 67 [61] on the systemic model. Administering DTPA disturbs the natural biokinetics of the radionuclides. Better *in vitro* and *in vivo* models

are needed to improve decontamination biokinetics. The coupling of compartmental models and biokinetic modelling of DTPA therapy is described in [62].

Furthermore, the biokinetic models needed for radiopharmaceuticals are somewhat different from most other biokinetic models used in radiation protection, as the half-life of radionuclides for radiopharmaceuticals is short (in the range of hours–days), as discussed by Dietmar Nosske (Federal Office for Radiation Protection, BfS, Germany). In case of MRT, especially peptide receptor radionuclide therapy, making use of peptides as vector molecules to target malignant cells, it is important to minimise late kidney damage (as presented by Mark Konijnenberg, University Medical Center Rotterdam, Erasmus MC, The Netherlands) [63–66].

Systemic effects of MRT, finally, were discussed in a presentation from Eva Forssell Aronsson (University of Gothenburg, Sweden). Transcriptional effects of normal tissues were studied for At-211, an alpha emitter with similar chemical behaviour as iodine. The exposure to At-211 results both in effects in the thyroid [67] as well as in a systemic response through transcriptional gene regulation [68].

## 11. Recent cellular models in low-dose radiation research

Researchers have tended to study single cell types arranged as monolayer cultures for many decades. To study radiation effects this however leads to a limited representation of the real situation of affected cells within a body [69, 70]. Indeed, single cell types arranged as monolayer cultures lack the microenvironment, the typical cell shape, and lack of polarisation means and differentiation. In order to overcome these shortcomings, *in vivo* studies could be envisaged. However, this is very costly, and therefore the idea to study 3D cultures (both homo- and heterotypic) can offer many advantages. 3D cell culture can incorporate both the spatial and differentiated function of the tissue *in vivo*. 3D *in vitro* models allow to study cell-to-cell and cell–extracellular matrix interactions, as well as the influence of the microenvironment on cellular differentiation, proliferation, apoptosis and gene expression.

Anna Acheva (STUK, Finland) presented two examples of 3D cultures that may be of great interest to study radiation effects: a skin and a bronchial epithelium equivalent. The skin equivalent is useful to study the effects on skin after radiation therapy. It could be used to characterise the DNA damage induction levels and repair capacity [71], to investigate the role of the apoptotic and differentiation processes, and to study the pro-inflammatory signalling pathways involved in the development of acute skin reactions. It could also be a starting point to find possible ways to modify the signal propagation by targeting key molecules in the signalling process. One of the most important conclusions from this talk is that there are substantial differences observed between the 2D and 3D cultures. The bronchial epithelium equivalent finds its application in studying molecular mechanisms of radiation-induced lung carcinogenesis, and in studying the role of the tissue microenvironment herein. This is part of the EPIRADBIO FP7 project. The focus areas are to study the epithelial–mesenchymal transition, the signalling pathways and the interactions between epithelial and stromal cells.

In addition there were talks devoted to the use of tissues and stem cells, instead of cell cultures, to assess radiation effects. For these presentations we refer to section 8.

## 12. New developments in dosimetry

In the session ‘New developments in dosimetry’, the state of the art in medical dosimetry and new developments were presented. A particular emphasis was put on RT and computed tomography, two fields with major breakthroughs and innovations during the past years.

The protection quantities of equivalent dose in an organ or tissue and effective dose are generally not measurable; while operational dose quantities giving a conservative estimate of the protection quantities are measurable. The control of dose limits, given in terms of protection quantities, needs to be performed by measurements of the operational quantities. However, the system of operational quantities is only well established for a limited range of particle energies, but shows deficiencies and limitations for higher energies. Different options to overcome those insufficiencies, from maintaining the current situation to the redefinition of the operational quantities and relationships with the protection quantities, were presented by David Bartlett (former Public Health England, PHE, UK) on behalf of the International Commission on Radiation Units and Measurements (ICRU) Report Committee 26 (Operational Radiation Protection Quantities for External Radiation).

In x-ray medical imaging, specific dosimetric quantities are to be used for different modalities. Annalisa Trianni (Medical Physics Department, Udine University Hospital, Italy) reviewed the most used ones in today's medical practice. Among those, one might cite the entrance surface air kerma and the kerma–area product in planar radiography, the cumulative air kerma at the international reference point in fluoroscopy, and the computed tomography dose index and dose length product in computed tomography. These quantities are standardised parameters to evaluate the output of radiological equipment; they are useful tools to compare different modalities, equipment and procedures, but they are no estimation of the patient dose. Conversion coefficients and simulation codes are available in the literature to estimate patient exposure based on specific dosimetric quantities and patient's characteristics.

Aside from the assessment of the examination exposure, the image quality is also an important parameter to take into account in x-ray medical imaging. Eeva Salminen (STUK, Finland) presented a clinical study which investigated the association between radiation exposure and image quality in CT [72]. The study concluded that the quality of imaging for diagnostic purpose was reflected in increased radiation exposure; the highest effective and organ doses were related to examinations with image quality exceeding the need for diagnostic purpose. A careful choice of the examination parameters is needed to avoid unnecessary high exposure of patients, the exposure being further increased for specific needs.

Cellular effects and risk of alpha and Auger emitters depend on the distribution of radiation energy at the cellular and molecular levels; organ and tissue doses used alone cannot describe deposition of radiation energy in micro/nanometre ranges. Micro/nanodosimetry is therefore an important tool in low-dose research. Inhomogeneous dose distribution at cellular level correlates better to biological effects at low doses. Weibo Li (HMGU, Germany) presented microdosimetric models of alpha emitters deposited in the central airways [73] and in the kidneys (not published); an example of Auger emitters (gold particles) in RT was also given [74].

In RT, organs situated out of the primary field might receive important doses, but are not modelled by the treatment planning system. However, the dose in specific volumes such as foetus, ovaries, testes and pacemaker is of interest for radiation protection; it could also be used in the framework of epidemiological studies on secondary cancer induction. The three main components of the out-of-field dose are the leakage radiations, the scattered photons from the collimation system and the scattered photons in the medium. Jérémie Vu Bezin (French Institute of Health and Medical Research, INSERM, France) presented a multi-source simulation code developed to model the scattered photons from the collimation system for different structures of linear accelerators [75]. The same framework could be used to model the other components of the out-of-field dose. Ultimately, a complete out-of-field dose estimation system could be integrated in the treatment planning system.

### 13. Risk communication and risk perception: how can science help us?

The workshop on risk communication and risk perception was organised in the context of the FP7 project OPERRA. The workshop was a further step towards the identification of the needs for future research related to perception and communication of low-dose radiation risks. The purpose of this workshop was thus to lay the foundation for a discussion between social, human and natural sciences. This should, at the later stage of the project, help identifying main issues and new topics of research related to perception and communication of risks related to low doses and medical uses of ionising radiation to be included by the European Commission in the radiation research area.

Despite 50 years of extensive research on risk perception and communication, ionising radiation has not yet played a major role in this field of social science. Previous research investigated ionising radiation risks more as a case study, rather than as a prerequisite for building an intellectual and theoretical capacity, for both scientists and the public at large.

Four interrelated challenges of risk perception and risk communication in the fields of low doses and field of medical use of ionising radiation were suggested to be discussed at the workshop in order to identify new research topics. First, the issue of technical information and the use of risk estimates; second, the issue of perception and communication related to uncertainty of scientific information; third, the goal of communication by experts and/or authorities (persuasion for acceptance versus information for informed decision-making); and finally, the role of new media and social networks (e.g. blogs, Facebook, LinkedIn, etc) in the interpretation of risks from low radiation doses.

Two invited keynote speakers opened the discussion: Britt-Marie Drott Sjöberg, social psychologist (Norwegian University of Science and Technology, Norway) and Peter Michael Booth, communication practitioner (Hylton Environmental, UK). They pointed out that although widely applied in daily life, radiation is discussed rather narrowly in the society. ICRP clearly defines principles of radiological protection, but leaves the essential element of interaction and communication with society rather underdeveloped. Radiological protection is an extremely complex science and the decisions taken at international and/or state level (not to mention local or individual level) are framed by ambiguous value choices and fraught with problems of uncertainty. The keynote speeches presented a justification why radiation research community needs to invest more in the R&D of interaction and communication with society and to promote a trans-disciplinary approach linking natural science, social science and humanities.

After the opening presentations, the participants, 44 researchers from different fields, discussed about the views, attitudes and experiences in the risk perception and risk communication field. They expressed that risk communication and perception related to low doses are a challenge and need to be further investigated, improved and applied.

The following specific ideas were then suggested by the participants: (i) communication should be a dialogue where social sciences can be of help in order to develop knowhow and practices so that people can make their own choices or decisions, (ii) improved participatory practices: people would participate not only to be better informed but also to act more responsibly to find solutions to problems; the scientific community should also better communicate what the limits of science are: science can(not) resolve all questions (epistemology), (iii) fear is a primal emotion: it is not only necessary to study risk perception, but also why people are afraid and what the specific role of their social environment is, (iv) better evaluation of the ethical basis of risk communication: what kind of communication do we want? It was suggested that we should look about the values that drive us: trustworthiness, honesty, communication

on an equal level, (v) cross-cultural studies of risk perception are needed in different countries or different sub-populations (e.g. specific regions, also outside Europe) to include societal and culture-specific aspects, (vi) an important point is the communication of scientific uncertainty. There is a strong need of specific studies with a focus on low-dose ionising radiation, (vi) social values in communication to stakeholders should be taken into account, i.e. it is inevitably necessary that (natural) scientists in a communication process need to take the social values of their partner into account.

The discussion was also dedicated to the various understandings of the concepts related to risk perceptions, risks and hazards from the different groups: social scientists, humanities and natural scientists. The focus of the discussion was thereafter about the definitions of risk, hazard, danger or harm from the point of view of the radiation protection society.

In addition risk perception concepts as seen by the natural scientists from radiation protection area were discussed.

From the discussion during the workshop it appeared clearly that good communication about ionising radiation is a matter of well-aligned values, for instance 'How safe is safe enough?'. We can more easily understand each other and reach decisions when there is some shared agreement about what is important for different stakeholders. When we communicate with stakeholders and different research communities about ionising radiation risk, we have to be aware of our own underlying values and of those of others, for instance health, feeling of safety, tampering with nature, moral values etc. Do we analyse and choose these values? Can we easily identify how our values differ from those of other people? How can we better identify our ethical positions, and better shape our communication about risk? These questions were identified as a starting point for a next discussion towards identification of the needs for future research related to perception and communication of ionising radiation risks organised in the context of the FP7 project OPERRA and linked to the FP7 project EAGLE (Enhancing education, training and communication process for informed behaviours and decision-making related to ionising radiation risks).

## 14. Conclusions

With the 221 attendees, and the 118 oral and 44 poster presentations this was the largest workshop since the start of the initiative. The 2013 edition of the MELODI workshop was also the first one including sessions with contributions originating from the entire field of radiation protection. Indeed, next to low-dose research, there were presentations regarding radioecology, emergency and recovery preparedness, and dosimetry. The strategic research agendas (SRA) of MELODI, ALLIANCE, NERIS and EURADOS were presented, indicating the interfacing research areas and/or disciplines between the four different areas of radiation protection. It is believed that interactions and further integration between the radiation protection areas will result in better radiation protection research in general. All MELODI workshop participants could vote for the priorities of the upcoming EU FP7 OPERRA call, and the participants were encouraged to express their ideas to update the respective SRAs.

The audience was updated about the latest situation in Fukushima after the nuclear accident in Spring 2011 as a result of the earthquake and tsunami. Dose estimations and health risks, with a focus on thyroid cancer and leukaemia, were presented. There were highly informative sessions on radiation-induced transgenerational effects on animals and plants, radiation effects on the wildlife, internal emitters, and mixed toxicity between radiation and other substances. Furthermore, new radiotherapy strategies, including new

radiopharmaceuticals for targeted treatment as well as the use of heavy ions in hadron therapy, were discussed. Heavy ions were also discussed in relation to space radiation. Non-cancer diseases, like the cognitive-, cardiovascular- and the eye lens-related disorders, were presented in the human health effects plenary session and in the session concerning the underlying mechanisms of radiation-induced diseases. The common theme in these sessions was that research should actively mimic the human situation of long-term disease presentation to better understand the related mechanisms. Furthermore, the audience was updated about the investigations regarding genetics and epigenetics in radiation biology, about the increasing use of high-throughput technologies like proteomic and microarray analysis, and next-generation sequencing, and about how to integrate data from different levels in order to provide a holistic view of the radiation effects in a systems biology approach. For future research in radiation biology, it was also emphasised that new *in vitro* models should be used, like 3D cultures (both homo- and heterotypic), to resemble more the *in vivo* situation. Next, new developments in dosimetry were presented. The dosimetry, as well as emergency preparedness experts, advised to involve the medical sector in the future Workshops. For all these research fields, constant improvement on collaboration on infrastructure and biobanks should be aimed for. Finally, risk communication and risk perception was discussed. A reference document about communicating risk for low-dose ionising radiation effects is currently under preparation.

In the summary session at the end of the Workshop several questions were raised that remain to be answered. (i) How can we better monitor long-term effects of radiation exposure from the onset of the disease, be it cancer or non-cancer disorders, to the first symptoms and diagnosis? (ii) How can epigenetics help us to understand late effects? (iii) How can we further enhance collaboration between epidemiology, radiobiology, dosimetry and radioecology? (iv) How can we translate low-dose research into improved regulations?

Scientists and chairs from different disciplines were invited to present their opinion and views concerning the above questions. Regarding the 100 mSv limit for low doses, quantifying the risk of the more commonly encountered low radiation exposures (especially from diagnostic and interventional medicine) remains difficult and subject to uncertainty. Long-term follow-up of low-dose exposed cohorts are needed and will certainly help in reducing this uncertainty. Therefore, a major challenge lies in providing a sound mechanistic understanding of low-dose radiation effects, taking into account the early events after exposure (stress response) as well as the late consequences (genetic, epigenetic and metabolic events) at the onset of cancer/non-cancer diseases. In that way we can insure a better integration between radiobiology and epidemiology. Dosimetry plays a major role in this process. By continuously improving dose calculation in humans and animal models, we can increase the confidence and reduce the uncertainty for risk estimate.

Finally, there were sessions devoted to education and training. These are important aspects to ensure knowledge transfer to the new generations. The way forward in organising training and education in radiation protection was discussed in terms of multidisciplinary, since it is evolving to a more integrated landscape. Several types of training need to be elaborated, such as academic courses, but also vocational and life-long trainings.

European low-dose radiation exposure research continues to evolve. During this Fifth MELODI Workshop, the intricacies and progression of the knowledge in the field were reviewed and new findings were presented. The field is very dynamic and the next-generation researchers from the different areas of radiation protection has shown to be active and eager to contribute jointly towards a better radiation protection.

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