The Joint International Symposium on EPR dosimetry and dating (EPR) and the International Conference on Biological Dosimetry (BioDose)

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Abstracts

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Invited Lectures

OP - 1

Beginning and development of the International EPR and Biological Dosimetry Conference Series - a flashback

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The Conference Series under consideration started in 1985 at Yamaguchi University at Ube, Ja-pan, entitled the “First International Symposium on ESR Dating”. It was organized by Motoji Ikeya, later on Osaka University. About 100 scientists from all over Asia and 12 overseas coun-tries participated. The conference subjects harvested among the innovative ideas and scientific results reached by then from the great number of pioneering research work done worldwide, all using electron spin (or paramagnetic) resonance spectroscopy (ESR or EPR). This technology had been invented in 1944 by the Soviet physicist Evgeny Konstantinovich Zavoisky at Kazan University, Tartastan. The key areas of interest of the First Symposium were archeological and geological dating, speleology for cave studies, marine geology, oil and gas prospection, forensic medicine as well as dose reconstructions, on pilot scale, using human and animal tissues applied to paleo dating but also to exposure assessment of atomic bomb victims from the close-by Hioshima and Nagasaki cities. Prominent presentations highlighted, among others, the radio-sensitivity of teeth and skeleton as well as of crystalline amino acids (alanine). Because of the obvious great interest in and success of the symposium, Ikeya together with the members of the International Advisory Committee, had the exceptional idea to make this symposium a start-up event for a future series of ESR conferences, to be named International Conference on ESR Dosimetry and Applications (acronym ESRDos), in a preferably triennial cyle. The present flashback reports on the main scientific focuses and streams of the starting conference and the eleven follow-up conferences which, after Japan, were held, in some countries repeatedly, in Germany, USA, Russia, Brasil and France, in the latter case jointly organized with Italy. It needs mentioning that starting with the EPRDos Conference 1998 in Obninsk located close to Moscow, and this upon suggestion of the two co-chairs Anatoli Tsyb and Leonid Ilyin, both internationally renowned in radiation medicine and biophysics, the framework and structure of the Conference got scientifically expanded by adding an International Conference on Biodosimetry to the established ESR Conference Series. This expansion has been welcomed by the scientific community and since then has led to the new acronym of the Conference, i.e. EPRBioDose. Besides, the EPRBioDose Conference Series served as a basis for founding the International Association of Biological and EPR Radiation Dosimetry (IABERD), in 2010, offering assistance to the following organisers of ESRBioDose Conferences. Moreover, most of the EPRBioDose Conferences got, from the beginning and at least conceptually, supported by international organisations such as WHO, IAEA, ILO and EC, apart from major national institutions, ministries and departments, governers, foundations, universities and academies.

Presently in 2018, the 12th International Symposium on EPR Dosimetry and Applications, backed-up with the meanwhile 7th International Conference on Biodosimetry, returns once again to the Research Center at Neuherberg/Munich, which meanwhile has been renamed to Helmholtz Zentrum München - German Research Center for Environmental Health. Thirty-three years following the launch conference at Yamaguchi University in Japan, we can proudly claim that the original idea to set-up an international EPR conference series has apparently become a great success. Translational EPR research has found manifold applications in human and natural sciences and proven an important societal impact. It contributed a remarkable share to the evolution of dating techniques for geological and archaeological fossils back to the roots of mankind history and beyond. EPR spectroscopy based on alanine made it possible to scientifically realize and organisationally establish a new and worldwide accepted technology of secondary, reference and transfer dosimetry standards for high-dose metrology. A relevant metrology for this dose range had been lacking internationally at that time. As a high-lighted output the International Dose Assurance Service (IDAS) based on alanine/ESR metrology has been settled, and operated through cooperation between the International Atomic Energy Agancy

(IAEA) and GSF Neuherberg/Munich; IDAS had the purpose to assist accredited IAEA Member States to observe legal high-dose regulations and trade requirements, nationally and internationally, and optimize product throughput of radiation processing plants for food preservation and product refinement. Meanwhile a number of Primary Standard and National Laboratories worldwide use the IDAS technique for their own tasks involving intercomparisons. EPR spectroscopy has meanwhile proven to biophysically complement biological cytometry in determining or reconstructing radiation doses from human tissues, even post-mortem. Apart, the EPR metrology with tissue-equivalent alanine detectors has also shown an unexpected potential of high measuring precision for therapy dose levels which makes it attractive for dosimetry in radiation oncology potentially even in the magnetic field of future MRI guided megavoltage therapy, and for different types of radiation. The application of EPR dosimetry for dose reconstructions within cohorts of radiation exposed populations promises a remarkable potential to validate radiation risk from chronicly exposed humans, taking radiation workers and civilians of the PO Mayak and of the Techa River, both Southern Ural, as examples (e.g. EU CORDIS/SOUL Project). The development of easy-to-handle and reliable triage EPR dosimetry techniques for large numbers of radiation-exposed members of the public has extensively been persued together with contributions to strategic plans, preventive simulations and medical counter measures for application in cases of radiological or nuclear threats. In addition, progress has been reported for automation in cytometry aimed to serve for rapid population triage in case of radiological emergency. The EPRBioDose Conference Series dealt with valuable impulses to and findings from international activities performing biophysical and particularly biological dose intercomparisons initiated and guided through the European Union as well as WHO and IAEA. These joint activities represent an important step forward to create a sustainable network of experienced laboratories worldwide able to significantly expand the capacity of triage dosimetry, which most commonly is found to be limited on a national basis (WHO BioDoseNet; EU MULTIBIODOSE and RENEB; IAEA RANET).

Concluding, the EPRBioDose Conference Series has found great acceptance internationally, in the past 33 years, which gets reflected in the remarkable number of participants reaching up to almost 300 at one conference (1995, Munich). From all conference presentations far more than 500 full papers have been published in peer-reviewed journals, such as Applied Radiation and Isotopes, Radiation Protection Dosimetry, Radiation Measurements, Health Physics, and others. With all these figures and experiences in mind, the EPRBioDose Conference Series has obviously reached a noteworthy scientific tradition. As we should conserve the best of what we have inherited from the past, so should we create more innovative ideas and developments in the future for the benefit of forthcoming EPRBioDose Conferences and stimulation of corresponding biophysical and biological research as well.

OP - 2

The Future of Biodosimetry

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Introduction
The future of biodosimetry is bright, because of the great need for information that only biodosimetry can provide, the already demonstrated capabilities of biodosimetry, and the reasonably anticipated developments that should occur. To maximize the beneficial impact of biodosimetry and to assure the support needed for its development and utilization, it is important that the participants in this meeting consider carefully the factors that have led to the current state of development and those that are likely to impact it in the future. The need for biodosimetry arises because in a radiation event that potentially involves the public, there will be many people who will be concerned that they may have received doses of ionizing radiation that could impact their health. It then becomes necessary that there be a means to assess the risk at the level of the individual. Experience has fully demonstrated that reassurances from public figures and experts that people have minimal risk will not be accepted by many people, so direct measurements are needed. Also, because of the risks for the administration of radiation mitigating drugs and therapy it is essential that there be an accurate assessment of dose prior to the treatment.

Methods
For physically-based biodosimetry in vivo EPR measurements of teeth has been demonstrated to be feasible as a deployable technique. In vivo nail dosimetry has been shown to be feasible but the instrumentation to carry it out in the field has not been fully developed. Biologically-based dosimetry based on genomic changes, metabolics, and proteomics have all been shown to be potentially useful techniques for individual biodosimetry. Changes in RBCs, especially the DCA but also other changes have been significantly advanced towards being applicable to meet the needs for large scale use.

Results
The pace and extent of further developments will be closely linked to the availability of sources of financial support for the technical developments and for preparing the biodosimetric techniques for deployment in response to events. The desired future developments include making the biodosimetric techniques more optimal for use in the field for initial triage and then assessing the dose more precisely in the environment where active therapeutic intervention is being considered. For many of the techniques additional data area needed on changes from concurrent processes such as wounds and stress and from prior physiological and pathophysiological processes in the individual. Correlations of the change observed with biodosimetry with outcomes could be especially valuable.

Conclusion
The need for biodosimetry for rapid and effective primary and secondary triage remains very high. The most effective use of the techniques will be in combination with other indicators of exposure. Much remains to be done, but the feasibility of the use of biodosimetry seems well-established.

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OP - 3

An Overview of Cytogenetic Dosimetry

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Cytogenetic dosimetry began almost 60 years ago and was quickly seized upon as a novel approach to the investigation of radiation accidents. The intervening years have seen a steady improvement such that the biological approach now forms an integral component of national radiological protection programmes, complimentary with the physical methods of personal dosimetry. The initial technique was the dicentric assay and for many years this proved its worth, usually producing credible estimates of dose, when set alongside any other information available about a radiation incident or accident. The dicentric has been described as the "gold standard" assay for biological dosimetry but experience gained in its deployment showed that it has its shortcomings. To some extent these have been overcome by a better understanding of the method and also the biology of the sentinel cells used; the peripheral blood lymphocytes. Additionally, the development of other chromosomal damage endpoints; micronuclei, stable translocations and DNA damage foci that can be assayed in lymphocytes, has helped to overcome some of the problems associated with the dicentric. We now have an impressive armoury of methods that can be used to evaluate persons known or suspected of having been irradiated.

When viewed world-wide the biological dosimetry community is quite small, often consisting of small single national laboratories which potentially could be isolated. It is gratifying therefore that over the years a strong spirit of mutual support and co-operation has developed. Important stimuli for this were a few large accidents such as at Chernobyl and Goiania. Several laboratories mobilised their resources to respond jointly and from this developed the close ties that we now have in regional networking and indeed world-wide networking facilitated by the UN agencies.

As well as the better ability to respond coherently to a major accident, or to the threat of radiological terrorism, the cohesion of the cytogenetic dosimetry community has brought a number of other advantages. The community has developed a strong ethos for quality assurance and quality control. Important milestones have been the development of ISO standards for the assays and the universal acceptance of the IAEA manual on cytogenetic dosimetry, now in its 3rd revised edition. Networking forms a valuable vehicle for quality assurance as it can facilitate the sharing of experience and training and, very importantly, performing inter-comparison exercises.

Another vital development within the community has been the establishment of a unified procedure for data handling and evaluation. Biologists, generally speaking, do not have advanced statistical skills and therefore the development of a suite of appropriate statistical procedures for tasks such as calibration curve fitting and deriving dose estimates with proper uncertainties has been of immense value. The availability of freely available and user friendly software tools such as CABAS and Dose Estimate has been a major advance. The attraction of these tools is that they emerged from the cytogenetics laboratories themselves, rather than from academic statisticians, and so they evolved in an environment where experience of the practical problems of dosimetry were well appreciated. Having produced the best possible estimates of dose it is important to communicate the results in an understandable way to the "customers"; safety officers, medical doctors and of course the patients themselves and their families. These people usually do not have a clear understanding of 95% confidence limits or probability distributions nor of the relationship between dose and risk.

Cytogenetic dosimetry has always been regarded as labour intensive and time consuming. However, automation within the laboratory has made tremendous advances and this is ongoing. Both the "wet work"; blood, culture and slide processing and the "dry work"; the microscopy, have benefitted from

automation. Probably the "wet" automation is not yet so widely adopted across the community. However computer driven microscopes are to be found in many laboratories. These can scan a slide rapidly, locating and presenting metaphases in focus at high magnification to the operator. Computer assisted analysis of the captured images has developed more slowly. To some extent this was delayed by commercial pressures; there being a greater market for full karyotyping for clinical cytogenetics. Now, however we have software that can scan the images and identify the lesions of interest to dosimetry; dicentrics, micronuclei, translocations and DNA foci. The ease with which high quality images can be transferred via the internet to partner laboratories has immensely expanded the possibilities for networking and rapid response to large scale emergencies. The community is currently coming to understand the extent to which these analyses can be performed totally "hands-off" or where reference to the human eye for final verification is still required.

Cytogenetic dosimetry is still evolving along several lines that undoubtedly will feature in presentations to the conference. Improved data analysis is ongoing; an example of which is the introduction of procedures that use Bayesian methods. Another area is a more refined approach to discriminating heterogeneous exposures. The traditional methods, like Qdr and Contaminated Poisson make very simplifying assumptions of partitioning the body into two components; an unirradiated and a uniformly exposed part. In reality of course a spectrum of doses is experienced by different parts of the body in a non-uniform radiation field. Interpreting aberrations due to internally incorporated radionuclides is another example of heterogeneous dose distribution with the added complications of protracted and changing dose rates. These complex problems are being addressed. Another active line of research is to use cytogenetic and DNA damage endpoints to determine variability in radiosensitivity among "normal" individuals, i.e., persons not suffering from the rare highly radiosensitive syndromes. A reliable method could have considerable implications for the medical uses of radiation particularly where high doses are used therapeutically.

In summary, cytogenetic dosimetry has a long history of practical application to the problems that inevitably arise with the widespread uses of radiation in medicine, industry and research. It produces credible estimates of dose when people are known or suspected of having been overexposed. Over the years the discipline has evolved into a readily deployable emergency response tool. It works!

Biomarker I

OP - 4

Metabolomics for radiation biodosimetry: designing a robust radiation signature

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The increased threat of nuclear attacks and the risk from accidental or intentional exposures to ionizing radiation have led to increased requirements for rapid and reliable methods for detection of exposed individuals. Individuals exposed to high doses of radiation (defined by the Health and Human Services and the National Institute of Allergy and Infectious Diseases as ³2 Gy) will require immediate medical intervention in the form of cytokine therapy, hematopoietic stem cell transplantation, and mitigators. In addition, emergency and medical personnel may also need a biological dose reading besides a physical dose to assess their risk regarding radiation related long term effects. Targeted and untargeted metabolomics of easily accessible biofluids (urine, blood, saliva) of rodents, non-human primates, and humans have produced a significant number of radiation specific metabolites utilizing liquid chromatography mass spectrometry (LC-MS). Untargeted metabolomics is defined as the collective assessment of small molecules <1kDa in a sample. Targeted metabolomics on the other hand relies on the quantification of a pre-selected panel of metabolites that can serve as biomarkers.

Regarding radiation biodosimetry, different radiation exposure scenarios have been investigated, including radiation quality (photons vs. neutrons), dose rate, internal exposures from radionuclides, and even the effects of the genetic background and inflammatory status of an individual. Specificity has been assessed through comparison to other types of stress (trauma, sepsis, endotoxin). The ultimate goal is to develop a radiation signature that is robust and can rapidly aid in identification not only of exposed individuals, but also distinguish between different radiation exposure scenarios. While cytogenetic analysis has been the gold standard for biodosimetry, new technologies such as metabolomics have been established as promising candidates to contribute to the field of radiation biodosimetry. Finally, the insight that metabolomics has provided into the metabolic status and the long term effects of radiation on individual tissues may aid in identifying and even designing better tissue specific mitigators or radioprotectors. Development of robust radiation signatures can therefore aid first responders to rapidly sort through potentially thousands of victims and provide the best medical treatment based on biodosimetry.

OP - 5

Biomarkers for assessing radiation injury identified using nonhuman primate model

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Introduction
Exposures to ionizing radiation, whether they are intended or unintended, are currently an undeniable reality and carry potentially catastrophic health consequences. Therefore, medical preparedness and countermeasures are critical security issues, not only for the individual, but for the nation as a whole. Identification of biomarkers for radiation exposure is an urgent need.

Methods
We have identified several promising biomarkers for radiation injury using hematology, cytokine/chemokine/growth factors, microRNA, proteomics, transcriptomics, metabolomics, and lipidomics. The rapid identification of specific affected lipid molecules represents possible targets for biodosimetry. We have analyzed several metabolites that are altered after irradiation, including compounds involved in fatty acid-β oxidation, purine catabolism, and amino acid metabolism. The machine-learning algorithm, Random Forest, separated unirradiated and irradiated nonhuman primates (NHPs).

Results
We identified a unique signature of seven miRNAs that are significantly altered with irradiation in NHPs. A combination of three miRNAs (miR-133b, miR-215, and miR-375) can differentiate irradiated versus unexposed NHPs. We have also identified a 5-miRNA composite signature that has the potential to identify irradiated NHPs and predict their probability of survival. Our study revealed a highly dynamic temporal response in the serum lipidome after irradiation. Marked lipidomic perturbations occurred within 24 h post-irradiation along with increases in cytokines and C-reactive protein. Metabolomic study demonstrates that several metabolites are altered after irradiation, including compounds involved in fatty acid-β oxidation, purine catabolism, and amino acid metabolism.

Conclusion
Our study demonstrates that the biomarkers discussed above will definitely help to determine the dose of radiation with which a victim is exposed to during any radiation/nuclear scenario. MicroRNAs appear specifically promising since we have developed a classifier based on two miRNAs (miR-30a and miR-126) that can reproducibly predict radiation-induced mortality. Such biomarkers will also play an important role in studying the efficacy of promising radiation countermeasures under development following the US FDA Animal Rule.

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OP - 6

Dotting the Eyes: Mouse strain dependency of the lens epithelium to low dose radiation-induced DNA damage

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Introduction
Epidemiological evidence regarding the radiosensitivity of the lens and radiation cataract development has led to changes in EU Basic Safety Standards for protection against ionising radiation. However, mechanistic details of lens radiation response pathways and their significance for cataractogenesis remain unclear.

Methods
In this work, two distinct regions of the lens epithelium have been analysed for DNA double strand break (DSB) repair responses to ionising radiation. The responses of epithelial cells at the anterior pole (central region) have been compared to those in the proliferative compartment, and up to and including the very periphery of the monolayer (peripheral region).

Results
Described here are different responses in the two regions and across four strains (C57BL/6, 129S2, BALB/c and CBA/Ca) over a low dose (0 – 25 mGy) *in-vivo* x-irradiation range up to 24 hours post exposure. DNA damage visualised through 53BP1 was present across the epithelium, repair kinetics appeared non-uniform. Epithelial cells in the central region generally have significantly more 53BP1. The sensitivities of different strains have also been compared: the radiosensitive strains 129S2 and BALB/c showed higher levels of damage, with BALB/c showing significantly less inter-individual variability and appearing to be a more robust model for DNA damage and repair studies.

Conclusion
BALB/c was identified as the most suitable strain for mechanistic studies of low dose ionising radiation effects in the mouse eye lens.

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OP - 7

Impairment and recovery of GI function following lower hemi-body radiation exposure in a Göttingen minipig model

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Introduction
Göttingen minipig (G-MP) displays classic gastrointestinal acute radiation syndrome (GI-ARS) following total body irradiation (TBI) which is100% lethal by 10-14 days[1]. Here, we developed a hemi-body/partial body irradiation (PBI) model in collaboration with BARDA by exposing only the abdomen and lower extremities to study natural history and digestive system impairment out to at least 30 days.

Methods
Twenty-four G-MP were exposed to either 12 or 16 Gy (LINAC Elekta); head, forelimbs, and thorax were unexposed, sparing ~40-50% of the bone marrow (PBI-50). CBC, clinical observations, food tolerance, digestive system processes, and morphology of small intestine were evaluated overtime. Assessment of digestive system processes (digestion, amino acid absorption) and small bowel mass and function (citrulline) was made from plasma using stable isotope tracers and citrulline assays. Animals were euthanized at set time points post PBI and histological assessment of small intestine was performed.

Results
PBI-50 at 16 Gy yielded higher lethality than 12 Gy. Unlike TBI, PBI did not cause severe pancytopenia or external hemorrhage. Compromised animals showed inactivity, anorexia, vomiting, weight loss and changes in stool consistency. Reduced food tolerance, amino acid absorption, and citrulline production was dose-dependent. Loss of citrulline reached a nadir between 6-12 days and then recovered partially. Protein digestion capacity was lost significantly earlier at 16 Gy. Histology revealed that the most dramatic intestinal lesions (villous blunting, lymphoid atrophy) occurred in early phase (day 5) and were more prominent in 16 Gy animals. Edema, atrophy, inflammation and ulcers were observed occasionally. Presence and severity of lesions decreased over time in a dose dependent fashion.

Conclusion
In conclusion, lower hemi-body irradiation G-MP model allowed for extended survival at otherwise lethal GI doses. Classical signs of GI-ARS such as vomiting, diarrhea, constipation, decreased citrulline and weight loss were seen. Food tolerance, protein digestion, amino acid absorption were impaired in both a dose and/or time-dependent manner resulting in decreased overall gut function. A partial recovery in citrulline production and improvement in severity of histological lesions at 12 Gy indicates that these parameters could be used as biomarkers to assess countermeasure efficacy.

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OP - 8

Validating the gene expression assay for biological dosimetry in emergencies involving exposure to mixed beams of high and low LET radiation

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Introduction
Following a large-scale nuclear accident or radiological emergency, the medical and radiological classification ("triage") of patients according to the degree of their injuries and the level of their radiation exposure will be required in the shortest possible time. In this context, the gene expression assay on peripheral blood lymphocytes (PBL) is a promising biological dosimeter.

Methods
A dedicated mixed-beam exposure facility is installed and characterized at the Stockholm University, which allows exposing cells to 241Am alpha particles and X-rays in a combined or single manner. Experiments were carried out with human PBL collected from three donors. qPCR was used to measure the relative expression levels of the genes XPC, FDXR, BBC3 and GADD45a 24 and 48 hours following exposure to doses in the range of 0-2 Gy.

Results
All analysed genes showed a positive dose response to the tested radiation types. Generally, alpha particles and mixed beams were strongest inducers of gene expression but the response was individually variable.

Conclusion
Analysis is under way to test whether the combined results from the different genes can be used to identify a fingerprint of exposure to radiations of different LET.

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Biomarker II

OP - 9

Cytogenetic Biodosimetry in Experimental Modeling of Inhomogeneous, Mixed Dose Radiation Exposure

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Introduction
The aim of the study was to examine experimentally the efficacy of conventional dicentric biodosimetry in the inhomogeneous, mixed dose radiation exposure scenario. A potential impact of a radiation-induced mitotic delay on the aberration-per-cell distributions and resultant dose estimates, and a possibility of distinguishing a mixed dose irradiation from other exposure scenarios were assessed.

Methods
Healthy donors" blood was irradiated *in vitro* to 3, 9 or 18 Gy acute γ-rays. Different volumes of blood exposed to different doses were mixed to simulate 12 scenarios, including total- or hemi-body homogeneous and 2- or 3-dose mix irradiations. Replicate lymphocyte cultures were set up for 50 h with a standard colcemid treatment or for 66 h with prolonged, low dose colcemid treatment. Data were collected by microscopy of the FPG-stained metaphase preparations. The yields of dicentrics plus centric rings (Dic+CR) and parameters of their aberration-per cell-distribution (AbCD) were analysed.

Results
In all mixed dose exposure scenarios 66 h lymphocyte cultures with prolonged colcemid treatment contained a remarkably elevated proportion of heavily damaged metaphases, compared to that in standard 50 h cultures. The effect of release of such cells from mitotic delay didn"t pertain to the homogenous, total- or hemi-body irradiations. The fit of the AbCD to 4 theoretical models – Poisson, Neyman type A, Negative Binomial and Gamma – were tested by $\chi 2$ method. Such a multimodel fit, being qualitatively expressed as "++/+/-/--" combinations, formed distinct profiles, by which total- or hemi-body homogenous and mixed dose, inhomogeneous exposure scenarios were clearly distinguished. Dolphin's CPM, applied to combined Dic+CR data from 2 fixation points, produced quite correct dose estimates.

Conclusion
To improve the accuracy of biodosimetry, a longer term culturing / multiply fixation regimen is recommended as a useful protocol in cytogenetic assay, if the inhomogeneous, mixed dose exposure is suspected. The statistical profiling of AbCD can provide more evidence for the identification of inhomogeneous irradiation.

Possibilities and limitations of the proposed methodology of radiation dose assessment are discussed in comparison with techniques based on unfolding mixed Poisson distributions in the scenario of mixed dose exposure.

References
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OP - 10

An improved statistical methodology for analysis of translocations for biodosimetry purposes

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Introduction
Due to the "stable" nature of translocations within the lymphocyte population, the Fluorescence *in situ* Hybridisation (FISH) assay is a useful radiation biodosimetry method when the time period between exposure and dose assessment is large (Barquinero *et al.*, 2017). However, statistical analysis of these data is usually based on the dicentric assay method, leading to potentially incorrect results.

Methods
A data driven approach to analysis of observed excess radiation induced translocations has been carried out to facilitate estimation of radiation dose and the associated uncertainty following application of the FISH translocation assay. Classical assessment of the most suitable statistical model(s), a detailed consideration of the uncertainty budget and the minimum detectable dose, followed by a pragmatic approach to propagation of errors is proposed, resulting in development of a full ISO standard-compliant method (JCGM, 2008) or Bayesian alternative for biodosimetric analysis translocations.

Results
A review of the literature reveals that, in contrast to methods for detection and scoring of translocations, data analysis methods are not standardised within the active biodosimetry community. For example, some laboratories use their own age-matched control populations to adjust for the background signal and others make use of published data in the literature (Sigurdson *et al.*, 2007).

Data from a number of case studies will be presented with the results of the original analysis compared with the newly proposed method. The results depend on a number of factors, however, in most cases, the newly proposed rigorous method of statistical analysis results in a larger and likely more correct assessment of the uncertainty associated with the estimated dose.

Conclusion
The standard methodology for translocation analysis, based on transferring the methods from the much simpler dicentric assay, is in most cases not suitable for translocation assay. This is due to the larger range of uncertainties and the relatively large contribution to the uncertainty in dose from the age adjustment. The newly developed methodology presented here provides a pragmatic framework for calculation of dose and uncertainty using the FISH translocation assay, based on a precise consideration of the translocation data and experimental set up.

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Thanks to the ISO WG18 committee.

OP - 11

STUDY OF CHROMOSOME ABERRATIONS AS BIOMARKERS OF PARTIAL BODY EXPOSURE IN CANCER PATIENTS IN EARLY STAGES OF RADIOTHERAPY COURSE

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Introduction
One of the most important tasks for biological dosimetry in radiation accidents including those of in medical field is to detect the cases of partial body exposure along with the dose estimation. We studied cytogenetic effects in lymphocytes of cancer patients to determine to what extent unstable chromosome aberrations worked as biomarkers for partial body acute and fractionated exposure.

Methods
Unstable chromosome type aberrations were analyzed in lymphocytes of 20 radiotherapy patients divided on three groups depending on tumor localization: with lung cancer, uterine body cancer, and with head and neck cancer. Blood sampling was performed during of γ-60Co radiotherapy or megavolt radiotherapy course on linear accelerator: before radiotherapy, after first fraction for all patients and also after second fraction of radiotherapy for 14 patients. Dose per fraction was 1.8 – 2 Gy.

Results
For all groups of patients with lung cancer, uterine body cancer, and with head and neck cancer the possibility to detect radiation exposure after first irradiation fraction and subsequently after second fraction was demonstrated. In some individual cases the data obtained could not be interpreted as partial body but as whole body exposure. The number of cases with clear detection of partial body exposure depended on tumor localization.

Conclusion
Mostly the radiation cytogenetic biodosimetry data concerning partial body exposure were obtained in *in vitro* experiments therefore *in vivo* model studies have to be further performed. In the chosen *in vivo* study design the confounding factors for detecting partial body exposure such as elevated level of chromosome exchanges in cancer patients before treatment, individual radiosensitivity and others will be analyzed. Some requirements for chromosome aberrations assay in cancer patients and data treatment for biological dosimetry of partial body acute and fractionated expose will be discussed.

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OP - 12

EURADOS review on retrospective dosimetry techniques for internal exposure to ionizing radiation

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Introduction
In 2011 the EURADOS Working Group on Retrospective Dosimetry (WG10) published a review of the applications of retrospective dosimetry techniques in cases of external exposures to ionizing radiation (Ainsbury et al., 2011). Subsequently, a joint collaboration was started with the Working Group on Internal Dosimetry (WG7) to perform a similar review in cases of incorporation of radionuclides.

Methods
Case scenarios involving internal exposures were selected for which biological and EPR dosimetry had been performed and also intake and internal dose assessment based on retention and/or excretion measurements were available. The scenarios were divided into incorporation of a single type of radionuclide and incorporation of mixtures. The available literature was reviewed and summarized, the appropriateness of the employed techniques was critically evaluated, the consistency between the two approaches for dose estimation tested and reasons for encountered inconsistencies discussed.

Results
The selected cases include intake of ^{137}Cs in the Goiânia accident, tritium intakes, medical administrations of Thorotrast (^{232}Th) and of ^{131}I, occupational exposures to ^{232}Th in the NORM industry, and incorporations of a mixture of radionuclides by thorium workers, by workers of the Mayak nuclear facility and by the populations living around the Semipalatinsk nuclear test sites and along the Techa River banks. In most of the cases the persons were simultaneously exposed to external gamma radiation, so that the biological signal is affected by both contributions and cannot be unequivocally associated to the internal exposure. Moreover, several studies estimated the internal dose using reference models, so that no comparison is possible with the individually assessed biological dose.

Conclusion
In conclusion, an acceptable agreement between the biological and EPR doses and the internal doses assessed with in vivo and/or in vitro monitoring data was observed only in very few specific cases of incorporation of a single type of radionuclide and where simultaneous external exposures could be excluded. The review highlighted also the need to elaborate a specific calibration of the biological response for incorporated radionuclides and to develop specific studies under controlled conditions for investigating this issue further.

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OP - 13

Biomarkers for use in early and late biodosimetry using lymphocytes from relapsed and refractory neuroblastoma patients treated with targeted ^{131}I-MIBG.

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Introduction
^{131}I-MIBG is a targeted radiation treatment in patients with neuroblastoma.[1] We have previously shown that peripheral blood gene expression analysis in these patients can predict internalized doses of ionizing radiation (IR) after treatment, as well as acute toxicity.[2,3] We now expand these studies to identify differences between early (3 days) and late (15 days) internalized exposures.

Methods
In this comparative study, total RNA was isolated from 5 patient sets treated with ^{131}I-MIBG for comparison to an in-house biodosimetry panel of transcripts. Samples were taken prior to treatment (untreated), as well as 72 hours and 15 days after exposure. Selected transcripts within the TP53 pathway, an apoptosis and cell signaling pathway, were validated and fold changes were determined with respect to untreated controls.

Results
We found that most biodosimetry panel transcripts that are predictive of early exposure returned to baseline levels 15 days post-exposure. Examples of early predictors include CDKN1A (p=2.65E-4), FDXR (p=3.61E-3), DDB2 (p=1.43E-2), and PCNA (3.38E-2) that were significantly up-regulated at 3 days post exposure and returned to baseline levels by day 15. Interestingly, several transcripts, such as BCL2 (p=1.23E-3) and IGF1R (p=7.55E-3), were significantly downregulated at day 15 as compared to baseline. In addition, MDM2 transcript levels also displayed significant down-regulation by day 15 (p=1.56E-2). Transcript levels for DNA repair and cell signaling genes were diminished by 15 days after exposure, while oxidative stress response remained repressed two weeks post exposure.

Conclusion
Our studies indicate the utility of externally-derived biodosimetry gene expression panels for internalized ^{131}I exposures over later time points and for use in children, a population not normally accounted for in irradiation exposure studies. The data also illustrates the need for complementary studies to identify and incorporate additional markers for later time points after exposure. Ongoing gene-expression analyses will allow us to expand the biodosimetry panel as well as identify susceptibility factors that are predictive of positive outcomes of treatment for neuroblastoma.

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OP - 14

A simulation study: Comparison of statistical methods for uncertainty estimation in biological dosimetry

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Introduction
The estimation of uncertainties is a central part in the workflow of biological dosimetry and improper use of statistical methods can lead to under- or overestimation of uncertainties. In the context of international networks for emergency response it will be particularly important to evaluate and then standardize methods for uncertainty estimation.

Methods
Based on *in silico* simulations, the most common statistical methods for uncertainty estimation in biological dosimetry are systematically compared for scenarios of whole and partial body irradiations. Further simulations are carried out to evaluate the association between scored cell numbers and false negative/positive exposure estimations with regard to low dose exposure. Moreover, the classification of individuals in cases of large-scale radiological incidences is systematically evaluated in association to cell number and dose.

Results
The suggested simulation strategy demonstrates the limitations and strengths of different methods for uncertainty estimation in biological dosimetry. Based on these results, technical limits for the statistical analysis of data from a given scenario are assessed, which enables the definition of statistical standards for uncertainty estimation. Moreover, simulation results enable the identification of sources for the improvement of statistical methods. Sample size comparisons allow the estimation of the required cell numbers for difficult situations in biological dosimetry, such as, for instance, the estimation of low dose overexposure and the classification in case of large scale radiological incidences.

Conclusion
For the first time, a systematic evaluation of statistical methods for uncertainty estimation in biological dosimetry was performed. The results provide guidelines for statistical analysis strategies, offer opportunities for standardization and improvements of statistical analyses and provide suggestions for the practical feasibility of dose estimations in difficult scenarios. The suggested simulation strategy can be used to evaluate the reliability of estimations in complex situations with several sources of uncertainty.

References
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OP - 15

A Novel and Sensitive Blood Test for Radiation Biodosimetry

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Introduction
Exposure to ionization radiation from a nuclear reactor accident or detonation of a nuclear weapon could have major consequences on human health. Depending on the absorbed dose and the geography of exposure, the intensity and onset of Acute Radiation Syndromes (ARS) will vary. Rapid triage is critical for timely administration of countermeasures and proper allocation of the resources.

Methods
Comparative analysis of dose and time dependent changes of circulating miRNAs detected in animal models of partial and whole body irradiation has identified biomarkers with potential to develop as biodosimeters. Utility of candidate miRNAs for estimating absorbed dose, dose response and evaluation of injury recovery have been demonstrated in non-human primate models and in human patient (radiation therapy) samples. Biomarkers discovered by an unbiased nanoString based profiling were validated by qRT-PCR and was used for developing internally controlled biodosimetry assay.

Results
Decrease in circulating miR-150 was detected in multiple animal models of whole body irradiation and in human leukemia patients in the dose-range relevant to triage in radiological events. Mouse model study demonstrated the feasibility to assess the normalized miR-150 levels of radiation exposure within ± 0.5 Gy at lower dose range (0.5 - 3.0 Gy gamma rays) at time points relevant for triage in radiological events. Robustness and sensitivity was validated by comparison with lymphocytic depletion kinetics. The response correlated with percentage of marrow exposed in partial body irradiation models. Evaluation of miR-150 reconstitution kinetics in samples collected weekly for up to 100 days from patients who received bone marrow transplantation following ablative total body irradiation, shows its utility for assessing recovery and the effect of countermeasures.

Conclusion
The assay developed shows capability to distinguish unexposed from 2 Gy exposed individuals using a drop of blood that can be collected by finger stick. The high sensitivity and broad analytical range allow analysis in hours to days after casuality. This will allow triage and follow-up of exposed individuals and help clinical/treatment decision making.

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Biological and EPR dosimetry for epidemiology

OP - 16

Establishment and validation of gene expression biodosimetry based on age and gender in human peripheral blood models of radiation exposure

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Introduction
Gene expression-based dosimetry is considered as a rapid, accurate and high-throughput tool for dose assessment after radiological disasters. Over the years, numerous radiation-induced genes expression alterations were well documented.

Methods
Our goal was to identify the highest reproducible radiation-responsive genes and develop the radiation-specific gene expression signature for dose assessment of radiation exposure. Bibliometric methods were applied to analyze the global research trend of radiation-responsive genes from 2000 to 2017. The highly reproducible radiation-responsive genes must possess consistent dose-effect relationships in more than three independent studies.

Results
Human peripheral blood from 30 healthy donors was γ-irradiated with doses of 0 (control), 0.5, 1, 2, 3, 4, 6, and 8 Gy. The alterations of highly reproducible radiation-responsive gene expression were assessed by quantitative real-time polymerase chain reaction at 6, 12, 24, 48 h after exposure. Inter-individual variation was also examined. We found 79 publications on radiation-responsive genes from 2000 to 2017. A total of 35 highly reproducible radiation-responsive genes were identified. Most genes are involved in response to DNA damage, cell proliferation, cell cycle regulation, and DNA repair. The p53 signal pathway was the top enriched pathway. The expression levels of 18 genes in human peripheral blood were significantly up-regulated in a dose-dependent manner at four time-points after irradiation.

Conclusion
Our findings in this study suggest that establishing the gene expression model based on age and gender using a certain number radiation-responsive genes may help to provide the accurate dose assessment.

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OP - 17

Chromosome aberration studies of peripheral lymphocytes obtained from orthopaedic surgeons involved in X-ray fluoroscopic surgery

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Introduction
Chronic exposure of orthopaedic surgeons to X-rays during fluoroscopic surgery can cause medical issues such as dermatitis, necrosis, and skin cancer. However, in Japan, the realistic radiation exposure dosage impacting orthopaedic surgeons is unclear. In order to evaluate the effect of X-ray exposure by X-ray fluoroscopic surgery, we examined chromosome aberrations in peripheral lymphocytes.

Methods
After informed consent was obtained, peripheral blood was collected from 18 orthopaedic surgeons who were engaged in X-ray fluoroscopic surgery and had skin disorders caused by X-ray exposure. The informed consent form used was approved by the Committee of Medical Ethics of Hirosaki University Graduate School of Health Sciences and Hirosaki Memorial Hospital. Blood count and blood chemistry were performed. PBMCs were isolated from peripheral blood, cultured for 48 h with PHA and colcemid, and chromosomal aberrations were analysed with Dic assay/DCA and translocation assays.

Results
The orthopaedic surgeons had necrosis, squamous cell carcinoma, Bowen's disease, and induration on fingers and discoloration or melanonychia on the finger nail. There were no notable abnormalities in the haematological examination. The frequency of the Dic in these surgeons was higher than that of healthy subjects or other medical staff [1]. However, it is difficult to estimate the partial irradiated dose as the dicentric cell distribution had a Poisson distribution. In addition, marker chromosomes formed by chromosomal translocation were observed in many doctors, showing a higher translocation frequency than the world average [2].

Conclusion
The results suggested that excessive chromosomal aberration due to X-ray exposure were induced in peripheral blood lymphocytes of orthopaedic surgeons engaged in fluoroscopy and surgery. Chromosome translocation analysis is expected to be applied to evaluate radiation exposure in orthopaedic surgeons who have involved in X-ray fluoroscopy and surgery for many years. Radiation protection in occupational exposure in medical field is insufficient in Japan. Analysis of chromosome abnormalities in occupational exposure will contribute to enlightenment of radiation protection and health management.

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OP - 18

Contribution of EPR and FISH methods to dose reconstruction for the Southern Urals Population

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Introduction
Radioactive releases into the Techa River from the Mayak Production Association during 1949–1956 and the Kyshtym accident of 1957 that created the East Ural Radioactive Trace (EURT) led to significant environmental contamination. Enhanced version of the Techa River Dosimetry System (TRDS-2016) was designed to estimate radiation doses to population residing in contaminated areas.

Methods
EPR and FISH methods were used to reconstruct doses in residents of the contaminated territories 50 years after the period of the major exposure (Degteva et al 2015). Since the residents were exposed to internal and external radiation, the EPR and FISH assays were supported by measurements of 90Sr content in the skeleton and teeth in order to estimate and subtract local internal doses from incorporated 89,90Sr (Shishkina et al 2014; Vozilova et al 2014). For each donor, individual doses of external and internal exposure from 137Cs intakes were calculated using TRDS-2016.

Results
The dose estimates obtained from EPR and FISH measurements in the upper-Techa Region (7-60 km from the site of release) were found to be consistent: mean values vary from 510–550 mGy for the villages located close to the site of radioactive release to 130–160 mGy for the more distant villages. The EPR- and FISH-based doses corresponded within uncertainty bounds to the estimates of external exposure plus 137Cs-internal exposure calculated with TRDS-2016. The settlement-average EPR-based external doses for the EURT evacuees decreased from 160 mGy at a distance of 12 km from the accident site to 50 mGy at a distance of 65 km along the axis of the trace. The EPR-based estimates were in agreement with the doses calculated for the EURT residents with the use of TRDS-2016.

Conclusion
The report discusses the usage of EPR and FISH methods to reconstruct doses in residents of territories contaminated as a result of the Mayak releases 50 years after the major exposure. Since the residents were exposed to internal and external radiation, the EPR and FISH assays were supported by measurements of 90Sr content in the skeleton and teeth. The EPR- and FISH-based estimates are in agreement with the corresponding doses calculated with the dosimetry system TRDS-2016 that uses data on radionuclide contamination of the Techa River and EURT.

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OP - 19

Model for estimation of mean doses absorbed in peripheral blood T-lymphocytes after local bone marrow exposure (based on the Techa River study)

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Introduction
FISH method applied to the analysis of peripheral blood T-lymphocytes is used in retrospective dosimetry, and doses derived from stable chromosome aberrations are usually interpreted as red bone marrow (RBM) doses. However, after local RBM exposure due to ^{89,90}Sr, doses derived from FISH can reflect doses absorbed by T-progenitors in RBM or/and absorbed by T-cells in other lymphoid tissues.

Methods
Modeling involves estimating doses absorbed by T-cells (T-progenitors and mature T-lymphocytes) in two main compartments: (1) in RBM where the main source of exposure is ^{89,90}Sr incorporated into the bone; target cells are T-progenitors and mature T-lymphocytes in the process of recirculation; (2) in extra-skeletal lymphoid tissues, where the main source of exposure is the external irradiation and radionuclides are uniformly distributed in the body, the target cells are immature T-lymphocytes in thymus and circulating mature T-lymphocytes.

Results
The concept of T-cell Genus (TG) was introduced and defined; TG combines all T-progenitor descendants with inherited specific aberration formed in RBM. The number of TGs produced over different age-periods of human life was estimated with the use of a mathematic model of T-cell homeostasis (Bains 2010). The rate of TG loss during the lifetime was assumed to be very small in comparison with production rate. Recirculation of mature T-lymphocytes in RBM (exposed to bone-seeking ^{89,90}Sr) was taken into account. According to our model estimates, at the time of blood sampling, the fraction of exposed T-lymphocytes (whose progenitors were irradiated) ranged from 20% to 80% depending on donors" age at the start of exposure to ^{89,90}Sr.

Conclusion
Some portion of blood T-lymphocytes could remain unexposed following local irradiation of RBM. The model was applied to FISH study of Techa River residents exposed due to external and internal (^{89,90}Sr) sources. Dose to T-lymphocytes derived from FISH studies should be about 0.6 – 0.9 of RBM dose for residents of the upper Techa region and about 0.4 – 0.8 – for the middle Techa region residents. Our results could explain the lower value of translocation yield per Gy obtained for Techa residents (Voziliva et al., 2014). Approaches for further model improvement and validation are discussed.

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OP - 20

Application of EPR tooth dosimetry for validation of the uncertainties of calculated external doses: experience in dosimetry for the Techa River cohort

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Introduction
EPR measurements of teeth are widely used in retrospective dosimetry to validate theoretically derived external doses. Now traditional deterministic approaches to dose estimation are supplemented by stochastic modelling to estimate both mean adiation doses and the corresponding uncertainties. Stochastic modelling includes assumptions and simplifications and need validation too.

Methods
We propose an approach how to use the results of tooth EPR dosimetry for validation of model predicted uncertainties. We suggest normalized root mean square deviations between individual EPR-derived and calculated doses (corrected on measurement error) as a characteristic of "true" uncertainty of calculations. "True" uncertainties have to be comparable to modeled values of uncertainties.

Methods of EPR measurements and uncertaintie estimations are described in Shishkina et al [1]. Description of TRDS-MC is in the [2].

Results
This approach was elaborated for validation of the Monte Carlo version of the Techa River Dosimetry System (TRDS-MC). External doses and corresponding uncertainties estimated for different groups of the Techa River Cohort were analyzed and compared to EPR dosimetry results. We would like to present an example of such a comparison.

Conclusion
It has been shown that in the previous version of TRDS-2009MC the uncertainties of external exposure doses were underestimated. As a result, some model improvements were undertaken. For example, the improved TRDS-2016MC reconsidered the component of overall uncertainty due to air kerma prediction at the Techa River shoreline. Additionally, the uncertainty of air kerma – organ dose conversion was included into the model.

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OP - 21

Assessment of exposure doses to uranium personnel of the mining enterprise and the population of the adjacent territories of Northern Kazakhstan using tooth enamel EPR method

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Introduction
To assess the radiation impact of uranium mining enterprises on the personnel of enterprises and the population of the adjacent territories, the personnel of the Shantobe uranium mine and the population of Stepnogorsk (Akmola region, Northern Kazakhstan) were examined by the EPR dosimetry method.

Methods
A special study has been carried out to develop a method for isolating the possible contribution of internal irradiation from alpha-emitting isotopes. The radiation induced signal (RS) from the incorporated alpha emitting isotopes is formed in the surface layer of the enamel from the adjacent soft tissues. Proposed method is based on the comparison of the amplitude of RS in the sample after bleeding of the enamel surface layer.

Results
On the basis of the measurements performed, a statistical analysis of the obtained values of the added doses obtained by the EPR method of dosimetry for tooth enamel separately for population groups and personnel was carried out. For the population of Stepnogorsk (50 teeth samples) the average dose was 4 +/- 11 mGy, of 51 mGy. For the personnel of the Shantobe uranium mining enterprise (30 teeth samples) the average dose value is 95 +/- 20 mGy, a variation of 85 mGy. For some samples of personnel, an assessment of the possible contribution of AI by comparing RS in samples before and after etching of the surface layer was carried out.

Conclusion
A higher average dose value and a larger variation for personnel are probably due to the contribution of occupational exposure. Probably, part of this contribution is due to internal irradiation from alpha sources in the soft tissues of the body. This work was supported by Russian Foundation of Basic Research RFBR 16-04-01276, and by the Ministry of Education and Science of Kazakhstan (5284/GF4 agreement No 47).

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EPR dosimetry and dating

OP - 22

ESR dosimetry of fossil tooth enamel: current status and challenges

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Although the radiation-induced signals measured in fossil and modern teeth are very similar, approaches and analytical procedures in ESR "palaeodosimetry" and retrospective dosimetry (Fattibene and Callens, 2010) may nevertheless differ in many aspects, mostly because of the magnitude of the dose involved: fossil tooth enamel samples may indeed register dose values of several tens to thousands of Grays. The present work aims at providing additional information to the comprehensive review recently produced by Fattibene and Callens (2010), by presenting an overview of the current status of ESR dosimetry of fossil tooth enamel and of the future avenues worth exploring in the future to increase its reliability and accuracy.

Since the first ESR dating applications to fossil teeth in the early 1980s", the analytical procedure for dose reconstruction has become more complex, although at the same time the principles have remains the same. Standard protocols still involve the measurement of enamel powder and the use of a multiple aliquot additive dose method. However, there is undoubtedly a better knowledge of the composition, nature and behaviour of the radiation-induced ESR signal with the dose, together with a better understanding of the major sources of uncertainty involved in the dose evaluation process. They may be linked to the sample itself (e.g., intra and inter-sample variability), to the experimental conditions (e.g., acquisition parameters, stability of the experimental setup; repeatability of the measurements; microwave frequency), or even to the data reduction process (e.g., evaluation of the intensity from the ESR spectrum; fitting function and fitting procedure; maximum irradiation dose selected).

Recent characterization works involving the measurement of enamel fragments have also showed the presence of various radicals with different thermal stabilities contributing to the main ESR signal, raising then new questions about the accuracy of the dose evaluation. However, this approach is technically and logistically much more complex than the standard procedure based on enamel powder, which may strongly limit its universal application. Nevertheless, this less destructive procedure has opened the possibility to date invaluable human fossil teeth whose age lies beyond the radiocarbon time range (e.g., see the recent works at Milsiya cave, Israel, or Jebel Irhoud, Morocco). However, these recent applications to human fossils also raise new challenges: most of these fossils are indeed systematically microCT-scanned, as part of the standard procedure in palaeoanthropology. This operation may actually significantly impact the ESR dating, as the X-ray dose given to the sample was found to be quite significant (>10 Gy). New procedures have therefore to be developed in order to accurately evaluate this laboratory dose and avoid any significant age overestimation.

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OP - 23

ESR dating of *Notiomastodon platensis* teeth from João Dourado, Bahia, Brazil

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Introduction
The chronology of the *Notiomastodon platensis* species is generally attributed to the Pleistocene and early Holocene, based on the estimated age of the sediments where the fossils were found. So, there are lack of definition of the temporal interval of the species. This study present new dates of the fossils of *N. platensis collected in the city of João Dourado, Bahia, Brazil, obtained by ESR.*

Methods
The soil associated to the teeth, a fraction of the enamel and dentin of each tooth was subjected to neutron activation analysis to determine the 234U, 232Th and 40K content. For elimination of the influence of alpha radiation, the enamel was subjected to an ultrasonic bath treatment with HCl 1:10, for a few minutes. Afterwards the enamel was ground manually and divided in 10 aliquots of approximately 60mg for irradiation, to determine the equivalent dose (De). The spectra of the original sample and each irradiated aliquot were recorded in a Jeol FA200 X-band spectrometer.

Results
The peak-to-peak intensity of the spectrum was associated with the additive dose for the construction of the dose-response curve. The fitting of the experimental data was done by a single saturating exponential function (1) and the equivalent dose value was determined. The age determination was done through the radioisotope concentration of enamel, dentine and soil and the local cosmic radiation that is 168uGy/a, using DATA(2) software resulting in the ages of 15.9 ± 2.3 and 11.5±2.0 in the Early U-Uptake model and 16.7 ± 2.4 and 12.7 ± 2.2 ka, respectively in the Linear U-Uptake model.

Conclusion
These results are similar to others of this species in the near region and, therefore, contribute to the knowledge of the chronology of the species in the Brazilian northeast.

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OP - 24

ESR dating on a late Pleistocene fossil from the Mirim Lake, southern Brazilian coast

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Introduction
Electron spin resonance (ESR) has been applied with good results to determine the ages of fossils found in Pleistocene deposits of the southern Brazilian coastal plain. Here is reported the results obtained from a tooth of a mammal (*Toxodon platensis*) found in the southeastern margin of the Mirim Lake

Methods
The specimen was found at a distance of 1.5 km from the present lake shore, together with other fossil fragments in a muddy sand layer exposed at a depth of about 2 meters from the terrain surface, along an irrigation channel excavated in a wide terrace on the lake margin. For ESR dating the X-Band JEOL spectrometer was used to obtain the dose-response curve and the Equivalent Dose (De) determined by fitting the experimental data points using single saturating exponential curve1, De was converted to age using the DATA software2. The concentration of radioisotopes was determined by NAA.

Results
The age obtained is 68 ± 13ka considering Early Uranium-Uptake model. A caliche nodule found 1 meter above the fossiliferous horizon was previously dated by optically stimulated luminescence (OSL) using the multiple aliquot regeneration (MAR) protocol giving an age of (29 ± 4) ka. The age from the fossil and the caliche agree with each other, and indicate that between ~68 and 30 ka ago either the lake shore reached farther inland than today, thus reworking fossils deposited on its shore, or that streams flowing along the terrace on the margin transported the remains to the lake

Conclusion
The ages also put this deposit in chronocorrelation with the fossil-bearing Santa Vitória Formation that outcrops along the Chuy Creek some 10 km to the east of Mirim Lake.

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OP - 25

ESR Dating Teeth from Medzhibozh, Ukraine: Using Isochrons to Track U Uptake in a Middle Pleistocene Open-Air Site

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Introduction
The Medzhibozh complex includes two multilayered open-air sites in western Ukraine at 49°35′ N 27°42′ E, 270 m amsl. Since ESR can date vertebrate enamel up to 2-4 Ma with 2-5% precision, three cervid teeth from Layer 16a at Medzhibozh I and one from ~ 500 m away in the Layer 1/2 boundary at Medzhibozh A were dated by standard ESR and by isochron analyses to assess U uptake rates, *p*.

Methods
Medzhibozh I has 17 geological strata with two alluvial cycles and two archaeological layers. Layer 16a yielded Paleolithic artefacts, mainly choppers, chopping-tools, lakes with little secondary modification, and bones with cutmarks. *Ursus deningeri* and other Middle Pleistocene fossils suggests that Layers 13-16 must predate 200 ka. At Medzhibozh A, six distinct archaeological layers were intercalated with gravel units. To measure the volumetrically and time-averaged sedimentary dose rates, sediment samples were analyzed by NAA.

Results
From geological data, ramped box models calculated time-averaged cosmic dose rates. Accumulated doses were calculated using the additive dose method using precisely characterized doses. From Medzhibozh A, AT29"s LU age agreed best with faunal analyses, but the isochron suggested extensive secondary U uptake. At Medzhibozh I, all the dentine samples contained > 100 ppm U, while AT45's enamels had > 10 times more U than all the other teeth. Both AT44 and AT45"s isochrons yielded strongly negative external accumulated doses, suggesting that secondary U uptake caused their standard ESR ages to overestimate their true ages.

Conclusion
Using p = 4, AT41"s ESR ages at ~ 373 ka, which correlates with late MIS 11, agreed best with the geologically expected ages from the faunal analyses, but p must be confirmed with coupled ESR-230Th/234U analyses. With p = 4, AT44 dated at ~ 440 ka, correlating with late MIS 12. With p = 6, AT45 correlates with MIS 11. More teeth must be dated to confirm these results and check for reworking. If correct, these ages make Medzhibozh"s hearths the oldest in the Ukraine. This is first site in which isochron analyses show the same secondary

References
U uptake mode in multiple teeth, hinting that one secondary U uptake event may have affected all Medzhibozh. More coupled ESR-isochron-ESR-230Th/234U analyses may better model Medzhibozh"s geochemical history, correcting its ESR ages for secondary U remobilization.

OP - 26

The development of in-vivo electron-paramagnetic resonance tooth dosimeter at SNU

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Introduction
In Korea, the increasing use of nuclear power has brought on a keen interest in an urgent availability of biodosimeters following an unforeseeable event where unspecified individuals may have been exposed to high-risk doses of ionizing radiation. In our project, we aim to develop a prototype of EPR tooth dosimeter at SNU, Korea.

Methods
We have developed three parts of the EPR spectrometer, which typically consists of (I) the permanent magnet, (II) the bridge, and (III) the resonator. The components in the bridge were selected in order to optimize for 1.15 GHz frequency. We designed software in LabVIEW, which can control a lock-in amplifier and sweeping magnetic coils. This software can also provide the spectra fitting and setting of instrument. We tested the developed tooth dosimeter with 15N-PDT and hydroxyapatite samples. Then, we established the curves of irradiated dose and EPR signal.

Results
The EPR spectrometer used dipole magnets which were designed and fabricated by Resonance Research Inc. (Billerica, MA). A bipolar power supply provides driving magnetic fields from 38 mT to 44 mT. A modulated field can supply 0.4 mT. A resonator was fabricated with appropriate transmission line lengths and loop sizes for measurements for incisor tooth. The resonance frequency of the resonator was approximately 1.15 GHz. Automatic frequency control system was used to minimize the difference between carrier and resonant frequency. A voltage controlled oscillator was used to monitor tuning of the resonator with a sample. The S11 of resonator was approximately -45 dB at 1.146 GHz. The established curves between dose and EPR signals show high linearity to comparable other group's instruments.

Conclusion
We successfully developed an EPR tooth dosimetry for the case of radiation emergency. We will continue to improve and utilize the developed EPR spectrometer for the nationwide needs.

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OP - 27

EPR investigation of new generation of smartphone touchscreen glass for radiological accident application

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Introduction
Touch screen (TS) of smartphone made of Gorilla glass were identified within Mutlibiodose EC project as a new possible fortuitous dosimeter for radiation accident. Since, new types of materials are implemented in TS as new generation of Gorilla Glass. Therefore, to evaluate if this approach remains valid, investigation dosimetric properties of new types of glass was performed.

Methods
New generations of Gorilla Glass produced by Corning (type 3, 4) were studied. EPR signals variability was investigated before and after gamma-rays and UV irradiation, as well as variability of dose response, energy dependence, and signal components stability.

Results
All Gorilla Glass types present the same EPR spectra feature before and after irradiation. The intensity of the signal prior irradiation varies significantly. For the different Gorilla glass generation, similar dose response and signal decay kinetic were observed. As for the first generation of Gorilla Glass, one of the main signal components is eliminated when exposed to UV light.

Conclusion
This study shows that the new generations of Gorilla glasses are also suitable for accident dosimetry, as the Gorilla Glass previously studied.

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OP - 28

Characterization of a lithium formate EPR-dosimetry system for proton radiation therapy.

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Introduction
Lithium formate dosimetry was earlier well characterized for photon irradiations and has successfully been used for audits[1]. The dosimeter material was earlier studied in high LET-irradiations, protons and light ions[2] but not before in a clinical proton beam. This investigation aims at an audit system for proton therapy with the primary objectives to accurately determine response and stability.

Methods
Lithium formate with 10% paraffin was pressed to tablets, mass 100 mg. The dose response homogeneity among the dosimeters was determined by photon pre-irradiation. For dose response measurements 5 sets of 4 dosimeters each were inserted in a phantom below 2.7 cm of solid water and irradiated by 150 MeV protons. The chosen doses were multiples of the reference dose, 0.680 Gy up to 8.84 Gy. The response was tested with a dose unknown for the analyzer. The stability was determined by irradiations of sets of 4 dosimeters, every week during 1 month and analyzed at the same day thereafter.

Results
The signal homogeneity within the dosimeter batches used was 98%, why their signal values had to be corrected with an individual calibration factor. The response was found to be linear following the regression line $S= 0.202\ D+0.648$, S is the EPR signal and D the absorbed dose, with an adjusted R^2 value, 0.998. A set of 4 dosimeters were irradiated with 6.70 Gy, unknown for the analyzer, who estimated the dose to be 6.63 Gy. Regarding signal stability, the fading curve was found to be best fitted with a polynomial regression and fading was found to be 6.6 % after 31 days. As a continuation, a preliminary test of possible phantom materials for audit of proton irradiations showed that teflon was found to be a suitable bone substitute.

Conclusion
Lithium formate dosimeters have been successfully characterized in a clinical proton beam with the main conclusions that the response is linear at least up to 9 Gy and therefore doses can be accurately estimated in this dose range using few points in the calibration curve. The fading was found to be less than 7% within 1 month following a polynomial slope, which is possible to correct for. This is different from photon irradiations, with stable dosimeters, but a phenomenon earlier found for alanine in high LET irradiations[3].

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Biological and EPR dosimetry for emergency I

OP - 29

Operational basis and capacity of the RENEB network

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Introduction
RENEB is a European dosimetry network that provides fast individual dosimetry in a large emergency event (1). It offers a battery of retrospective dosimetry assays which complement each other with respect to sensitivity, speed of analysis and signal stability. The aim of this poster is to present the characteristics of the methods, the capacity and how RENEB maintains its operational readiness.

Methods
The following retrospective dosimetry assays are implemented in RENEB: dicentrics, micronuclei, premature chromosome condensation (PCC), fluorescence in situ hybridisation (FISH), gammaH2AX, gene expression, optically stimulated luminescence (OSL) and electron paramagnetic resonance (EPR) (2). Regular intercomparisons are being carried out to test the efficiency of the network and the precision of dose estimates. The capacity of the network is estimated by questionnaires where each network partner declares his/her level of stockpiling and available manpower.

Results
Several intercomparison have been carried out with intermittent training sessions to improve performance. Also, two table top accident simulation exercises were organised to test and train the logistics of activating the network and managing dosimetric results. The evaluation of performance clearly demonstrates the usefulness of intercomparisons and exercises. The network is currently able to handle ca 1000 - 4000 cases per week, depending on the accident scenario and the choice of the applied assays.

Conclusion
The EU network RENEB is operational and ready to carry out retrospective dosimetry in a large-scale radiological emergency. Regular intercomparisons are carried out to maintain efficiency both with respect to speed of analysis, precision of dose estimates and logistics of sample and data handling.

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OP - 30

RABiT-II-DCA: Automating the Dicentric Chromosome Assay using a commercial robotic platform

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Introduction
The Dicentric Chromosome Assay (DCA), currently the gold standard for radiation biodosimetry has, to date, resisted useful automation. Following up on our success in implementing the micronucleus and γ-H2AX assays using a commercial high-throughput/high-content screening robotic platform (RABiT II; Rapid Automated Biodosimetry Tool), we have also implemented the DCA using the same platform.

Methods
RABiT-II DCA is based on a finger stick of blood (30 µl), and performed robotically in a 96-well format, using a Perkin Elmer cell::explorer. Rather than the standard Giemsa staining and morphometric analysis, which require a highly skilled scorer and high quality images, our approach is based on a variant of fluorescent in situ hybridization, using PNA or BNA probes to mark the centromeres. Scoring is thus performed by identifying chromosomes with two green spots (centromeres) as dicentrics. This method allows us to use a faster, low magnification imager (BioTek Cytation, operated at 20x).

Results
The hybridization protocol has been simplified, removing many of the wash steps and temperature cycling; hybridization is performed by incubating at 37°C, eliminating the need for a hot plate. The modified assay uses half the number of reagents of the IAEA assay and requires less than 1h of active processing time per plate (i.e. not including incubation) compared to 7h with the IAEA assay.

While the standard dicentric assay is typically only used up to 4 or 5 Gy. We have seen no problems with our assay up to 10 Gy and above, using ex-vivo irradiated blood.

We present first results from this fully automated dicentric chromosome assay, demonstrating that high-throughput radiation biodosimetry is practical using current commercial high-throughput/high-content screening robotic systems.

Conclusion
We demonstrate here a fully automatic DCA, implemented on a Perkin Elmer cell:explorer (A similar assay can be run on platforms available from other vendors). The advantage of using commercially available platforms rather than custom built robotics for implementing high throughput biodosimetry is clear. These systems are already deployed in universities and big pharma and have a wide base of knowledgeable users and maintenance personnel.

This approach will allow much wider access to high-throughput biodosimetric screening for large-scale radiological incidents than is currently available.

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OP - 31

Population-scale biodosimetry with the Automated Dicentric Chromosome Identifier and Dose Estimator (ADCI) software system

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Introduction

ADCI released for laptop systems running MS-Windows meets IAEA criteria for triage cytogenetic biodosimetry [1, 2]. Rapid triaging using fewer metaphase images may be less accurate. We present a high performance software system for cytogenetic biodosimetry using the IBM Blue Gene/Q supercomputer, with the requisite throughput to accurately stratify individuals based on computed exposures.

Methods

The BG/Q version of ADCI streamlines dose estimation by optimal scheduling of dicentric chromosome detection for varied numbers of samples and metaphase cell images in each sample. Our previous proof-of-concept implementation [3] was optimized by extending a master-slave model of sample and image analysis to a General Manager-Manager-Worker hierarchical processing model. Additionally, local threading enhanced overall performance. This model handles samples with larger numbers of images, as the worker processor requires memory to hold only a single image at a time.

Results

The BG/Q system processed 6480 samples, consisting of 500 metaphase images each, with 55,296 CPUs in 1 hr 17 min 47 sec. Dose estimation for those samples was completed in 32 sec with 1024 CPUs. A single sample consisting of 5219 images was analyzed in 20.6 min. To compare results from the Windows and BG/Q versions, 50 samples of 500 images were processed on both systems. The Windows version of ADCI required 11.17 hr vs. 30 min 52 sec on BG/Q. The DC frequencies and dose estimates produced by both versions were identical for all samples.

Conclusion

The BG/Q implementation of ADCI achieves adequate performance to deliver timely and accurate dose estimates in a mass casualty radiation event. Population-based biodosimetry should facilitate realistic simulations of biological exposures in nuclear incidents of various yields.

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OP - 32

FDXR is a biomarker of radiation exposure in vivo

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Introduction
Previous investigations in gene expression changes in blood after radiation exposure have highlighted its potential to provide biomarkers of exposure.

Methods
Here, FDXR transcriptional changes in blood were investigated in humans undergoing a range of external radiation exposure procedures covering several orders of magnitude (cardiac fluoroscopy, diagnostic computed tomography (CT)) and treatments (total body and local radiotherapy). Moreover, a method was developed to assess the dose to the blood using physical exposure parameters.

Results
FDXR expression was significantly up-regulated 24 hr after radiotherapy in most patients and continuously during the fractionated treatment. Significance was reached even after diagnostic CT 2 hours post-exposure. We further showed that no significant differences in expression were found between ex vivo and in vivo samples from the same patients. Moreover, potential confounding factors such as gender, infection status and anti-oxidants only affect moderately FDXR transcription. Finally, we provided a first in vivo dose-response showing dose-dependency even for very low doses or partial body exposure showing good correlation between physically and biologically assessed doses.

Conclusion
In conclusion, we report the remarkable responsiveness of FDXR to ionising radiation at the transcriptional level which, when measured in the right time window, provides accurate in vivo dose estimates.

References
None

OP - 33

Non-Coding RNAs as Biomarkers for Radiation Biodosimetry

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Introduction
Rapid and reliable methods for conducting biological dosimetry are critical in the event of a nuclear disaster. Coding and non-coding RNAs (microRNAs and lncRNAs), in whole blood represent potential valuable candidates as non-invasive biomarkers. Early prediction of possible acute, intermediate, and delayed effects of radiation exposure will enable timely therapeutic interventions.

Methods
Whole blood was collected at 6, 24, 48-hour, and 7-day time points after 2, 4, 8, 12, and 15Gy irradiation. Sham irradiated animals served as controls. Differential miRNA, lncRNA and mRNA expression patterns were evaluated using mouse whole genome microarray followed by qRT-PCR validation analysis. To detect the significant biomarkers that changed by dose response or time course due to radiation, a two-way analysis of variance (ANOVA) was implemented to determine the main effect and interaction of dose and time of treatment.

Results
miR-193b-3p and mir-92a-3p were upregulated for all doses at earlier time points. We observed downregulation of miR-17 family (miR-17-5p, miR-20a-5p, miR-93-5p and miR-106b-5p) in response to radiation from 2 Gy onwards at 24 h, 48 h and at higher doses for the 7-day time-point. mRNA targets of these altered miRNAs are involved in hematopoietic cell lineage, cell cycle, and extracellular receptor pathways. Among the significantly altered lncRNAs, *Trp53cor1*, *Dino* and its neighboring gene cyclin-dependent kinase inhibitor 1A (*Cdkn1a*), were consistently upregulated in whole blood and in heart, lung and liver tissues after irradiation. Among the organ specific radiation induced lncRNAs, the lncRNA Braveheart (*Bvht1*) showed significant dose responsive upregulation in heart.

Conclusion
A combined approach of identifying biomarkers by assessing functional miRNAs, mRNAs and lncRNAs to assess radiation exposure after mass-casualty incidents could provide a valuable tool in implementing effective and timely medical countermeasures. Circulating non-coding RNAs can be powerful tools to monitor organ specific injury during radiotherapy or accidental injury that can be utilized as predictors of late effects. Developing biomarker signatures for organ specific injury is also vital for assessing partial and total body exposure to ionizing radiation for dosimetry applications.

References
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OP - 34

The higher detections of dicentric chromosomes in metaphases and in prematurely condensed chromosomes permit to reevaluate the dose effect curves with low dose exposure.

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Introduction
The dicentric assay is the international gold-standard method for biological dosimetry and classification of genotoxic agents. The introduction of telomere (T) and centromere (C) staining renders the scoring of dicentric chromosomes more reliable and robust not only in stimulated metaphases (ref) but also in non-stimulated lymphocytes following premature chromosome condensation (PCC) (Ref).

Methods
The scoring following TC staining in metaphase revealed a significantly higher frequency of dicentric ($p<10-3$) (up to 30%) with respect to uniform staining mainly due to underestimation by conventional techniques of T-C dicentrics or two closely spaced centromeres (C-C dicentrics).

Results
We used this approach to re-establish dose-response curves at low and high doses (10mGy to 6Gy). The news curves are builded on the analysis of dicentrics on metaphases and dicentrics on PCC-fusions 8 hours after exposure. We also added the micronucleus detection technique after low and high doses for these same donors.

For each donor, the curves were established 3 times with the 3 biological dosimetry techniques with one month of interval which will make it possible to check a possible variation of radiosensitivity over time.

Conclusion
This new calibration curve can be used for biological dosimetry in radiation emergency medicine in our lab but also for all dosimetry labs.

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OP - 35

Recent Advances in the Imaging Flow Cytometry Cytokinesis-Block Micronucleus Assay for Radiation Biodosimetry

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Introduction
The cytokinesis-block micronucleus (CBMN) assay is an accepted method for radiation biodosimetry. It is traditionally performed using microscope-based scoring which can be labour-intensive, time consuming and subject to inter-scorer variability. This assay has been adapted to the ImageStream$^{®X}$ (ISX) imaging flow cytometer and recent advances in this methodology will be discussed[1,2].

Methods
Since developing the automated ISX-CBMN assay, improvements were made to the throughput and specificity by optimizing sample processing protocols. Whole blood lysing and fixation methods were modified to maximize binucleated cell (BNC) yield and optimize the lysis of red blood cells. Furthermore, the volume of sample required for analysis was reduced to allow sample acquisition in a 96-well plate following processing on the Rapid Automated Biodosimetry Tool (RABiT-II) system. In addition, image analysis algorithms were improved using the Image Data Exploration and Analysis Software (IDEAS®).

Results
Improvements to the ISX-CBMN assay include modifications to fixation and lysing procedures, changes to blood-to-media culturing ratio, optimizing the nucleus staining titration, minimizing sample volume and use of a 96-well plate autosampler. These improvements have simplified sample processing and have resulted in a protocol that is compatible with the RABiT-II system, capable of processing thousands of samples per day[3,4]. In addition, modifications to the ISX acquisition and IDEAS® templates have increased the specificity and sensitivity of detection of BNCs and micronuclei. With these improvements, dose response curves have been generated between 0 and 4 Gy at three partnering laboratories and the validity of the assay for triage biodosimetry has been tested through intercomparisons.

Conclusion
Improvements to the ISX-CBMN assay have led to a small volume method which can provide triage quality dose estimates in the dose range of 0-4 Gy. The use of small blood samples is compatible with both the RABiT-II system for automated sample processing and the 96-well plate ISX autosampler for data acquisition. These modifications have resulted in a CBMN assay in which sample processing, sample acquisition and data analysis in IDEAS® are completely automated. This methodology has the potential to increase capacity for biodosimetry response during a large-scale radiological/nuclear event.

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Biological and EPR dosimetry for emergency II

OP - 36

Biological and EPR dosimetry for emergency

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In this presentation, we will discuss the possible role and the needed capacities of biological and EPR/TL/OSL dosimetry (referred as biodosimetry) for so called emergency situation. The concepts of emergency, triage, large-scale accidents, and medical managements will be clarified. Many different situations are commonly qualified as emergency and this terminology may lead to an uncomplete comprehension of the real needs in terms of delay and capacity of biodosimetry measurements. As a consequence, present efforts in technical developments and in terms of organization do not necessarily address all the real needs.

Therefore, in a first part, we will try to provide an overview of the different known situations in order to identify the needs in terms of triage and dose assessment (capacity, detection limit, delay) and therefore the remaining technical gaps. Depending on scenario, the role of biodosimetry techniques in the management of an event may be very different. In the literature, as a dogma, the role of biodosimetry is mainly envisaged for triage performed for large numbers of individuals but also rapidly after the event in order to provide medical management in the shortest delay. Based on examples of past radiological accidents, we will discuss this axiom and identify when this approach may not be always realistic and efficient. Triage based on clinical signs should not be ignored. In addition, after the triage phase, it would be necessary, in a second phase, to provide precise dose estimation. For the medical management, the same level of accuracy in dose assessment will be required whatever the size of the event, which means for large scale accident to also develop large capacity, but with different criteria (i.e. accuracy). It is worth to stress, that laboratory resources that could be engaged for triage will be also very probably requested at the same time for accurate dose assessment: both sequences overlapping each other. This point will be crucial, especially if the same resources are used (i.e. network of lab), whereas in the case where dedicated field triage capacities can be deployed, complementarity of fixed and field resources can be played.

In a second part, the use of the different typologies of approach (network of lab, in situ measurement) and the different possibilities in identification (clinical signs, bio-indicators, dosimetry) and dose assessment will be also discussed in the light of the first part conclusion. The aim of this presentation is to open and stimulate the discussion based on the doctrine maturated at IRSN after more than two decades of involvement in radiological accident management.

OP - 37

Radiation dose, a predictor with limitations regarding patient outcome and clinical support needs of the ARS

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Introduction
The relation of dose to different severity degrees of the hematologic acute radiation syndrome (HARS) may differ over the dose range, making the use of dose alone a less reliable predictor of clinical course. We sought to understand the relation of absorbed dose and risk of clinically relevant HARS in humans.

Methods
We used the database SEARCH (System for Evaluation and Archiving of Radiation Accidents based on Case Histories) containing the history of radiation accident victims. From 153 individuals we extracted data on dose estimates using the dicentric assay as the measure of individual biological dosimetry. These data were analysed according to the corresponding haematological response categories of clinical significance (H1-4) based on the medical treatment protocols for radiation accident victims (METREPOL).

Results
Age at exposure, gender, and ethnicity were considered potential confounders in unconditional cumulative logistic regression analysis. Most of the Caucasian (82.4%) male (92.8%) victims originated either from the Chernobyl (69.3%) or Goiânia accident (10.5%) and almost 60% were aged 20-40 years at exposure. All cases received a whole body exposure (mean 3.8 Gy, stdev +/- 3.1) and the reported single exposures (79%) predominated. Seventy per cent of victims with H0 had a dose < 1 Gy with rapidly decreasing proportions of H0 seen at doses up to 5 Gy. Those with H4 HARS were infrequent at doses of 1-2 Gy, while 82% of H4 HARS occurred at doses > 5 Gy. HARS 1-3 varied in dose ranges between 1-5 Gy.

Conclusion
In summary, single whole body doses below 1 Gy and doses > 5 Gy roughly corresponded with H0 and H3-4 HARS and this was consistent with medical expectation. However, whole body doses between 1-5 Gy poorly corresponded to H1- H3 HARS. The dose range of 1-5 Gy was of limited value for medical decision making regarding e.g. hospitalization for H2-3 but not H1 and treatment decisions that differ between H1-3. Also, some instances of H0 were observed at high doses and outcomes H2-4 were seen at low doses, making an individual recommendation based only on dose essentially impossible.

References
none

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EPR dosimetry in TBI patients - a feasibility study and assessment of reliability of the method in nails irradiated in vivo

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Introduction
EPR dosimetry in nail clippings was suggested as a promising technique to be applied in radiation accidents. Initial works in this field done on nail clippings irradiated *in vitro* showed increase of amplitude of EPR signal with doses in the range of interest in emergency dosimetry [1-4]. So far no study on dosimetry of nails samples irradiated *in vivo* under controlled exposure was reported.

Methods
In this work we measured EPR signals in nail clippings from 10 patients undergoing Total Body Irradiation (TBI). The total doses delivered in 4 or 6 fractions during 2 or 3 days of TBI were about 11 or 15 Gy, respectively, according to radiotherapy treatment planning verified by alanine dosimetry. EPR signals in irradiated nails were compared with signals measured in nails collected from the same patient before TBI. The unirradiated samples were also used for individual calibration of the nails' radiation sensitivity. In a few patients, the calibration was performed by additive dose method.

Results
The doses measured in all samples were significantly lower than the actual delivered doses. In several cases, the doses calculated on the basis of the EPR data were negative. Better results yielding the TBI doses of 7.6, 9.8 and 16.5 Gy, were obtained in frozen samples (-28 °C) from toenails, than from fingernails, what can be attributed to difference between these samples in their exposure to water in daily hygienic procedures of the patients during the 2-3 days between the first and the last dose fraction. Some of the samples were collected directly after the first 2 Gy fractions, avoiding their exposure to water - however, our analysis did not show a statistically significant, radiation induced increase in their EPR signal.

Conclusion
It was concluded, that EPR dosimetry in nails irradiated *in vivo* using the applied experimental method was not reliable mainly due to (1) large scatter of EPR amplitudes in unirradiated nails even from the same individual, (2) fading of the radiation signals caused by subsequent washing of irradiated fingers/toes, (3) unpredictable (using the applied methodology) differences between samples in stability of their EPR signals. All these effects caused EPR signal variations within range of its magnitudes comparable to the amplitudes of signals induced by radiation at the examined range of doses.

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A comparative study of EPR and TL signals in Gorilla® glass samples for potential emergency dosimetry

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Introduction
Thermoluminescence (TL) and phototransferred TL (PTTL) properties of Gorilla® glass (GG) samples, obtained from several tens of modern smartphones, have been studied recently by Chandler et al. (2017). In the current study, we tested the same samples with electron paramagnetic resonance (EPR) in an effort to establish possible correlations between the EPR and TL (PTTL) properties.

Methods
99 different Gorilla® glass samples from 57 different smartphones and 3 different on-line vendors were used in the present study. TL measurements were carried out using a Risø DA-15 TL/OSL system. EPR tests were conducted on a Bruker EMX spectrometer equipped with a Bruker 4119 resonator. The samples were exposed to either beta particles from a 90*Sr*/90Y source or ultraviolet (UV) photons from a 3UVTM lamp. A matrix spectral deconvolution method was used for analysis of the EPR spectra.

Results
EPR spectra of both unirradiated samples and samples exposed to either beta particles or UV photons were recorded and analyzed. At least 6 different patterns of EPR signals were detected in the irradiated samples; the spectra were fitted using a combination of 5 reference EPR signals. Large inter-sample variability was observed for the EPR signals, and for the TL and PTTL signals, both in signal shapes and intensities. Strong background EPR signals were also observed in some samples and these were usually found to correlate with strong background TL/PTTL signals in the same samples. From analysis of the data the background signals (EPR and TL/PTTL) are proposed to be caused by UV exposure of the touchscreen glasses during the UV curing processes employed as part of phone manufacture.

Conclusion
Several different types of EPR spectra and TL curve shapes were observed from a variety of GG samples. Some general correlations between the recorded EPR spectra and the TL data were found. Samples with a large background (zero-dose) TL signal were also observed to have a large background (zero dose) EPR signal. UV exposure of the samples during manufacture are suggested to be the origin of the background signals. EPR may work better as a dosimetry method for some GG samples while TL and/or PTTL may provide more accurate dose estimations for others.

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An advance in EPR dosimetry technique with nails

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Introduction
Recently, a vacuum-stored dry nails dosimetry technique was proposed by Sholom and McKeever (2016). According to this technique, nails should avoid any contact with water and should be stored in vacuum for all times until EPR measurements, which may be difficult in practice. In the current work, an oil-stored version of the EPR dosimetry technique with nails is described.

Methods
The nails were collected from several volunteers during routine hygienic practices. Olive oil (specifically, extra virgin olive oil with a low percentage of water in its composition) was purchased from a grocery store. EPR measurements were conducted on a Bruker EMX spectrometer. The following effects were studied: (1) possible use of oil as a replacement of water for nails cleaning; (2) stability of different EPR signals in oil-stored nails; (3) the possible influence of oil on the EPR response of nails; and (4) the dose response and minimum detectable dose for oil-stored nails for dosimetry.

Results
Olive oil is an efficient agent to be used for nails cleaning because it helps to remove any dirt not affecting the radiation-induced signal. Olive oil is also a convenient medium for nails storage: the properties of radiation-induced, mechanically-induced and background signals in nails stored under oil were found to be quite similar to those obtained from samples stored in vacuum. No extra EPR signals were detected in samples stored in oil for long times (several days). The dose response was linear up to 10 Gy and minimum detectable doses were about 0.5 Gy. A protocol for the oil-stored dosimetry technique has been developed.

Conclusion
A new effective medium (olive oil) is proposed for both nails cleaning and storage for possible application in the emergency EPR dosimetry with nails. The corresponding dosimetry protocol has been proposed and tested on several samples irradiated *in vitro*.

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Criticality dosimetry based on alanine pellets: state of the art and new developments

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Introduction
Criticality accident dosimeters (CAD) are usually based on the activation of metallic foils to estimate the maximum neutron dose received by an individual. As an alternative to this time- and- labor consuming analysis, alanine dosimetry was implemented in the IRSN"s CAD and successfully tested during the last international exercise. A new design of alanine CAD is proposed to improve performances.

Methods
Alanine is sensitive to photons and neutrons and with proper calibration can be used in a mixed radiation field to determine neutron dose, when photon dose is given by a gamma sensitive dosimeter. In the IRSN"s CAD, photon dose is assessed with a RPL Glass dosimeter. Dosimeters were exposed during the international exercise of criticality dosimetry organized in 2016 in USA around a metallic core reactor (Godiva IV). Three irradiations of different intensities were performed with dosimeters placed at 5 distances. Analyses were then performed on site within 24 hours.

Results
Compared with the reference neutron dose alanine results remain within the acceptance dose criteria from the ANSI 13.3- 2013 standard for all 3 bursts. Future developments are foreseen to also measure the thermal neutron fluence with doped, high-Z material alanine pellets and various shielding. Having two types of alanine pellets with different sensitivity to neutrons of varying energy gives an opportunity to build a new type of criticality dosimeters based on the same dosimetric material (alanine) and readout method, e.g. EPR. In order to enhance the photon-neutron differentiation alanine application of two different filters is proposed. Design of the first multiple pellet alanine dosimeter will be presented. The results of the prototype testing will be discussed.

Conclusion
The results of the international comparison showed that alanine application for neutron dosimetry has a high level of performance for minimal effort and short analysis time. New developments are foreseen to provide enhanced capacity of measurements.

Disclaimer. The views expressed in this abstract are those of the authors and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, nor the U.S. Government.

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Retrospective ESR/EPR cattle tooth enamel doses given by the radioactive nuclei released by the accident of Fukushima Dai-ichi atomic power plants

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Introduction
ESR/EPR tooth enamel dosimetry with mammal teeth is one of the recent research topics after the one with human tooth is established. In the actual accidents, it is not easy to obtain human teeth, but there are much more chances to obtain mammal teeth. In this study, basic studies on the properties of the ESR signals were performed for cattle teeth in comparison with those of human permanent teeth.

Methods
In the occasion of evacuation just after the Fukushima accident, the cattle ranchers had to abandon the cattle, some of which were gathered in several ranches for scientific studies. Cattle teeth were obtained from the cattle in these ranches in the contaminated area. The enamel samples extracted from cattle teeth were irradiated by 60Co gamma rays up to 5 Gy. The dosimetric signals were obtained with an ESR spectrometer. The obtained spectra were processed with a computer program, New ER. From the initial signal intensities and the dose responses, retrospective doses were obtained.

Results
The signal shape of the dosimetric signal observed in cattle teeth are similar with those of human teeth so that the signal processing computer program works for these teeth. As the signal intensities increase linearly with given doses, ESR dosimetry is found to be possible with cattle teeth in the dose range several Gy. The dose for one tooth of a cattle of 12 years old is 1.2 Gy, being consistent with the calculated value considering the temporal change of the environmental doses. The dose for another tooth of one of 6 years old is 900 mGy while one is less than 100 mGy from the ranch with lower environmental dose.

Conclusion
The slopes of the dose responses, hence, the sensitivity were found to be quite uniform within a variation of 10 %, also being consistent with that of human molar teeth. ESR/EPR retrospective doses were for the first time successfully obtained with cattle teeth, which were given in the actual radiation accidents.

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Networking in biological and EPR dosimetry, QA&QM

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The standardization of physical and biological tools for a better evaluation of the dose in emergency situations and research projects

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In a radiological emergency, a retrospective evaluation of the dose using dedicated assays (dicentric chromosome, micronuclei (MN), gamma H2AX, Premature Condensed Chromosome (PCC), Electron Paramagnetic Resonance (EPR) and Optically Stimulated Luminescence (OSL) could be useful tools for determining the doses received by the victims.

The number of victims will depend on the scenario but in many cases the capacities of one lab might not be sufficient to cope with all the samples. The objective of the network in biodosimetry and EPR/OSL dosimetry is to increase the analysis capacities in order to achieve the needs of an emergency situation involving many victims. This means that the results of all the labs are of equal quality and can be pooled.

In addition, new biomarkers of dose and health risks are under study to reduce the time spend for dose evaluation, to assess the heterogeneity of the dose, to evaluate locally the dose or to increase the sensitivity. They can be used both in case of accidental situations but also to strengthen epidemiological studies. However, all biomarkers have different limitations and are not at the same level of validation.

Both to be able to pool results from different labs but also to validate some new biomarkers quality assurance/quality control (QA/QC) programs are required. Several approaches have been applied in the RENEB project and their benefit will be presented.

Inter-laboratory comparison (ILC) has allowed the detection of labs requiring training to improve their performance in terms of signal identification but also dose estimation. Even with well calibrated assays each ILC is the opportunity to learn more about the assay and the practices of each lab (Grégoire, 2017; Ainsbury, 2017). Such ILC have to be performed periodically and should cover different aspects. As an example, one of them was conducted to evaluate the dosimetric reference used for calibration of assays and has stressed some unexpected results (Trompier et al. 2017)

Trainings have been offered to improve staff performances and have resulted in the improvement of biological and physical dose estimation.

QA&QM manual on biological and physical dosimetry assays was produced which states a common basis and harmonized procedures for each assay. Some key parameters have been identified with an impact on the results. A questionnaire was established to evaluate the implementation of RENEB QA&QM manual within the different partners of the network

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Results of a global inter-laboratory comparison on the cytogenetic and genomic assays in the frame of the European Network of Biodosimetry - RENEB

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Introduction

In the frame of the RENEB network, great effort of harmonization has been performed to validate biological dosimetry assays in order to support emergency situation management. To use those assays also for research activities, the aim of this inter-laboratory comparison was the requirement of a precise dose assessment and the associated uncertainties.

Methods

For this global exercise, 36 laboratories (21 from the RENEB network) from 23 countries participated using different assays for dose assessment (dicentric chromosome, cytokinesis-block micronucleus, prematurely condensed chromosome, gamma-H2AX and gene expression) (Ref 1-5). Blood from healthy donors was irradiated *in vitro* at two doses (low and high). Coded samples (irradiated and

control) were sent to the participants. The task was to report the amount of signals analysed for each respective assay, to assess precise radiation doses with reference to an appropriate calibration curve.

Results

The results of the inter-comparison for the dicentric assay specifically will be presented and discussed. A high number of cells (500 cells) per dose point was analysed and used for precise dose assessment. Some differences in confidence interval calculations have been observed between participants. Reasons for differences between labs will be evaluated. In addition, the benefit of common vs individual dose-response curves for precise dose assessment will be discussed. Statistical analysis will be conducted to confirm if each laboratory is capable of assessing radiation dose accurately and correctely in the case of a radiation accident.

Conclusion

The identification of further requirements to improve the performance of the participating labs will help to optimise international networking in the field of biological dosimetry. Harmonisation of confidence interval calculations is required since the most important result is not the mean assessed dose but whether the confidence interval of the dose assessment includes the delivered dose. Therefore, intercomparisons are imperative to ensure maintenance of readiness and efficiency of the RENEB network members to respond to a large scale radiation accident or incident.

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RENEB - network contribution to emergency preparedness and response

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Introduction
Large scale radiological emergencies pose a particular problem for emergency preparedness because exposed people have to be identified as quickly as possible. The primary aim is speed of performance and not precision of dose estimate. Therefore, triage dosimetry should permit a correct categorisation of a victim into a low (below 1 Gy), intermediate (1-2 Gy) or high (above 2 Gy) dose category.

Methods
The European Commission has been financially supporting research and coordination activities with the aim of building an EU-wide dosimetry network that would guarantee fast individual dosimetry in a large emergency event. Specialised laboratories have joined forces and performed a number of intercomparisons and exercises with focus on different key aspects, which are essential to successfully handle large scale scenarios. A short overview of the network activities will be given to test the current capability and capacity of the network and to identify need for improvement.

Results
Individual retrospective dosimetry, an indispensable element to help to classify people according to the absorbed dose, is possible also in large scale emergencies by involving a well-trained network of laboratories. Today RENEB is established with a battery of validated assays and experience from several intercomparisons. The network can handle up to 1000 - 4000 cases per week, depending on the scenario, shipment of samples works fine within the EU. Doses can be estimated in tissue samples and in portable electronic devices. Each assay has advantages with respect to sensitivity, speed of analysis and signal stability and a complementary approach is possible, depending on particular needs of an emergency. Various Stakeholders are informed about the network capabilities and capacities.

Conclusion
The EU network RENEB is operational and ready to carry out retrospective dosimetry in a large-scale radiological emergency. Regular intercomparisons will be continued to maintain efficiency both with respect to speed of analysis, precision of dose estimate and logistics of sample and data handling. Stakeholders have to be informed about the network capabilities and capacities and should be included in further activities. The possibility to contribute as analysis platform to research projects has to be followed and investigated to enable activities beyond emergency preparedness.

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All authors signed the articles of RENEB e.V. Special thanks is given to MoU partners.

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A network of networks in biodosimetry – partnerships between EURADOS Retrospective Dosimetry WG10 and RENEB

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Introduction
The European Radiation Dosimetry Group, EURADOS, promotes cooperation in research and development for ionising radiation dosimetry (https://eurados.org). WG10 focuses on retrospective dosimetry. RENEB is a network of laboratories and institutions for individual retrospective dosimetry emergency radiation response (www.reneb.net). The complementarity of the networks will be discussed.

Methods
Under the RENEB project, partners validated and implemented methods, including quality assurance processes, for operational biological and physical retrospective dosimetric assays. Within the resulting network, RENEB laboratories maintain readiness, integrated in emergency preparedness and response.
The aims of EURADOS WG10 include: to establish a multi-parameter approach to dose assessment; to disseminate knowledge to stakeholders; to evaluate newly developed methods; to improve uncertainty estimation, and to elaborate an approach for dosimetry after partial body or internal exposure.

Results
Maintenance of expertise and capacity for emergency response requires regular validation of current techniques, and also scientific development to ensure that the most up to date techniques can be validated for emergency preparedness. Networking between networks is thus required! Intercomparisons are a key part of this. Members from RENEB and EURADOS WG10 have collaborated on a number of these to both validate existing techniques and laboratories (a necessity for RENEB) and identify areas in which further development is needed (a theme for both networks).

Furthermore, scientific development will involve partners from both networks – for example new developments in uncertainty assessment techniques could improve operational dosimetry capabilities of RENEB partners.

Conclusion
While there is clear overlap between the aims of RENEB and EURADOS WG10, and indeed many RENEB members are members of EURADOS WG10 and vice versa, there are also distinct motivations which mean that these two networks are highly complementary. The justification and benefits of mutual collaboration will be presented.

The partnership will continue to be developed going forward, with perspectives for future activities including collaboration with wider networks such as the WHO BioDoseNet (http://www.who.int/ionizing_radiation/a_e/biodosenet/en/).

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All authors contributed equally. With thanks to RENEB and EURADOS WG10 partners.

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Proposal for a European Metrology Network for Metrology Support to Radiobiology and Biological Dosimetry

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Introduction
The progress made in radiation metrology during the project BioQuaRT [1] by elucidating the link between particle track structure and biological effects [2] raised the question to what extent radiobiological investigations would benefit from the development of a metrological support of the applied methodologies.

Methods
A panel consisting of 18 experts from the medical field, fundamental research and radiation protection was invited to a workshop held at PTB to give advice on metrology needs in different areas related to biological radiation effects. Conclusions drawn were submitted and have been presented at several international conferences (NeuDos2017, Micros2017, 1st ESTRO Physics Workshop) for further discussion with the scientific community.

Results
The expert panel identified a number of metrological needs including the further development of experimental and computational techniques for micro- and nanodosimetry together with the determination of related fundamental material properties and the establishment of rigorous uncertainty budgets. In addition to this, a strong call for developing a metrology support assisting quality assurance of radiobiology experiments has been expressed. Concrete suggestions included the development of standard cell systems or the establishment of reference irradiation facilities that ideally also should be suited for animal experiments. The input from the expert panel has been used for defining the strategic direction of one of the five departments within the ionizing radiation division of PTB.

Conclusion
A first example of the benefits of metrological approaches to the quantification of DNA double strand break yields has been presented at the 17th Microdosimetry Symposium [3]. Further discussions with stakeholder groups and within the metrology community has led to the idea of proposing the exploration of a European Metrology Network on metrology in radiobiology for funding within the 2018 call of the European Metrology Programme for Innovation and Research (EMPIR).

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Concepts of Operations for a U.S. Biodosimetry Network

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Introduction
A U.S. Biodosimetry Network (USBN) based on the integration of several biodosimetry approaches is envisioned to meet the biodosimetry needs of mass casualty incidents. The goal of the USBN is to maximize currently available resources and to provide an integrated biodosimetry capability, using several diverse techniques that are currently available.

Methods
For establishing a multiple-parameter diagnostics approach, a number of currently available techniques including dicentric chromosome assay, electron paramagnetic resonance (EPR), whole body counting radioimmunoassay are being considered. The capabilities of the USBN are intended to complement evolving U.S. federal capabilities to estimate point-of-care triage dose (i.e., <2 Gy, >2 Gy) and total-body dose assessment at 0-7 days after exposure that are based on molecular endpoints.

Results
Initial goals are to expand a co-operative program to support annual laboratory inter-comparison exercises and to obtain certification to manage clinical samples for laboratories not currently certified to do so. In addition to assessment of whole body absorbed dose, the USBN will define and verify criteria for identifying partial-body exposures. Additional capabilities include dose assessment via whole-body counting, electron paramagnetic resonance (EPR) dosimetry using finger- and toe-nail clippings, and cytogenetic-based biodosimetry techniques such as the premature chromosome condensation assay. Examples will be presented of actual cases referred to REAC/TS and the NDC that illustrate the use of multiple biodosimetry approaches.

Conclusion
The USBN is designed to provide integrated diagnostic capabilities that are not currently available with sufficient capacity elsewhere. It will be available in mass-casualty incidents to generate estimates of biodose. The USBN will seek to establish cooperative linkages with international partner laboratories, networks, and agencies (Blakely et al. 2009). This multiple parameter diagnostic approach will be useful for precisely estimating the absorbed radiation dose and for devising effective medical countermeasures.

References
The views expressed in this abstract are those of the authors and do not necessarily reflect the official policy or position of the DOE, DON[BWFCA1] , AFRRI, USUHS, NDC, DOD or the U.S. Government. Funding support has been provided by DOE, ORAU, and AFRRI (RBB43523, RBB44313).

Biological and EPR dosimetry for medicine I

OP - 49

Contribution of biodosimetry for different medical issues

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Biodosimetry is a well-established field in science and essential for many different areas such as dose reconstruction after an accidental exposure. However, depending on the medical issue the contribution of biodosimetry might differ. In this presentation we will discuss about the contribution of biodosimetry regarding three medical subjects such as (1) diagnosis of acute effects after ionizing radiation (Acute Radiation Syndrome), (2) impact in the field of conventional and molecular epidemiology, (3) occupational medicine.

OP - 50

The effects of chronic inflammation on chromosomal aberrations and DNA damage after 1.0 Gy X-ray irradiation in type 2 diabetes mouse model

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Introduction
Inflammation contributes to increased radiation damage, as seen from combined injuries [1] and cancer patients with diabetes receiving radiotherapy [2]. Accurate dose estimation using cytogenetic biodosimetry, such as DCA and CBMN assay, is essential for effective medical treatment after a radiation accident. However, its reliability may be affected by the presence of chronic inflammation.

Methods
8 week old male B6.Cg-Lep^{ob}/J (ob/ob) and C57BL/6J (B6J) mice were irradiated with 1.0 Gy X-ray at 1.0 Gy/min and sacrificed 24 hours after exposure. Blood was collected via cardiac puncture for blood glucose measurement and blood count. DCA and CBMN assay were conducted on primary spleen cell culture and γH2AX/53BP1 double foci were identified on bone marrow cells. Histology was performed on 3 to 5 μm sections of H&E stained paraffin-embedded ileum. Villi morphology was examined at 200x magnification and villi length was measured using Fiji (is Just ImageJ) on 100x magnified images.

Results
Blood glucose concentration significantly increased ($p < 0.05$) in both mice strains after irradiation. Leukocyte cell count also significantly decreased, caused by both irradiation ($p < 0.001$) and presence of chronic inflammation ($p < 0.001$). With regards to chromosomal aberrations and DNA damage, approximately 1.8 times more Dic/cell ($p < 0.001$), 2.3 times more MN/BN cell ($p < 0.001$) and 3.2 times more γH2AX/53BP1 double foci ($p < 0.001$) were observed in ob/ob than B6J mice after 1.0 Gy irradiation. No significant differences in villi morphology were seen and villi length was unaffected in both mice strains 24 hours after 1.0 Gy X-ray irradiation.

Conclusion
The presence of chronic inflammation seemed to play a role in increasing the amount of chromosomal aberrations and DNA damage after irradiation, which can affect dose estimation and radiation injuries. Blood glucose concentration could also be an indicator of inflammation due to its increase after irradiation. 24 hours after 1.0 Gy X-ray irradiation was not enough to induce visible changes in ileum villi morphology and length. Various inflammatory markers, higher dose exposure and longer recovery period will be analysed in the future to better understand the mechanism behind this phenomenon.

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OP - 51

Application of biodosimetry techniques to determine the biological effects of heavy ions in human lymphocytes

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Introduction
The development of cellular and molecular biomarkers is an important goal in cancer research. A study involving multiple end points following irradiation was initiated in our laboratory using human blood lymphocytes from three healthy donors.

Methods
Human cells were irradiated with different doses (0.10 to 1.0 Gy) of Carbon (290MeV/u, LET 70 keV/micron) ions at National Institute of Radiological Sciences, Chiba, Japan. Gene expression profiles using microarray analysis were generated from blood lymphocytes irradiated at G0 state to identify signature genes of exposure to heavy ion radiations. Chromosome alterations induced were detected by using fluorescence in situ hybridisation (FISH) using telomere/centromere specific probe as well as by multi-colour FISH.

Results
A dose dependent increase in the extent of DNA damage and double strand breaks formation was observed in the study. Cytogenetic analysis revealed a dose-dependent increase in the percentage chromosome aberrations such as dicentrics and translocations. In this study, it appears that carbon ions produced greater and complex chromosome aberrations compared to gamma rays. Microarray analysis revealed that low doses of carbon ion irradiation induced differential gene expression.

Conclusion
Collectively, our results indicate that irradiation with low doses of carbon ions induces varied molecular and cellular changes including chromosomal aberrations. Gene expression profiles are very distinct from those of gamma radiation exposure. The results obtained in this study would, hopefully, provide us with functional relevance of early biomarkers of exposure as well as in the manifestation of heavy ion therapy. It is anticipated that such biodosimetric techniques could be of clinical significance in treatment planning.

References
NONE

OP - 52

Biological effects in non-target tissues observed in nuclear medicine patients undergoing radium-223 chloride (223RaCl2) therapy

Antonella Federica Testa[1], Clarice Patrono[1], Maria Balduzzi[1], Valentina Dini[2], Valentina Palma[1], Rosa Sciuto[3], Antonella Soriani[3], Lidia Strigari[3], Raffaella Marconi[3], Maria Antonella Tabocchini[2]
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Introduction
The use of Alpha emitters in nuclear medicine is increasing even if the delivery of the α-particle energy to the cancer cells without toxicity to healthy tissues is still challenging. This study aims at correlating the effective dose to non-target tissues to the radiation-induced chromosome damage in blood lymphocytes of prostate cancer patients with bone metastasis treated with 223RaCl2 (1).

Methods
Four patients undergoing 223RaCl2 therapy for skeletal diseases have been enrolled in this prospective trial. The effective dose to non-target tissues per injected activity was calculated considering the alpha, beta and gamma emission of Ra-223 and considering a standard man weight of 70 Kg. Blood collection and peripheral blood lymphocytes cultures for dicentric assay were performed before treatment (T0), 6 days (T1) and 30 days (T2) after the first cycle of treatment and after the end of the therapy (T3=180 days). Haematological toxicity parameters have been monitored during therapy.

Results
The administration of 223RaCl2 produces a high dose dependent increase of chromosome damage in peripheral blood lymphocytes (non-target tissue) both in terms of dicentric yield and damage complexity. The dicentric distribution showed a progressive increase of complex damage which accumulates during the therapy reaching the highest value after the completion of the treatment (T3). Surprisingly, the increase of chromosome damage observed between T1 and T2 is not due to an 223RaCl2 addition dose, suggesting that circulating lymphocytes were exposed to an extra dose by the emissions from the target organs. In addition, clinical monitoring during the treatment showed a progressive increasing fatigue, leucopenia and anemia with a partial recovery after some months after the end of therapy.

Conclusion
The cytogenetic data suggest a persistence of the radiation emission from the target organs to non-target ones and seem to be correlated to the observed haematological toxicity, highlighting possible adverse effects related to this type of therapy. Moreover, our preliminary results suggest that the observed chromosome damage could reflect the delivered dose to the circulating lymphocytes (non-target organ) after repeated treatments. These data need further investigation in order to evaluate the potential side effects to normal, non-target tissue in patients treated with alpha emitters.

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OP - 53

Automated scoring of dicentric chromosomes to investigate age dependent radiosensitivity after Computer Tomography (CT)

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Introduction
The dicentric chromosome assay is currently the most specific method to detect radiation induced DNA damage. In the last years, technical advances provided the opportunity to increase the number of scored cells necessary to obtain reliable results in the low dose range (< 100 mSv). Here, the method was applied to study the age-dependentradiosensitivity after CT scan exposure

Methods
Blood samples taken from healthy individuals representing three different age groups [new-born, young children (2 – 5 y.) and adults (> 18 y.)] were exposed *in vitro* to 41 mGy and 978 mGy X–rays in a CT scanning unit. Chromosomal aberrations were at first manually analysed with 2000 – 2400 cells/dose point/age group. In a second step automated scoring based on a considerable higher number of scored cells (13 000 – 23 000 cells/dose point/age group), was performed.Results for the low dose point (41 mGy) were validated by increasing the manual analyses to 26 000 cells /dose point/age group

Results
For the high dose point of 978 mGy a small number of manually analysed cells (2000 – 2400) was sufficient to reveal a clear age dependent radiation effect. This effect was not observed for the low dose point of 41 mGy, due to insufficient statistical power. With the assistance of an automated analysing system the number of cells was increased by a factor ten. Compared to controls, a significant elevation of dicentric chromosomes was now shown at 41 mGy for the age groups. Moreover, differences between the age groups could now be resolved also for the low dose, revealing a significant increased risk to obtain dicentrics for young donors compared to adults (=3.04, P=0.0041, 95% CI: 1.46-6.76) also at 41 mGy

Conclusion
The results demonstrate very clearly the usefulness of the automated dicentric scoring method for the detection of age-dependent radiosensitivity at low dose level after CT exposure. The study shows clearly that increasing the number of cells for chromosomal aberration analysis enables research at low dose range and assists in differentiating radiation sensitive human groups. Furthermore, the reduction of the extensive workload becomes obvious

References
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OP - 54

A NEW METHODOLOGY FOR DIAGNOSIS OF FANCONI ANEMIA ISSUED FROM BIOLOGICAL DOSIMETRY.

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Introduction
Fanconi anemia (FA) is a syndrome associated to chromosomal fragility. Laboratory tests for this disease diagnosis are based on the scoring of chromosomal aberrations induced in peripheral blood lymphocytes by chemical agents, namely: diepoxybutane (DEB) and mitomycin C (MMC). This research evaluated a new methodology of analyses which replaces these clastogenic agents with gamma radiation.

Methods
Two groups were studied: one of normal subjects and another group of DEB-positive patients (FA). From each volunteer, a sample of peripheral blood was collected and separated into two aliquots: one was kept as control (non-irradiated), while the second one was irradiated and analyzed based on a patented methodology for scoring unstable chromosomal aberrations in lymphocyte (Deposit No. BR10 2013 0256684). Concerning each aliquot, after lymphocyte cultures, and slide preparation, 200 metaphases were scored using the IAEA criteria for biological dosimetry.

Results
Statistical analyses indicated that is possible to differentiate the normal group from the one formed by Fanconi-positive patients (FA), at a significance level of 5%, after irradiation of the samples. The methodology employed in this research emphasized, for each group, a pattern of distribution of frequencies of dicentrics, fragments, chromosomal breaks and failures. Moreover, only the samples from FA patients presented radial figures.

Conclusion
The current laboratory tests to diagnose diseases associated to chromosomal fragility commonly employ toxic chemical agents, which are potential carcinogens, and precautions should be taken when handling these compounds. The methodology proposed in this work uses standard safety procedures for sample irradiation, followed by well-known cell culture protocols for metaphase analyses of lymphocytes. This work, which is essentially based on the biological dosimetry knowledge, paves the way to an alternative, safe and affordable methodology of laboratory test for Fanconi anemia diagnosis.

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OP - 55

Clinical Applications of Biomarkers of Radiation Exposure: Limitations and Possible Solutions through Coordinated Research

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Introduction
The recent activity of the International Atomic Energy Agency aimed at strengthening the biodosimetry in the IAEA Member States (the IAEA Coordinated Research Project E35008, 2012-2017) inspired the search for new potential applications of dosimetric biomarkers beyond the areas of radiation medicine and radiation protection at emergencies.

Methods
Particularly, it was recognized that radiation cytogenetics laboratories can contribute substantially with their research and service to general medical practice where patients are exposed to radiation for diagnostic or treatment purposes. The group of international experts, coordinated by the IAEA, conducted an extensive review and discussion of available data on the possibilities and limitations of the use of dosimetric biomarkers in radiotherapy, diagnostic and interventional radiology and nuclear medicine.

Results
An IAEA Technical Report is being prepared for publication, that describes main patterns of in vivo induction of radiation biomarkers in clinical exposure scenarios and summarizes data on the application of these markers measured in vivo or after ex vivo irradiation for various practical tasks. The clinical usage of radiation biomarkers can be classified as follows: - Biodosimetry dose reconstruction in patients after the first radiotherapy (RT) fraction; - Measurements of biomarkers in RT and diagnostic radiology patients during the course of their procedures in trying to generate in vivo empirical dose response curves; - Comparison of the in vivo genotoxicity of various schemes of external radiotherapy, internally administered radionuclides and radiological diagnostic procedures; - Post-RT follow-up for retrospective dosimetry and evaluation of RT-related cancer risk; - Biodosimetry of accidental overexposures in radiological practice; - Testing and validation of new biomarkers of radiation exposure;

Conclusion
- Studies involving ex vivo irradiation of patients' cells to identify possible correlations between the induction of biomarkers as a measure of individual radiosensitivity and normal tissue radiation toxicity; - In vitro assessment of the potential genotoxicity and cytotoxicity of therapeutic beams of different quality, therapeutic and diagnostic radionuclides and modulations of diagnostic procedures (contrast media, technical regimens of exposure) in normal cells; - Predictions of tumor response in vitro to therapeutic irradiation alone or in combination with various modulators (radiochemotherapy or other combined RT modalities).

References

A number of problems, gaps in knowledge and limitations in the methodology for each of the aforementioned applications were identified. This work provided a conceptual background for the initiation of a new IAEA project (2017 – 2021), which is aimed specifically at the development and improvement of applications of biodosimetric markers in clinical practice.

Biological and EPR dosimetry for medicine II

OP - 56

Dosimetry with alanine/ESR in magnetic fields

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Introduction
The combination of photon irradiations and magnetic resonance (MR) imaging in hybrid devices called MR Linacs is emerging in radiotherapy (RT). The magnetic field in an MR Linac cannot be switched off easily; thus, dosimetry in MR-guided RT has to take place in the presence of the magnetic field. The standard dosimeter in clinical RT is the ionization chamber (IC). However, the responses of ICs

Methods
in magnetic fields have shown deviations of up to 11% [1], mainly due to the curved trajectories of secondary electrons. The application of ICs in MR-guided RT involves correction factors compensating for that. The experimental determination of these correction factors with a small uncertainty requires a well-defined secondary standard. We investigate the suitability of alanine/ESR as such a secondary standard. To this end, we examine the response of alanine for photon irradiations in magnetic fields.

We used pellets of pressed crystalline alanine (diameter 4.9 mm, height 2.6 mm)

Results
as detectors. Ionizing radiation creates free radicals in the alanine. Their concentration is proportional to the deposited dose and can be measured via ESR spectrometry [2]. We performed five photon irradiations (6 MV, (5x10) cm² field, 18 Gy) of alanine, each one at a different magnetic flux density – namely at (0.3, 0.6, 0.9, 1.2, 1.4) T. In order to do so, we positioned our electromagnet, with a water phantom between its pole shoes, in front of our clinical linear accelerator. The alanine pellets were positioned in the phantom (10 cm depth) using a PMMA holder which also prevented direct contact between the pellets and water. The alanine pellets were read out in our ESR spectrometer following the irradiation.

We found deviations in the response of alanine in magnetic fields that were

Conclusion
smaller than 0.6%. Our results are preliminary and have not yet been corrected for the shift of the depth dose curves in the magnetic fields or for the impact of the stray magnetic field on the transmission chamber. We expect that considering these effects will diminish the deviations even further.

The findings presented indicate that dosimetry with alanine/ESR is scarcely influenced by static magnetic fields. This makes alanine/ESR a promising candidate for the experimental determination of the correction factors needed in order to perform reliable measurements using ICs in magnetic fields.

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OP - 57

The effect of a strong magnetic field in alanine dosimetry

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Introduction
With the advent of MRI-guided radiotherapy, the suitability of radiation dose detectors needs to be addressed. Recent works have shown that the uncertainty of ion chamber based dosimetry is increased by the presence of strong magnetic fields [1-3]. This work investigated the effect of the magnetic field on alanine dosimeters and assessed its suitability to act as a reference detector.

Methods
Alanine pellets were placed in an electromagnet and irradiated using ^{60}Co and by a conventional 8 MV linac beam at five magnetic strengths (0–2T). In ^{60}Co the dosimeters were irradiated in a PMMA phantom, and in the linac beam in a water tank. The effect of the magnetic field (B-field) on the alanine/EPR signal was determined through measurements, while the effect of the B-field on dose to water, D_w, was calculated for both energies using MC simulations. The B-field correction factor of alanine, $k_{B,Alanine}$, was obtained as the ratio between calibration coefficients with and without B-field.

Results
The percentage change of D_w per T was found to be -0.04% and -0.35% for ^{60}Co and 8 MV, respectively. It was also found that there is a weak dependence of the alanine signal on B-field strength, which is of the order of -0.4% and -0.02% per T, for ^{60}Co and 8 MV respectively, with a standard uncertainty of 0.2%. The $k_{B,Alanine}$, after allowing for the effect of B-field on D_w, at 1.5 T was found to be 0.994 and 0.997 for ^{60}Co and 8 MV, respectively, with a standard uncertainty of 0.2%. The small quality-dependence of the magnetic field correction is within the measurement uncertainty ($k=1$).

Conclusion
The strong magnetic field in an MRI-linac has a measurable but small effect (0.5% at 1.5 T) on the sensitivity of alanine in terms of absorbed dose to water. Independent determinations of the magnetic field correction factor, $k_{B,Alanine}$, were made at different B-fields for two beam qualities, and was found to be in a range of 0.1% to 0.6%. We conclude that alanine is a suitable dosimeter for reference dosimetry in MRI-linacs and for the transfer of absorbed dose standards from zero magnetic field conditions to MRI-linacs.

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OP - 58

EPR/alanine dosimetry for verification in Helical Tomotherapy Stereotactic Radiosurgery (HT SRS) treatments

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Introduction
Intracranial stereotactic radiosurgery (SRS) is a technique to deliver an ablative radiation dose with an extremely sharp dose gradient to small brain tumors.
In this study the accuracy of the dose delivered in SRS by a non conventional radiotherapy machine, the TomoTherapy Hi-Art System, was investigated using an "end-to-end" test using alanine pellets and gafchromic films.

Methods
Dose verifications were made using alanine dosimeters placed in an antropomorphic head phantom (Alderson Rando Phantom) under different treatment conditions in case of both single and multiple brain tumors. 1.25mm slice kVCT scan of the phantom was used to generate SRS plans on the TomoTherapy Planning Station platform. Commercial alanine dosimeters (Synergy Health, Germany) were irradiated in various positions of the phantom. EPR measurements were carried out through Bruker spectrometer at room temperature.

Results
The dose values for 6 different possible clinical scenarios characterized by the presence of one, two or three tumor lesions were reconstructed by means of alanine dosimeters and gafchromic films. The dose values measured through both experimental techniques show a good agreement with the dose values calculated by the TomoTherapy Treatment Planning System, for both tumors and organs at risk (such as optical chiasma and brain stem).

Conclusion
Alanine absolute dose measurements showed to be useful for the dosimetric validation of HT SRS treatments.

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OP - 59

Clinical Applications using in vivo EPR, adapted from Advancements in in vivo EPR Dosimetry

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Introduction
Dartmouth has developed the technical and practical capacity to successfully perform in vivo EPR Tooth Dosimetry for quickly and accurately assessing exposure to clinically significant levels of ionizing radiation under emergency conditions following a large-scale radiation disaster. These developments have been adapted to facilitate the clinical applications of EPR such as for oximetry.

Methods
Developments of the EPR instrument needed for emergency use included making the instrument capable of being transported easily, requiring minimal facilities, and operable with minimal training and expertise. These features have been adapted for in vivo EPR oximetry so that measurements of patients can be feasibly incorporated into their usual care such as during a course of radiation therapy for cancer, with the goal of improving treatment outcomes by identifying hypoxia and responsiveness to hyperoxic treatments via immediate feedback to clinicians of oxygen levels in the tumor itself

Results
In vivo EPR oximetry requires an initial implantation of an oxygen sensor into the tumor. Thereafter, measurements can be made repeatedly to monitor the oxygen during the several weeks of treatment. To date, about 40 patients with relatively superficial tumors, e.g., cutaneous tumors or head and neck cancer, have been measured at Dartmouth or Emory medical centers. Changes in the baseline level of oxygen over time as well as changes in tissue responsiveness to breathing 100% oxygen delivered through a nonrebreather mask has been assessed. In addition, further instrumental adaptations have been made, such as adapting the RF resonator to produce an acceptable SNR when operating in lossy conditions e.g., on the tongue or ulcerating tumors and with motion e.g., breathing.

Conclusion
These initial adaptations are very promising for providing an instrument that can be easily operated by technicians already involved in usual clinical care, such as radiation therapy for cancer, with information that can be instantly available for clinical decisions. Other clinical uses of oximetry such as in wound healing and colonoscopy will benefit from adaptions made to the dosimetry instrument to become more rugged and transportable. Moreover, having multiple uses of EPR both clinically and in emergency settings significant increase the value of EPR instrument.

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POSTER PRESENTATIONS, Session 1: PP-1 – PP-35

POSTER PRESENTATIONS, Session 2: PP-36 – PP-81

Biomarker

PP - 1

Intercomparison in cytogenetic dosimetry among 49 laboratories in China

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As Medical Emergency Response Centre for Nuclear Accident, we organized the nation intercomparion every year. Totally 49 laboratories participated the cytogenetic dosimetry intercomparison in 2017, We sent out two blood samples after exposure. Slides for chromosomal aberrations were prepared by the participant labs respectively, some labs made the slides in their own lab, some labs which located far from Beijing made the slides in NIRP"s lab. After onemonth participant"s lab submit their own results. For estimates of dose, each laboratory scored the frequency of dicentrics in metaphases. The whole bloods were irradiated with 60Co g-rays (1.7, 2.2Gy, 2.9Gy and 3.6Gy), Each laboratory got one group of the samples. 29 of the 98 estimates of dose fell within ±5% of the true physical dose, 31 fell within ±5~10%, 18 fell within ±10~15%, 9 fell within ±15~20%, only 11 fell >20%. The evaluation of the respective gamma dose was achieved by 42 laboratories.

PP - 2

Predicting exposure to ionizing radiation by biochemically-inspired genomic machine learning

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Introduction
Analyzing gene expression in peripheral blood mononuclear cells reveals profiles that predict radiation exposure in humans and mice by probit regression[1,2]. Using biochemically-inspired methods3, we derive gene signatures to predict the level of radiation exposure in blood samples.

Methods
GEO GSE6874[1] and GSE10640[2] were preprocessed via nearest neighbor imputation and quantile normalization. The expression of genes responsive to radiation exposure and differentially expressed orthologs from species resilient to radiation exposure (n=998) were ranked by Minimum Redundancy Maximum Relevance[3,4]. Optimal gene signatures were derived by backward, complete, and forward sequential feature selection using Support Vector Machines (SVM), and then tested or validated using leave-one-out cross validation or k-fold validation on independent datasets.

Results
The best human signature trained on GSE6874GPL4782 (n=78) included the top 61 mRMR ranked genes. The corresponding SVM distinguished irradiated from unirradiated individuals in GSE10640GPL6522 (n=85) with 80% sensitivity and 88% specificity. The murine signature with the lowest misclassification rate trained on GSE10640GPL4783 (n=103) consisted of the Phlda3, Bax, Cdkn1a, Cct3, Tfam, Pold1, Cd72, Cd79b, Ei24, Galt, Eif2ak4, Ms4a1, Ccng1, Glipr2, Gga2, Sh3bp5, Hexb, Gcdh, Pou2af1, Swap70, Apex1, Ptpn1, Mdm2, Tpst1, Ly6e, Sdcbp, Lcn2, and Suclg2 genes (89% sensitivity and 97% specificity).

Conclusion
In conclusion, we present strictly validated gene signatures with low error rates, improved generalizability, and improved granularity for dose estimation. These models suggest the feasibility of accurate quantification of radiation exposures by molecular diagnostics[5].

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PP - 3

mFISH visualizing chromosomal abnormalities in mesenchymal stem cells induced by low-dose X-ray radiation

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Introduction
Human mesenchymal stromal cells (hMSC) have great potentialities for clinical use in cell therapy. But the safety of MSC because of genetic and oncogenic transformation of the cells is under discussion, as that they acquire genomic changes ex vivo. Visualization equipment can delivered low doses to patients and cells [1], so, long-term cytogenetic control of irradiated cells is necessary [2].

Methods
Study was carried out in the long-term culture MSC from human gum. Cultivation was performed under the standard conditions of CO2-incubator (37°C, 5% CO2, saturated humidity). hMSC cells were exposed to the 100 kV X-rays at the dose rate of 40 mGy/min (0.8 mA, 1.5 mm A1 filter) using RUB RUST-M1 X-irradiator (Russia). The cells were irradiated from the start of the cultivation in 0(control), 80, 250 and 1000 mGy doses. The level of spontaneous and inducedrandom chromosome aberrations was estimated using mFISH: at the 1st and the 10th passages before exposure and post-irradiation.

Results
Immunophenotype was consistent with the MSCs and didn"t change. At the passages 1 and 10 of the control, the level of chromosomal aberrations was 7.5 and 10%, respectively. And after exposure: 80mGy - 20.75 and 5%, 250mGy - 11.4 and 6%, 1000mGy - 12.5 and 8.8%. Combined translocations, dicentric chromosomes, insertionswere detected. A significant increase of the chromosomal aberrations, compared to control, was at passage 1, after 80 mGy only. By passage 10, the level of chromosome aberrations didn"t differ from the control. A clone with tetrasomy 8 (48XY,+8,+8) was identified at passages 10: control - 15%, 80mGy - 22%, 250mGy - 13%, 1000mGy - 23.5%, and wasn"t found at passage 1. But the frequency of additional random chromosomal abnormalities increases in irradiated cells.

Conclusion
Our results indicate that although excess cells with chromosome aberrations were present at passage 1 post-irradiation with 80 mGy, the progeny of the irradiated cells did not display differ from control. Although, the clonal aneuploid cells were found both in control and post-irradiation, irradiated clonal cells have additional chromosomal abnormalities. Possible aneugenic effects, caused by low-dose irradiation did not get much attention, despite the growing interest for the relation between aneuploidy and carcinogenesis [3], it will be investigated in this ongoing study.

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PP - 4

Effect of acute whole-body gamma irradiation on circulating microparticles levels in rats

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Introduction
Damage to cellular membrane and disruption of the cytoskeleton is a well recognized complication of the irradiation. The disorganization of the cytoskeleton leads to form membrane blebs, which is called microparticles (MP). Our objective was to determine the gamma-irradiation effect on the circulating MP as biomarker of cellular membrane damage in blood of rats.

Methods
The Wistar rats were divided into six groups: a control group and 5 groups of rats receiving a different dose of irradiation (0.5, 1, 2, 4 and 8 Gy) for different times (24h, 72h and 1 week). MP in blood of rats were counted by flow cytometer after 24h, 72 h and one week post-irradiation.

Results
Quantified MP showed that there was increased in MP count in irradiated rats compared to control group, ($p<0.05$) at all the time points and in a non-dose dependant manner, Whereas at one week post-irradiation the increase in MP levels is clearly less pronounced with lethal dose (8 Gy, $p=0.09$). After one day of irradiation, the levels of MP in rats irradiated with 4-8 Gy was significantly lower than those in rats irradiated with doses of 1-2 Gy, without reaching their values in controls. However, we observed a significant decrease in the number of MP (72h and one week) post irradiation at all doses except for 0.05 Gy compared to those found 24h after irradiation. It seem that there a partial restoration in MP levels with time elapsed from the exposure to gamma irradiation

Conclusion
The number of MP in rats exposed to whole-body gamma irradiation was increased in a dose-dependent manner and it partly recovered during the 72h interval after irradiation. We suggest that MP count may be an early indicator of the membrane damage induced by ionizing radiation.

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PP - 5

Biomarkers and Multiparametric Biodosimetry after Exposure to Mixed-Field (Neutron and Gamma) vs Pure Gamma in Mouse Total-body Irradiation Model

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Introduction

There is a current need for quality-specific radiation biodosimetry that might be applied on hand-held, field-deployable, point-of-care, biodosimetry device to accurately determine exposure levels and acute radiation sickness prognostic factors where mixed neutrons and γ-rays are a threat for mass-casualties and also essential for optimal use of scarce therapeutic resources.

Methods

Biomarkers and multiparametric biodosimetry were evaluated in mouse total-body irradiation (TBI) model following mixed-field (MF, neutrons and γ-rays) or pure γ-ray exposure. TBI of mice were carried out in the AFRRI Training, Research, Isotope, General Atomic Mark-F nuclear research reactor and 60Co pure γ-rays facilities over a broad dose range (1.5 - 12 Gy), dose rates of 0.6 and 1.9 Gy/min, and different proportions of neutrons/gammas in MF studies from 1 to 7 days after TBI. Protein biomarkers were measured using a Meso Scale Diagnostics" MULTI-ARRAY platform.

Results

Ratios of biomarkers in groups exposed to the matched radiation doses MF or pure g-rays ranged from 1.5 to 2.7, reflecting that neutron-inclusive radiation injury induced by MF is significantly severe than one induced by pure gamma radiation. Mean differences in radiation dose prediction regression slope coefficients in MF vs pure gamma studies for selected radiation-specific biomarkers ranged from 1.7 to 2.6. Biodosimetry results are consistent with a radiation dose detection threshold of ~1 Gy and ~0.5 Gy for γ-rays and a MF exposure, respectively. It was shown that the combination of biomarkers provides greater accuracy for radiation dose prediction and a separation of animal groups than any one biomarker alone (Ossetrova et al. 2009-2016).

Conclusion

Equivalent doses of pure g-rays and mixed neutrons/γ-rays fields do not produce equivalent biological effects due to the differences in the patterns of energy deposited. Therefore, the hematopoietic syndrome occurs at lower doses of MF radiation. These findings generally agreed with AFRRI dicentric calibration curves created using different radiation sources **(**Prasanna et al. **2002).** Results were also in concurrence with RBE=1.95 (Dn/Dt=0.67) previously reported by AFRRI scientists in radiation countermeasure survival studies (Ledney et al. 2010**,** Cary et al. 2012).

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PP - 6

Identification of Bioindicators of Exposure to Chronic Low Dose Ionising Radiation in Two Populations of b-Lymphocyte Cell Lines

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Introduction
While bioindicators, including miRNAs, for acute exposure to ionizing radiation have been widely studied, less is known about the bioindicators for exposure to chronic, low doses of ionizing radiation (CLD). A study of differential intra- and extracellular miRNA expression after exposure to CLD was thus undertaken, using b-lymphocyte cell lines (bLCLs) as a model.

Methods
bLCLs were derived from adult (aged 21-62 years old) male donors of Chinese racial descent. Two populations were chosen: 2 donors were obtained from an American population, and 2 donors from a Singaporean population. Control cells were left untreated, while treated cells were exposed to Cs137 at 0.1Gy over 66 h. Cells and exosomes were subsequently harvested for miRNA. Gene expression was quantified using Nanostring"s miRNA gene expression analysis panel and statistical analysis was performed on Partek (n=4).

Results
Principle component analysis (PCA) revealed that the greatest source of variation stemmed from the different cell lines in both intra- and extracellular (exosomal) miRNA. Additionally, it appeared that geographical location (American vs Singaporean) was also a source of variation. This suggests that although Chinese males were used, other individual variation exists which may impact the identification of differential gene expression. 2-way ANOVA identified 13 differentially expressed miRNA in the Singaporean samples, and 23 in the American samples. Of these, only miR-508-3p was common. Intra- and extracellular miRNA gene expression could also be seen by PCA as two distinct clusters, suggesting that the intracellular miRNA gene expression is distinctly different from the exosomal miRNA.

Conclusion
The results suggest that bLCLs may be used as a surrogate to whole blood in the study of bioindicators. Subsequently, the correlation to whole blood should be investigated. Furthermore, the study also suggests that individual genetic variation, including the geographical location from which samples are obtained, should not be overlooked. Further work needs to be conducted in this regard, using samples from a wider population. Lastly, the study also suggests that miRNA that influence processes within the cell after CLD may be different from those that influence extracellular processes.

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PP - 7

Research progress of nucleoplasmic bridge levels in human lymphocytes as a radiation biomarker

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Introduction
Cytokinesis-block micronucleus (CBMN)-cytome assay can be used to analyze the biomarker of early chromosome damage, such as the micronucleus, nucleoplasmic bridges (NPB), nuclear buds. NPB originates from dicentric chromosomes, so that it might be the potential biodosimeter.

Methods
Few studies have shown that the yields ionizing radiation-induced NPB in human cells are dose dependent. Firstly, a positive correlation was observed between the frequencies of NPB and dicentric chromosome. The dose-response curve between the NPB frequency and the absorbed dose of ionizing radiation (0-6 Gy 60Co γ-rays) was established. The dose response curve was followed the linear-quadratic model.

Results
Secondly, the NPB frequencies in human peripheral blood lymphocytes exposed to low-dose 60Co γ-rays (0–1 and 0–0.4 Gy) were also explored. Complex anomalies, including fused nuclei (FUS), horse-shoe nuclei (HS), and circular nuclei (CIR), which possibly originated from multiple NPBs, were also scored. All dose–response curves followed the linear model for both NPB frequency and PFHC (NPB plus three complex nuclear anomalies) cell frequency. The lowest analyzable doses of NPB and PFHC were 0.12, 0.08 respectively. Thirdly, the spontaneous and ionizing radiation-induced NPB frequencies in Chinese population were investigated. The effect of age and gender on the NPB frequencies was also analyzed.

Conclusion
Lastly, the dose estimation using the NPB frequency was carried out for a radiation accident exposure individual. Nucleoplasmic bridges; Radiation exposure biomarker; Dose response curve; Spontaneous and radiation induced NPB; Dose estimation

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PP - 8

Dicentric dose estimates for patients undergoing radiotherapy enrolled in the RTGene study to assess 1) blood dosimetric models and 2) the Bayesian zero-inflated Poisson finite mixture method for estimating partial body gradient exposure.

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Introduction
The RTGene study was focused on the development and validation of new transcriptional biomarkers for prediction of individual radiotherapy (RT) patient responses to ionising radiation. In parallel, for validation purposes, the study has included conventional biomarkers of radiation exposure, i.e. the dicentric assay (DCA) and the γ-H2AX foci assay (FA).

Methods
Peripheral blood samples were taken with ethical approval and informed consent from 20 patients undergoing external beam RT for breast, lung, gastrointestinal or genitourinary tumours. Five samples were taken from each patient: prior to RT, 0.5-2 and 24 hours after the 1st fraction, before the 5th and last fractions. Blood samples were processed using standard methods (1) for the DCA (samples 1 and 5) and FA (samples 1 to 5). The five samples per patient for gene expression (GE) were used to assess the temporal responses from ~1000 coding and non-coding RNAs using the nCounter system.

Results
Whole body and partial body (PB) dicentric doses, calculated using standard methods (1), were compared to the dose to blood derived using two newly developed ICR/RM dosimetric models. Initial comparisons indicate the relationship looks very promising, with a correlation of 0.860 ($p=0.001$). Success of these models will allow further development to take place. A new Bayesian method (2) was applied to the dicentric data to estimate PB doses assuming 2, 3, 4, 5 and 6 irradiated fractions. Initial results of the Bayesian analysis suggest a PB irradiation with 2 irradiated fractions is the best fit for the data in all patients. The Bayesian PB dose estimates will be compared to those calculated by the standard method and the ICR/RM models. Initial FA and GE data will also be presented.

Conclusion
To date, these initial results for conventional biomarkers indicate they can be used to validate future gene expression data. The RTGene partners will explore the possibility of combining the cytogenetic, DNA damage and gene expression data to form a multi-assay panel of biomarkers to inform on individual radiation exposure and effects. A lot more work is needed, but the next step will be validation in a larger cohort.

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PP - 9

Neutrophil to lymphocyte ratio as a radiation biomarker in multiple radiation model systems

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Introduction
The neutrophils to lymphocytes ratio (NLR) has been introduced as an inflammation biomarker for a variety of medical conditions. In 2005 Zhang et al. reported it application as a radiation biomarker based on human responses from the Chernobyl nuclear accident. Validation studies using animal radiation model systems have confirmed the utility of the early-phase NLR as a radiation biomarker.

Methods
Mouse studies are based on the use of BALB C males exposed to TBI 60Co gamma rays (2-7 Gy; 0.1 Gy/min) and CD2F1 males exposed to TBI and PBI of 250-kVp X-rays. Canine studies involved TBI using 60Co gamma rays (2-5 Gy; 0.4 Gy/min). Radiation studies with Rhesus NHP included exposures to: a) 4.9 to 6.2 Gy 6 MV X-rays (LINAC) at 0.8 Gy/min, b) 6.5 Gy 60Co-gamma rays (0.4 Gy/min), and c) 0-8.5 Gy 60Co-gamma rays (0.6 Gy/min). Data from archived baboon studies involved exposure to: a) 0-8 Gy mixed field (neutron to gamma ratio of 5.1) and b) 2-8 Gy 60Co gamma rays.

Results
Characterizing baseline hematology data are critical in the use of the NLR biomarker. The NLR values are quite different in various species (mouse: mean = 0.31 ± 0.14, 95% CL=-0.18 to 0.80; canine: range =2-3.5; Rhesus NHP: mean= 0.73 ± 1.15, 95% CL: 0.26 – 2.57; baboon: mean = 1.75± 1.06, 95% CL = 0.6453 - 8.2598). Mean values for human are 2.1 ±0.125. In the case of baboon, baseline hematology data transformation using log base 2 provides an improvement of the baseline histogram fits to a normal distribution. Time course radio-responses in the early-phase after radiation exposure for the various animal species will be shown.

Conclusion
Preliminary analysis of the baboon results indicates an RBE = 1 for NLR when comparing mixed field (neutron to gamma of 5.1) with pure gamma rays. Comparison of results from animal studies with limited human data will be discussed. The views expressed in this abstract are those of the authors and do not necessarily reflect the official policy or position of the AFRRI, USUHS, DoD nor the U.S. Government. Funding support provided by AFRRI RBB43523 and RBB44313.

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PP - 10

Influence of confounding factors on radiation dose estimation in in vivo validated transcriptional biomarkers

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Introduction
For triage purposes following a nuclear accident, blood-based gene expression biomarkers can provide rapid dose estimates for a large number of individuals. Ionising radiation responsive genes are regulated through the DNA damage response pathway, including activation of multiple transcription factors.

Methods
Modulators of this pathway could potentially affect the response of these biomarkers and consequently compromise accurate dose estimation calculations. In the present study, four potential confounding factors, cancer condition, gender, simulated bacterial infection (lipopolysaccharide) and curcumin, an anti-inflammatory/anti-oxidant agent, were selected. Their potential influence on the transcriptional response to radiation of the genes *CCNG1* and *PHPT1*, two biomarkers of radiation exposure ex vivo, was assessed.

Results
Firstly both *CCNG1* and *PHPT1* were detected in in vivo blood samples from radiotherapy patients and as such validated as biomarkers of exposure. Importantly, their basal expression level was slightly but significantly affected in vivo by cancer condition. Moreover, lipopolysaccharide stimulation of blood irradiated ex vivo led to a significant modification of CCNG1 and PHPT1 transcriptional response in a dose- and time-dependent manner with opposite regulatory effects. Curcumin also affected their response counteracting some of the radiation induction. No differences were observed depending on gender. Dose estimations calculated using linear regression were affected by lipopolysaccharide and curcumin.

Conclusion
In conclusion, several confounding factors tested in this study can indeed modulate the transcriptional response of *CCNG1* and *PHPT1* and consequently affect radiation exposure dose estimations but not to a level which should prevent their use for triage purposes.

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PP - 11

Plasma soluble proteins as potential dose-assessment biomarkers

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Introduction
Beyond DNA double strand breaks, ionizing radiation induces immunological and inflammation processes, and as a consequence of these, changes in the cytokine composition of blood plasma. Our aim was to identify immunological markers of radiation exposure in head and neck cancer patients treated with radiotherapy, in order to find soluble markers correlating with the delivered dose.

Methods
Plasma was collected from 11 head and neck cancer patients at the COG before, directly after and one month following radiation therapy. Plasma samples were loaded on proteome profiler antibody array membranes (R&D Systems). Membranes were washed and incubated with biotinylated detection antibody coctail, streptavidine-HRP and chemiluminescent detection reagents as suggested by the supplier, followed by a simultaneous exposure of membranes for 5min to an X-ray film. X-ray film was digitalized by an Epson scanner and analysed with ImageJ sofware. Statistical analysis was performed using the Prism software.

Results
Twelve cytokines changed in all patients after RT compared to the pre-irradiation values. Changes in secretion of Adiponectin (one month after treatment, P

Conclusion
Several plasma proteins have been found to correlate with radiation treatment parameters and outcome, but experiments of a higher sample size are statistically required. Correlation of adiponectin and BAFF with dose per fraction and total dose are already significant in the studied sample size. These also have to be validated in a larger number of samples and could be potential biomarkers of radiation exposition. Further investigation of dose- and time dependence of plasma levels of the above mentioned proteins could also be important.

References
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Sensitivity of the dicentric assay for low-dose biodosimetry of therapeutic radiation exposure

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Introduction
To determine the cytogenetic risk associated with the therapeutic exposure to low doses of ionizing radiation (e.g. low-dose radiotherapy (LDRT) or radon spa therapy), a sensitive detection method is essential. We present the reasons for choosing semi-automatic analysis of dicentrics for low-dose biodosimetry, show the established reference X-ray dose-effect curve and results from LDRT patients.

Methods
To determine the background frequencies of different aberration types in lymphocytes of unexposed individuals of different age, chromosomal aberrations were analysed using mFISH. For biodosimetry, semiautomatic scoring of dicentric chromosomes was performed using DCScore (Metasystems, Germany). The technique was applied to lymphocytes from a normal donor irradiated *in vitro* with a large range of X-ray doses (25 mGy to 6 Gy) to establish the reference dose-effect curve. Dicentric chromosomes were scored in lymphocytes from patients undergoing LDRT (samples from before and after therapy).

Results
The mFISH analysis showed that the background level of dicentric chromosomes is very low compared to other aberration types. With the semiautomatic dicentric scoring, a dose-effect curve based on 140′000 analysed metaphases was established which followed a linear-quadratic dose-response relationship. The lowest dose tested so far (25 mGy) could be distinguished from the control level (1.64±0.20 vs 1.03±0.17 dicentrics per 1000 cells, based on >35′000 analysed metaphases per point). Results from low-dose radiotherapy patients will be presented.

Conclusion
The low background level of dicentric chromosomes together with the fast semi-automatic scoring makes dicentric scoring a suitable tool for low-dose biodosimetry. Doses well below 100 mGy can be detected if a sufficiently high number of metaphases is analysed. The application of semi-automatic dicentric scoring for low-dose therapeutic radiation exposure will be discussed.

References
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A “three in one” biodosimetry assay as a potential tool for triage dose assessment in case of large scale radiological emergency

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Introduction
In case of mass radiological emergencies, new strategies are requested for an efficient triage classification of casualties, using biological and clinical endpoints. In this regard, we are validating a speedy biodosimetry assay established in our laboratory, combining three different cytogenetic techniques.

Methods
The proposed protocol was originally developed in our laboratory for in situ radiobiology studies on mammalian cells (1) and subsequently it was modified for biodosimetry purposes. This protocol combines 1) the dicentric assay 2)the micronuclei assay and 3)the FPG staining generally used to discriminate between metaphases in first (M1) and second (M2) cell cycle. In order to validate this novel method for dose assessment, we established a calibration curve exposing blood lymphocytes from 2 healthy donors to X-rays (doses 0-3 Gy). About 500 M1 were analysed for low doses, 200 M1 for doses ≥1 Gy.

Results
We observed that on a single slide, at least 100 M1 and 1000 binucleated cells (BN) could be simultaneously scored. This amount of cells could be considered adequate to perform a triage mode dose assessment. As far as the dicentric scoring data obtained for each dose, by using this new protocol, they have been compared to those produced by the standardized methods (2) which has been simultaneously performed on blood samples from the same donors. The comparison reached an excellent data matching.

Conclusion
This method needs further validation through inter-laboratory comparisons involving different biodosimetry institutions, in order to verify its reproducibility. Moreover, the possibility to apply the already existing software for automation for dicentric and micronuclei assays, could be evaluated. In case of satisfactory results of additional validations, this protocol could be considered as a fast, cheap and minimally invasive tool to be potentially used for triage purposes in case of mass casualties events.

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The impact of dose rate on the cytogenetic calibration curve for gamma radiation

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Introduction
The gamma calibration curve for cytogenetic biological dosimetry should be generated at a dose rate of ca 1 Gy/min (1). In practice, different sources are used and the impact of dose rate on the precision of dose estimate based on a single calibrations curve is not well defined. The aim of this work was to assess the impact of dose rate on the shape of a micronucleus calibration curve.

Methods
Freshly drawn blood of a single donor was exposed at 37 °C to 0, 1, 2 and 3 Gy of gamma radiation (^{137}Cs) at three dose rates: 0.4 Gy/min, 0.8 Gy/min and 6.0 Gy/min. Standard whole blood cultures were set up for the micronucleus (MN) assay (2), cytochalasin B was added after 44h and cells were harvested after 72h of culture time. MN was manually assessed in 1000 Giemsa-stained, binucleated cells per dose. The replication index (nuclear division index) was estimated in 500 cells per dose. Scoring was carried out blind. 3 independent experiments were performed.

Results
The scoring was not completed at the time of abstract submission. Preliminary results show that the slope of the dose response curve increases with increasing dose rate, especially with respect to the square dose component. This result is expected based on earlier publications (3). No impact of dose rate was detected at the level of the replication index. The exact relationship between the dose rate and the slope of the curve will be assessed together with the impact of the dose rate on the precision of dose estimate following a radiation emergency. Also, the method presented by Bauchinger at al. (4) will be applied to verify if a correction factor can be derived to adjust the calibration curve to an existing exposure situation.

Conclusion
The observation that even a relatively small difference in the dose rate (in the range of 0.4 Gy/min) has an impact on the shape of the calibration curve demonstrates the importance of applying the right curve to the right dose rate of the accidental exposure. If the dose rate of the accidental exposure is not known, then an uncertainty may need to be included in the estimate dose. It appears advisable to carry out a large intercomparison study with a broader range of different dose rates in order to more closely define the impact of dose rate on the precision of dose estimate.

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RABiT-II: The use of ANSI/SLAS microplate formats for development of biodosimetry assays on commercial high-throughput biotech robotic systems

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Introduction
Previously, we proposed the use of plates and tubes with ANSI/SLAS microplate formats at all stages of biodosimetry assays (1-2) and developed automated CBMN assay on commercial biotech systems (3), named as second-generation Rapid Automated Biodosimetry Tools (RABiT-II). Here, we update the development of biodosimetry assays on different RABiT-II systems at Columbia University Medical Center.

Methods
10-200µl blood samples in 1ml Matrix tubes in racks of 96 and 96-well plates were processed on RABiT-II systems: **cell::explorer** was used for γ-H2AX, CBMN and Dicentric assay sample preparation and **Microlab Star** was used for CBMN assay without centrifugation. After culturing, fixation, washing and transferring of samples into 96-well glass-bottom imaging plate and staining, samples were imaged on **Cytation** and **IN Cell Analyzer** workstations (imaging RABiT-II systems). Images were analyzed by commercial (IN Cell Analyzer workstation and Gen5) and custom-designed software (4).

Results
At Columbia Center for High-Throughput Minimally Invasive Radiation Biodosimetry/Columbia Genome Center protocols for automated processing of 10-200µl blood samples and automated imaging of fixed samples on universal biotech robotic systems (RABiT-II) in multiwell plates and tubes compatible with ANSI/SLAS microplate formats were developed for γ-H2AX, CBMN and Dicentric assays. Different approaches and strategies were used for minimizing the time of sample preparations and increasing the overall speed of imaging on automated high-throughput screening stations. Particularly, for ÿ-H2AX the total volume of blood was decreased to 10ml and for Dicentric assay new FISH-protocol with minimal steps was developed. Radiation dose-response curves were established for three biodosimetry assays.

Conclusion
The use of biotech robotic systems for biodosimetry assays allows to overcome the limitations of automated cytogenetic workstations for throughput. Results demonstrate that the well-established γ-H2AX, CBMN and Dicentric assays can be successfully implemented within a large network of universities and pharma companies equipped with different commercial high-throughput biotech robotic systems used as RABiT-II, thus, considerably increasing the current throughput of regional and worldwide biodosimetry networks.

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Increased Retention of Radiation-Induced γ-H2AX Foci by Phosphatase Inhibitors for Biodosimetric Applications

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Introduction
The objective of biodosimetry during a mass exposure scenario is primarily to provide accurate, sensitive measures of radiation exposure for medical decisions (Sullivan et al 2013). This study aims to investigate the potential of phosphatase inhibitors for their enhanced γ-H2AX signal persistance for its biodosimetric implications.

Methods
Human peripheral blood lymphocytes were isolated from healthy individuals after obtaining the Institutional Ethics Committee approval and informed consent form the blood donors. The lymphocytes were irradiated *in vitro* with X-rays (Faxitron -160) and stained for γ-H2AX foci analysis. Initially, the assay was compared for its sensitivity between fluorescent microscopy and flow cytometric methods and then for reproducibility. Further, the effect of protein phosphatase 2A inhibitors like Calyculin A, Fostriecin and Okadiac Acid on the retention of foci were studied in 10 individuals.

Results
The results from flow cytometry and fluorescence microscopy measurements of γ-H2AX assay indicated a linear increase in the γ-H2AX signals with increasing dose. However, the latter methodology was more sensitive method when compared to flow cytometry though more time-consuming. The repair kinetics indicated a steady decrease in the number of foci with the progression of DNA repair. Among the three phosphatase inhibitors used, Calyculin A showed 1.5 fold increase in the retention of foci signals at 6h.

Conclusion
Microscopic method may be more relevant for rapid analysis required for early triage. Further, the addition of Calyculin A at the site of sample collection may prove beneficial in early triage management to get the precise dose measurements due to increased retention of foci signals.

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Radiation-induced NF-κB activation and expression of its down-stream target genes as biomarker of radiation quality

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Introduction

Activation of Nuclear Factor κB (NF-κB) and the resulting gene expression profile after exposure to different radiation qualities have been evaluated to a very limited extent. Therefore, the activation of NF-κB after exposure to low and high linear energy transfer (LET) radiation and the expression of its target genes was analyzed in human embryonic kidney (HEK) cells.

Methods

Activation of NF-κB was visualized by the cell line HEK-pNF-κB-d2EGFP/Neo L2 carrying the destabilized Enhanced Green Fluorescent Protein (d2EGFP) as reporter. The NF-κB dependent d2EGFP expression was evaluated by flow cytometry. The biological effectiveness (RBE) of NF-κB activation and reduction of cellular survival as determined by the colony forming ability test was compared for heavy ions having a broad range of LET (~ 0.3 - 9674 keV/µm). Furthermore, the effect of LET on NF-κB target gene expression was analyzed by real time reverse transcriptase quantitative PCR (RT-qPCR).

Results

The maximal RBE for NF-κB activation and cell killing occurred at an LET value of 80 and 175 keV/µm, respectively. There was a dose-dependent increase in expression of NF-κB target genes NFKB1A and CXCL8. A qPCR array of 84 NF-κB target genes revealed that TNF and a set of CXCL genes (CXCL1, CXCL2, CXCL8, CXCL10), CCL2, VCAM1, CD83, NFkB1, NFkB2 and NFKBIA were strongly up-regulated after exposure to X-rays and neon ions (LET 92 keV/µm). After heavy ion exposures, it was noted that the expression of NF-κB target genes such as chemokines and CD83 was highest at an LET value that coincided with the LET resulting in maximal NF-κB activation, whereas expression of the NF-κB inhibitory gene NFKBIA was induced transiently by all radiation qualities investigated.

Conclusion

Taken together, this study clearly demonstrates that NF-κB activation and NF-κB-dependent gene expression by heavy ions are highest in the LET range of ~50-200 keV/µm. The up-regulated chemokines and cytokines (CXCL1, CXCL2, CXCL10, CXCL8/IL-8 and TNF) could be understood to be important for cell-cell communication among hit as well as unhit cells (bystander effect). The gene expression profile will be further evaluated as possible biomarker for exposure to different radiation qualities.

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Dose estimation with uncertainty quantification from the gamma-H2AX assay

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Introduction
Over recent years, the suitability of the gamma-H2AX foci assay as a biomarker for ionizing radiation has been clearly established in principle. However, dose estimation and uncertainty quantification from this assay requires special care due to intra-individual, inter-individual and inter-laboratory variation. This contribution discusses adequate statistical methodology and presents a web applet.

Methods
We distinguish two steps in this process: Firstly, the construction of an adequate dose-response curve from in vitro laboratory data, and secondly, the estimation of radiation dose, using the calibration curve, for a new sample of foci counts, from, say, a potentially exposed individual. Due to the count data character of the response, standard least squares regression is not adequate, and instead a quasi-Poisson modelling approach is taken. Dose estimation is carried out through inverse regression, where uncertainties can be decomposed into different sources via the delta method.

Results
While there is a physical argument for the calibration curves to be linear, in practice the curves show a quadratic shape with significant negative quadratic coefficient due to a saturation effect. With the help of a reference sample [1] to account for inter-laboratory variation if required, doses can be estimated generally with reasonable accuracy. For instance, from mean foci yields obtained from 50 sample cells 1h after exposure, standard errors normally do not exceed 0.5Gy. The uncertainty contributed by the sampling error will generally overwhelm other sources of uncertainty (especially the one related to the calibration curve). For estimation 24h after exposure, the resulting standard errors can become much higher, and reach 2Gy or more.

Conclusion
For the gamma-H2AX assay, the uncertainty of (`whole body') dose estimates has been assessed by decomposing this uncertainty into its individual sources. For foci counts obtained after 1h, the uncertainties are relatively small and allow for precise dose estimates. After 24h, uncertainties can be large which however does not render the dose estimates useless as they may still be usable for triage purposes, or in conjunction with other measurements/biomarkers. Accompanying this work, an (R Shiny) web applet has been produced, which will be made freely available.

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High-sensitive biomarkers of blood total antiradical activity in mice exposed to gamma–irradiation

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Introduction
Identification of total-body-irradiation-induced specific biomarkers is important for assessment the possible consequences of radiation exposure, provide medical management of incidents triage, definitive care of exposed population (1). The goal of study was to determine high-sensitive markers of blood redox-status in relation to dose of irradiation and evaluation the effectiveness of treatment

Methods
Male white mice (6 weeks old) were randomly assigned to the sham and irradiated groups. The mice were exposed to Gamma irradiation (Cr137) at a total dose of 5 and 7Gr. After 7 days blood samples was drawn post euthanasia under anesthesia from inferior vena cava. Blood plasma total antiradical activity (by 2.2-diphenyl-1-picrylhidrazyl (DPPH)-scavenging assay) and antioxidant enzymes (catalase, superoxiddismutase) activity was determined by spectrophotometry (2). Regression Models of Survival Analysi's were used for comparison of redox-status characteristics in different groups of animals.

Results
After 7 days of irradiation, the total antiradical activity of blood plasma decreased dose-dependently with increasing of irradiation dose (at irradiation with 7 Gr it was 2,1 fold lower as at 5Gr). Activity of catalase was reduced by an average of 65% and 73% and of superoxidedismutase (SOD) by 70% and 81%, at irradiation regimes 5Gr and 7Gr, respectively. The results of the study showed that alterations in the overall antiradical activity of mice' blood are strictly reduced with an increase in the dose of irradiation. This parameter is characterized by low variability among the animals of individual groups (in contrast to the antioxidant enzymes activity) and strictly correlates with the index of animal"s general physiological state in the individual group – animals' survival.

Conclusion
Blood plasma total antiradical activity (by 2.2-diphenyl-1-picrylhidrazyl (DPPH)-scavenging assay) is characterized by low variability among the animals of individual groups and strictly correlates with the index of animal"s general physiological state in the individual group – animals' survival. Based on the results of the study, we propose to use an indicator of the blood total antiradical activity, as a marker of general physiological state of the irradiated animals and the effectiveness of therapeutic strategy of treatment.

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The Potential Biomarkers for Screening Lung Cancer Risk in High Residential Radon

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Introduction
Considering that radon is likely the second most common cause of lung cancer after smoking and the need to incorporate new biomarkers useful for early screening would be promising for the improvement of the treatment outcome. So, our study aims to evaluate the potential clinical use of serum biomarkers and teleomeres length in lung cancer patients and high residential radon.

Methods
A passive radon-thoron discriminative monitor (RADUET) using a solid-state track detector (CR-39) was used to evaluate the indoor radon in 227 dwellings in a 5-7 months period. According to indoor radon measurements, serum samples from 38 lung cancer patients and 38 matched healthy controls (low- and high radon group) were analysed for 7 proteins (CEA, Cyfra 21-1, IL-8, TNF-alpha, HE4, MIF, VEGF) and teleomere length using the luminex multiplex assay and monochrome multiplex real-time PCR (MMQPCR), respectively.

Results
The radon concentration were distributed in the range of 23- 229 Bq/m^3 with an average value of 50 Bq/m^3. The data indicated that the radon concentration seems quite high when considering the climatic condition and housing structure. Interestingly, the result showed that CEA, Cyfra 21-1, IL-8 levels were significantly higher in lung cancer patients than in healthy volunteers. However, the levels of CEA and IL-8 were higher in high radon group than low radon group. Consequently, a high level of CEA and IL-8 are sound to indicate the at high risk for lung cancer from high radon exposure. Further, lung cancer patients had significantly shorter telomere length compared with healthy controls. This may indicate that shortened telomere length with increased lung cancer risk.

Conclusion
The results suggest that CEA, IL-8 and short telomere length should be a useful biomarkers of lung cancer risk in high residential radon area and for future studies on personalized therapy of lung cancer.

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Application of autologous adipose tissue-derived stromal vascular fraction (SVF) cells in patients affected by Cutaneous Radiation Syndrome.

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Introduction
Skin exposed during radiotherapy treatments or during X-ray guided cardioangiology procedures, usually presents an apparently normal evolution in the short term, developing Cutaneous Radiation Syndrome (CRS) months or years after exposure to IR. For this reason, CRS is not frequently associated with over-exposure to IR, misdiagnosed and the prescription of treatment inaccurate.

Methods
Previous and after the application of autologous adipose tissue-derived stromal vascular fraction (SVF) cells, the therapeutic response was evaluated through clinical follow-up, serial photographic record, complementary test and the expression of adhesion molecules β1-integrin on granulocytes and lymphocytes, as well as changes in subpopulations of T lymphocytes and the level of C-reactive protein.

Results
Preliminary results using flow cytometry from periferal blood samples revealed a higher expression of β1 Integrin on gated lymphocytes of two patients after treatment. It was also noted a decrease in its expression value during the follow up of these patients which might be an indicator of a good response to therapeutic treatment.

Conclusion
The present work presents a methodology based on the extraction and purification of Autologous Vascular Stromal Fraction (SVF), rich in adult mesenchymal stem cells, obtained by liposuction. The technique represents a new alternative of treatment through the application of a simple, fast and economical protocol. These preliminary results based on follow-up studies of these patients show evidence that suggests the superiority of this alternative in comparison to the current standard for treatment.

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The use of lymphocyte prematurely condensed chromosomes as a biomarker to study biological effectiveness of different radiation qualities

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Introduction
There is an interest in the use of high-LET radiations for cancer treatment based on their unique characteristics, which allows escalation of tumor doses while reducing toxicity in normal tissue. However, data on RBE values and risks for different radiation qualities are sparse due to complications introduced in cell cycle kinetics and the inability of irradiated cells to reach mitosis.

Methods
G0 human lymphocytes isolated from whole blood were exposed to a proton beam with an incident energy of 2.2 MeV and LET of 28.5 keV/μm, to alpha particles using a Curium-244 alpha source with particle energy 4.70 MeV at the cell surface entrance and LET at 92 keV/μm, and to accelerated Carbon-12 ions at 56.5 MeV with LET at 295 keV/μm, in the dose range 0-6 Gy. To overcome the cell cycle kinetics issues following irradiation, the initial number and repair kinetics of excess chromosome fragments were investigated using the fusion premature chromosome condensation (PCC) methodology.

Results
A significant increase in the initial excess PCCs by protons, alpha particles and carbon ions when compared to those obtained by γ-rays using a Co-60 irradiator. The results revealed as well differences in the repair kinetics as quantified by the number of residual un-rejoined fragments after 2, 6, 12 and 24 hours post irradiation incubation at 37°C. The distribution of residual G0-PCC breaks as well as the mean break number for protons differed from those for α-particles and C-ions and all were significantly higher when compared to those obtained for γ-rays. The RBE values based on damage induction were calculated to be 2, 2.5, and 4.5 for protons, C-ions and Alpha particles, while based on repair 4.2, 5 and 10 respectively.

Conclusion
PCCs in G0-lymphocytes are useful cytogenetic biomarkers to study the mechanisms underlying biological effectiveness following exposure to various radiation qualities. The results obtained reinforce the notion that the LET-dependent structure in the irradiated lymphocytes is reflected in the repair processes. The different RBE values obtained for protons, α-particles and C-ions, based on chromatin breakage and formation of chromosomal aberrations are indicative of their effectiveness and toxicity via micronuclei formation and induction of chromothripsis.

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Validation of translational potential of the Göttingen minipig model of H-ARS for radiation countermeasure testing using abbreviated Neulasta regimen

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Introduction
Only Neupogen and Neulasta have been approved by the FDA for radiation-induced myelosuppression. We previously showed that minipig is a suitable model to test the efficacy of Neupogen in adults and pediatrics. Here, we administered Neulasta to irradiated minipigs, determined its efficacy on survival, recovery of myelosuppression, and mechanisms of action in addition to its neutrophilic effect.

Methods
Twenty male Göttingen minipigs were exposed to 2.2 Gy (radiation dose equivalent to LD70/45 leading to hematopoietic acute radiation syndrome [H-ARS], total body irradiation, Cobalt-60, 0.6 Gy/min). Animals were assigned to one of the two groups and received either Neulasta (300 mcg/kg; n=10), or dextrose (equivalent volume; n=10), at day 1 and 8 after irradiation; survival was monitored over a 45-day period. Blood samples were obtained longitudinally from peripheral veins for blood cell counts and tissue samples were obtained at necropsy for molecular signatures

Results
Neulasta significantly decreased mortality over the control animals by 50% (p =.03). Among the survivors, Neulasta reduced the nadir and duration of neutropenia and improved the recovery of ANCs. Among the decedents, ANCs dropped more rapidly in the Neulasta treated animals than the control group. Overall organ hemorrhage and the incidence of frank bleeding episodes was lower in the Neulasta group (1/10) with respect to controls (3/10). Neulasta also increased the plasma concentration of vaso-protective hormone IGF-1 and to a lesser degree, of CRP. In the heart, Neulasta promoted the activation of the IGF-1 receptor, Akt, and coupling and activation of eNOS. Plasma NO levels were higher in the Neulasta than in the control group. Catalase and SOD were marginally affected.

Conclusion
There are only two drugs (Neupogen, Neulasta) approved for the treatment of H-ARS. Both drugs were successfully tested in the minipig, confirming the translational potential of the minipig for radiation countermeasure testing. As expected, Neulasta increased survival over the vehicle control and improved recovery of myelosuppression. Mechanisms of action by Neulasta may extend beyond its ability to prevent neutropenia-associated sepsis. Neulasta activated the IGF-1/Akt/eNOS pathway, increased production of nitric oxide, and reduced the extent of vascular damage.

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Biological and EPR dosimetry for medicine

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Exploring the variability of in vivo cytogenetic damage yield in radiotherapy patients for adverse effects assessment: Palliative mathematical solutions

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Introduction
To date biodosimetry-oriented cytogenetic analysis has had rather limited applications in radiation oncology, because aberration yields induced *in vivo* in patients by radiotherapy (RT) are extremely variable and cannot be interpreted in a straight dose response manner. Mathematical interventions are needed to increase the value of biodosimetry markers for the assessment of RT clinical effects.

Methods
Conventional dicentric assay was performed in 30 mammary cancer patients and 70 patients with gynecological cancers treated with various schemes of gamma-therapy. Cytogenetic data and relevant clinical information were analyzed statistically to reveal possible correlations between early adverse effects in normal tissues (AE) and (1) chromosome aberration (ChA) yields, or (2) combined sets of clinical and cytogenetic parameters. Also this dataset was statistically treated to assess factors contributing to the heterogeneity of individual rates of *in vivo* ChA yield induction during RT.

Results
No direct correlation was found between AE and *in vivo* ChA yields. However, combinations of clinical variables like age, tumor grade, treatment details, etc., with individual ChA yields, rates of ChA induction per RT fraction and multimodel fits of aberration-per-cell distribution (AbCD) to several statistical functions appeared to be suitable for AE prognoses. Multiply linear regressions (MLR) with good prognostic efficacy were generated for epidermitis, entherocolitis and leucopenia expected in external irradiation schemes, and for epitheliitis and cystitis in schemes involving brachytherapy. ChA induction rates had an apparent linkage to anatomic location and RT modality, but their inter-individual heterogeneity didn"t show much dependence on clinical factors.

Conclusion
The *in vivo* ChA yield cannot be considered as a reliable "stand-alone" prognostic biomarker for normal tissue toxicity assessment in RT patients. Meanwhile, Principal Component Analysis and MLR technique, being applied to combined sets of cytogenetic and clinical data, provided a good palliative solution, allowing the introduction of biodosimetry assays into clinical practice. The AbCD multimodel fit appeared to be especially useful cytogenetic prognostic index. However, such MLRs work correctly only if all their parameters fall within the range of values used for MLR construction.

References
A formalization of the heterogeneity of ChA induction rates in RT patients pointed at dominant roles of radiation exposure scenario and physiological factors in the cytogenetic response to the RT.

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Construction of dose response curves for cytogenetic biodosimetry in the low dose range based on five persons

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Introduction
In order to estimate radiation dose, it is important to establish DRCs. Each lab has their own DRC usually based on chromosome aberration (CA) of a single blood sample according to the IAEA protocol. We constructed DRCs for dicentric chromosome assay (DCA) and translocation (TR) assay applicable to low dose range. Five samples from different person were used to evaluate individual variability.

Methods
Peripheral blood lymphocytes were collected from five Japanese individuals: four males (23, 35, 44 and 55 years old) and one female (33 years old). They did not have the history of smoking and medical exposure. Aberration yields were obtained from eight dose-points of gamma irradiations (0, 10, 20, 50, 100, 200, 500, and 1000 mGy) with DCA and TR-assay by three staining methods: DCA; Giemsa staining and centromere-fluorescence in situ hybridization (centromere-FISH), TR-assay; Chromosome painting using the probes for chromosomes 1, 2, and 4.

Results
About 2,000 metaphases for DCA and 5,000 metaphases for TR-assay were analyzed for every dose point of each sample, we obtained DRCs with good correlation for three staining methods. The results from Giemsa staining [$Y = 0.0013\ (\pm0.0005) + 0.0067\ (\pm0.0071) \times D + 0.0313\ (\pm0.0091) \times D^2$], centromere-FISH [$Y = 0.0010\ (\pm0.0004) + 0.0186\ (\pm0.0081) \times D + 0.0329\ (\pm0.0104) \times D^2$], and Tr-assay [$Y = 0.0015\ (\pm0.0009) + 0.0049\ (\pm0.0155) \times D + 0.1033\ (\pm0.0223) \times D^2$], gave a good fit to the linear-quadratic models ($r = 0.9985$, $r = 0.9998$ and $r = 0.9993$, respectively); Y: yield of chromosome aberrations, D: dose (Gy), r: correlation coefficient [1]. In the TR-assay, we could construct an LQ model with crossing points closer to the origin by age-adjustment using the report of Sigurdson *et al* [2].

Conclusion
We constructed three types of DRCs between 10 mGy to 1000 mGy for DCA using Giemsa staining and centromere-FISH, and for TR-assay using a painting method. The DRCs showed good radiation dose-responsiveness even in the lower-dose range. However, all DRCs showed individual variability caused by background CAs, suggesting a possibility that multiple samples are required to establish DRCs to correct individual variations especially for low-dose range. Therefore, we should consider to evaluate the background factors such as smoking which affect CAs frequency.

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Establishing gene expression for biodosimetry and prediction of acute health effects after radiation exposure

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Introduction
Gene expression changes after radiation exposure develop as a recognized new tool for biodosimetry as well as a tool for early prediction of acute radiation health effects. Within this overview we would like to contribute to the following questions/topics:

Methods
(1) Using gene expression for biodosimetry purposes - overview. How well depict in vitro measurements the in vivo situation? (2) Developing gene expression as a tool for effect prediction after radiation exposure- overview. (3) Pros and cons of gene expression used either for biodosimetry or radiation effect prediction. (4) Where are we now and where will we go?

Results
see above

Conclusion
see above

References
see above

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Evaluation of absorbed dose on mouse bones by EPR spectroscopy for radiobiology studies

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Introduction
In radiobiology studies, the exact knowledge of the delivered dose is crucial. For experimental rodent model involving low energy X-rays used in interventional radiology (IR), variability in terms of bone density/composition can also cause variability in bone absorbed dose. The aim of this work was to evaluate EPR spectroscopy technique to validate dosimetry for bone irradiation in IR conditions.

Methods
To modelize IR conditions, the SARRP platform was used to irradiate mice with 80 kV X-rays. Collimated irradiations (4 x 4 cm²) of the 2 legs of immunocompromised Nude mice were performed with a dose of 30 Gy (in terms of air kerma). After irradiation, tibias were collected, cleaned, dried and cut in small pieces for EPR analysis with the MS5000 X-band spectrometer. The additive dose method was used to estimate absorbed dose in bones. Post-irradiations were performed with 4 MV X-rays in air, given that at this energy air kerma is almost equal to bone kerma.

Results
Both tibias from nine irradiated mice (18 bones total) were harvested for EPR analysis. An average absorbed dose of 187.4 ± 19.7 Gy was found in bones initially exposed to 30 Gy (air kerma) with 80 kV X-rays on the SARRP. The observed inter-bone variability remained within the measurement uncertainty. These measurements allowed us to determine an averaged conversion factor of 6.24 ± 10.5% between the dose determined in air kerma free in air using ionization chamber and the actual dose deposited in mouse bone. Nevertheless, a maximal dose variation among all samples of about 40 % was observed. An important difference in terms of dose could be also observed for a same mouse between left and right tibias, reaching up to 35%.

Conclusion
With the proposed approach, it is possible to determine the dose deposited on mouse bones when irradiated using IR-like conditions on the SARRP platform. A variability between absorbed doses in samples has been observed that justifies performing a dose estimation with EPR spectroscopy for each irradiated tibia. Complementary EPR dosimetry measurements are in progress to complete these first results and better quantify the inter-sample and inter-mouse variability using immunocompetent C57BL/6 mice.

References

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EPR Alanine Dosimetry in a Prostate Radiotherapy Simulation with Metallic Implants.

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Introduction
Clinical applications of EPR alanine dosimetry is increasing due to its interesting properties [1,2,3]. As the population ages a considerably number of patients that need radiotherapy for prostate cancer have one or two metallic hip prostheses. For this reason, the treatment planning for these patients become complicated to deliver the right dose to the prostate and healthy tissues.

Methods
A phantom was built to simulate the pelvic area and the legs. It was filled with water simulated the soft tissue and real human bones with metallic prostheses were used to simulate a real situation. Cylindrical L-Alanine dosimeters, 4mm diameter and 10 mm length, were glued to the sacrum, acetabulum area and close to the prostheses stem in the femur, 10 dosimeters were used in each side. A treatment was planned to give a dose of 2Gy to the prostate per fraction. Two fractions were delivered with a planned dose of 4Gy to the prostate and around 2Gy to the bones.

Results
The results show a dose to the femur for the right side of 42% higher than planned, in the dosimeters positioned at the right hip an increase in dose of 64%, 70% and 64% was found. For the left hip, the results also indicated an increase of 69%, 70%, 64% in the dose than planned.

Conclusion
The results show that care must be taken at the planning to spare also the bone structure close to the prostheses; the possible explanation for the dose enhancement could the difference in the materials and possibly backscattering of radiation. The dose at the hip left and right area was higher than expected; again, the possible reason could be scattered radiation from the prostheses. The correction for material inhomogeneity during the planning could be an important factor to deal with this problem.

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PP - 29

End-to-end audit – comparison of TLD and lithium formate EPR dosimetry

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Introduction
The aim of this study was to test two different solid state dosimetry systems for the purpose of end-to-end audits of radiotherapy VMAT technique; a lithium formate EPR system and a lithium fluoride TL system. As a complement to the solid state systems, ion chamber measurements were performed.

Methods
A polystyrene phantom with a PTV and an OAR structure was scanned in the CT. A VMAT dose plan was optimized to deliver 2 Gy to the target volume and minimize the dose to the OAR. The different detector systems were inserted into the phantom and the dose plan was delivered twice, i.e. in total 4 Gy. The measured doses were compared to TPS calculated doses.

Results
Good agreement was found between TPS calculated and measured doses for both the TL and the EPR systems. It was also a good agreement in results between the two systems. Additional results using an ion chamber agreed well with the two solid state dosimetry systems in the PTV but deviated by 4% in the OAR. Similar results were obtained in another study by an IAEA multicentre group which found the distribution of dose measurements in the PTV consistent whereas that in the OAR showed standard deviations of approx 5% for both TLD and ion chamber measurements. The greater results' scatter in the OAR was attributed to experimental uncertainties related to steep dose gradients in this area.

Conclusion
Both the TL and the EPR dosimetry systems showed results well accepted for dose determinations in remote dosimetry audits of VMAT treatment technique.

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PP - 30

Integrated dose estimation in Chernobyl clean-up workers.

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Introduction
It is known that individual doses of irradiation were not estimated for many of Chernobyl clean-up workers at the time of the accident and now up to 3 decades passed since the accident this question arise again especially in connection with medical problems of irradiated persons. Therefore, dose estimation was performed in Chernobyl clean-up workers using different dosimetric approaches.

Methods
74 Chernobyl clean-up workers were cytogenetically investigated. Blood samples were collected 27-30 years after irradiation. Analysis of unstable aberrations and FISH-analysis of translocations was performed according to IAEA recommendation. The internal incorporation was measured with a whole-body spectrometry counter that lets to assess of internal exposure to gamma-emitting radionuclides and transuranic radionuclides with low photon energy (plutonium, americium etc).

Results
Biological doses of irradiation by FISH-analysis were estimated in 13 persons and ranged from 14 to 34 cGy. For the rest of the persons dicentrics and rings were found in 35% of them with frequency above the control level. Dicentrics suggested about radiation exposure but doses received could be lower the sensitivity of FISH-analysis. 9% of patients had rogue cells, that are considered as a result of hot particles incorporation, but no internal contamination was detected. Moreover, more than 2000 clean-up workers were investigated and Cs-137 was not detected after 1994 and long-lived radionuclides were not found in 450 clean-up workers. Therefore, the suggestion that rogue cells could be a biomarker for exposure to long-lived radionuclides could be under discussion.

Conclusion
Results of our work demonstrate that integrated dosimetric approach using cytogenetic techniques for stable and unstable aberrations and physical dosimetry could give a relevant information about the dose of irradiation in Chernobyl clean-up workers exposed to low doses. Physical dosimetry using whole-body spectrometry counter does not support the idea about long-lived radionuclides incorporation in clean-up workers and induction rogue cells as a consequence of incorporation.

References
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Dose evaluation by chromosome aberrations at a remote time after different radiation accidents

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Introduction
The persons suffered in the accident at the Chernobyl NPP were observed into the Clinic of Burnasyan FMBC for more than 30 years after irradiation. Also survived victims in various other radiation situations periodically were admitted in the remote periods for examination and treatment regarding various diseases, allowing to produce dynamic monitoring of their chromosome damage levels.

Methods
The classical method of staining chromosomes was used in this work for the analysis of chromosome aberrations in peripheral blood lymphocyte cultures. In general, variants of standard methods, consistent with IAEA recommendations, have been used for the cultivation of lymphocytes, preparation of chromosome preparations and their coloration [1, 2]. The results of physical calculations, studies of the EPR signal in tooth enamel, hematological and cytogenetic data were used (in various combinations) as the initial dose estimates.

Results
In total repeated cytogenetic analysis of lymphocytes was carried out among representatives of the following groups of victims: 1) 4 persons after gamma-irradiation (4 accidents), 2) 14 persons after gamma-beta-irradiation (5 accidents) and 3) 6 persons after gamma-neutron irradiation (5 accidents). Most cultures of peripheral blood lymphocytes of these patients was studied, or in terms that are close to the end of the observation for Chernobyl patients, or in a much later time after irradiation (from 17 to 51 years). The multiple regression equations obtained from the results of cytogenetic analysis of patients at a remote time after the Chernobyl accident by means of a special computer program were used for a retrospective dose estimate after other radiation accidents.

Conclusion
Retrospective dose evaluation by the multiple regression equation including computer restored dose evaluation and time after irradiation generally gives poor results as there is a clear exit of many points outside the 95%-confidence intervals for individual values in the direction of higher dose evaluations. Multiple regression equation which includes computer restored dose evaluation and frequency of atypical chromosomes in the remote terms after irradiation produced better results as most of obtained dose estimations were within the 95%-confidence interval for individual values.

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PP - 32

The TOP-IMPLART proton linear accelerator: characterization of the 35 MeV beam

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Introduction
The TOP-IMPLART collaboration (funded by Regione Lazio) among the Italian National Agency for New Technologies, Energy and Sustainable Economic Development (ENEA), the Istituto Superiore di Sanità (ISS) and the Regina Elena National Cancer Institute (IFO), is developing and constructing a compact, modular proton linear accelerator with final energy of 150 MeV, devoted to radiotherapy.

Methods
Currently, four accelerating modules driven by a 10 MW klystron allow the delivery of protons with a 35 MeV of energy or 27 MeV with the fourth structure off. The beam current varies from 0.5 to 30 μA with pulse duration of 3 μs and repetition frequency in a range 10-50 Hz. A dosimetric characterization of the 35 MeV proton beam has been carried out with a 2D ionization chamber, LiF crystals, MOSFET, alanine and a PTW microdiamond. Short and long term stability as well as uniformity of the beam have been studied. The dosimeters have been irradiated in air with laterally spread pristine beam.

Results
A preliminary characterization of the proton beam was performed at 27 MeV at a repetition frequency of 10 Hz before mounting the fourth accelerating module. That study demonstrated uniformity of the beam within 4%, in a circular spot of 1.6 cm in diameter and short term stability of 5%. Since the operation the fourth structure improvements in the RF line have been introduced to enhance the beam stability by the installation of a new klystron/modulator system and the implementation of resonant frequency feedback control systems on the accelerating structures. A full study at the nominal energy of 35 MeV has been done, to evaluate the performances at this stage of the accelerator development for *in vitro* and *in vivo* radiobiology studies.

Conclusion
One of the peculiarities of the TOP-IMPLART accelerator is its intrinsic extensible modularity: it can deliver a usable beam during its construction. This permits an immediate characterization and virtually continuous improvement of its performances; moreover the unique (for hadrontherapy) pulsed structure of the beam requires a careful study of its therapeutic potentialities that can be performed by radiobiological studies at the low energies currently available, once the beam dosimetry is assessed. In this work, the time stability and uniformity of the beam at 27 and 35 MeV are presented.

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PP - 33

Dose-dependent DNA damage after ex-vivo irradiation of blood with radionuclides frequently used in Nuclear Medicine

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Introduction
Here report on our work on DNA double strand break (DSB) damage and dose relationship in blood leukocytes exposed to internal in solution irradiation with Ga-68, Y-90, Tc-99m and Ra-223, and correlate our findings with previous observations in the low dose range made with I-131 and Lu-177 [1], altogether the most frequently used radionuclides in Nuclear Medicine today.

Methods
Blood samples were exposed to Ga-68, Ra-223, Tc-99m or Y-90 in solution, followed by 1h incubation at 37°C. Activities of samples were determined with a calibrated germanium detector. The calculation of the ADBlood for β-/γ-emitters was based on simulation of energy deposition [2]. For Ra-223, ADBlood was calculated assuming local energy deposition of all non-penetrating particles of Ra and its progeny. Leukocytes were isolated, fixed and immunofluorescently stained for γ-H2AX+53BP1. Colocalizing γ-H2AX+53BP1 DSB foci and DNA damage tracks were counted in 100 cells per sample.

Results
We observed that the leukocytes irradiated with β-/γ-emitters showed randomly distributed small γ-H2AX+53BP1 DSB foci (Ø≤1.1µm), likely representing simple DNA double-strand breaks. Ra-223-irradiated cells in addition to small foci display α-induced DNA damage tracks and large foci (Ø>1.1µm) likely containing complex DNA damage. For Ga-68/Tc-99m/Y-90-irradiated samples, the number of radiation-induced foci (#RIF) was proportional to the absorbed dose to the blood (ADBlood) ranging from 0 to 108mGy, being in agreement with our previous results. For the Ra-223-irradiated samples, a linear relationship was only evident for the number of α-tracks and ADBlood (range: 0 to 142mGy).

Conclusion
In conclusion, there is a linear relationship for the # RIF to the ADBlood for β-/γ-emitters, while the number of γ-H2AX DNA damage tracks proves to be a suitable parameter for describing the dose-response relationship for α-emitters. Potential differences between different β-/γ-emitters are under further investigation. Our data may prove useful for biodosimetry approaches in accident and malevolent scenarious where radionuclides have been incoporated.

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Evaluation of inhomogeneous dose distribution in real cases- Different approaches

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Introduction
The aim of the biological dosimetry is to ensure the availability of reliable biological dosimeters to evaluate doses in different overexposure scenarios and different distribution of the dose in the body. The objective of the present work is to distinguish between homogeneity and inhomogeneity in dose distribution in real clinical and accidental cases, through different mathematical approaches

Methods
The intercellular distribution of the unstable chromosomal aberrations observed and their conformity with the Poisson distribution were analyzed using the Papworth u test, considering the dispersion and the variance/mean relationship, comparing such results with the data obtained using the exact method proposed by Fisher and with the frequency of zero using the exact test proposed by Rao and Chakravarti.

Results
Inhomogeneity can result from the differential absorption of radiation in soft tissues and bones. Also considering that only 3-5% of the total T lymphocytes of a healthy adult individual reside in peripheral blood, that the average residence time is around 20-30 min. and that most of the T lymphocytes are stored in lymphatic tissues and other organs, it is understood that the evaluations take into account irradiated and non-irradiated populations of T lymphocytes. This mixed population of irradiated and non-irradiated lymphocytes, which increase zero frequency, produces a distribution of aberrations that does not fit the Poisson distribution and that is generally overdispersed. Thus, could be evidenced using asymptotic or exact methods in the localized overexposures analyzed.

Conclusion
These methods would provide useful tools for treatment decisions both, in clinical applications and accidental overexposures, based on the distribution of aberrations evaluated.

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Characterization of phenolic solid state pellets for ESR dosimetry with radio-therapeutic photon and electron beams

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Introduction
Among the various dosimetric techniques used for characterizing the radiation beams used in radiation therapy, the electron spin resonance (ESR) arouses increasing interest for applications in various therapy procedures. In this work we report the ESR investigation of particular phenol compound (IRGANOX 1076) exposed to clinical photon and electron beams (Gallo et al., 2017).

Methods
Phenol (IRGANOX 1076 - Sigma Aldrich) pellets were produced also with paraffin (10% by weight). Phenol pellets were exposed to clinical photon and electron beams at various energies produced by a linear accelerator (LINAC) Siemens Primus (Siemens Medical Systems, CA, USA) installed at the Radiotherapy Department of A.R.N.A.S. – Hospital Civico-Di Cristina-Benfratelli (Palermo) with absorbed doses ranging between 0 and 13 Gy.

ESR measurements were performed through a X band Spectrometer. Readout parameters were optimized to maximise the signal without excessive spectrum distortions.

Results
Basic dosimetric properties of phenolic dosimeters, such as reproducibility, dose-response, sensitivity, linearity and dose rate dependence were investigated. A satisfactory intra-batch reproducibility of the ESR signal of the manufactured dosimeters was obtained. The analysis of the ESR signal as function of absorbed dose highlights that the response of this material is linear in the dose range investigated (1-13 Gy) and is independent of the beam energy.

The presence of an intrinsic background signal limits the minimum detectable dose to a value of approximately 0.6 Gy. Reliable and accurate assessment of the dose was achieved, independently of the dose rate. The dosimeters were tested by measuring the depth dose profile of a 6 MV photon beam.

Conclusion
Such characteristics, together with the fact that IRGANOX 1076® is almost tissue-equivalent, and the stability of the ESR signal, make these dosimeters promising materials for ESR dosimetric applications in radiotherapy.

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Biological and EPR dosimetry for emergency

PP - 36

Relaxation Time Measurements Using Pulse Electron Spin Resonance (ESR) in Tooth Enamel for Retrospective Biodosimetry

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Introduction
This study examines radiation-induced paramagnetic defects in the enamel layer of the human tooth using advanced pulse ESR methods, with the ultimate goal of applying these methods in retrospective biodosimetry (RBD). The main challenge for RBD is to quantify exposures to ionizing radiation in the dose range of 0.5–6 Gy, based only on monitoring their effects on the human body.[1,2]

Methods
In this work, we use advanced pulse ESR techniques in order to measure the relaxation time, T_2, related to spin-spin interaction. This parameter was measured as a function of radiation dose to characterize the relation between them. Our hypothesis is that this type of ESR data can be correlated well with the **concentration** of defects, and thus enable the development of new markers for *in-vivo* estimation of dose without the need for quantitative measurements of both the ESR signal and enamel volume.

Results
Despite its great potential, and its proven results when applied to extracted teeth, ESR is still struggling to provide accurate *in-vivo* readings. This is partly because all available ESR-based dosimetry methods rely on quantitative signal measurements in order to derive the concentration of radicals, and hence the dose received.[3,4] However, such quantitative measurements have an inherent limitation for *in-vivo* studies, since the volume of the measured enamel cannot be known *a priori*. A potential alternative to the quantitative method that may overcome these limitations could rely on other types of ESR properties, such as spectroscopic characteristics and/or relaxations that may be correlated with dose and would not depend on the tooth volume

Conclusion
In our initial experiments we worked with teeth irradiated with relatively high doses of 10-100 Gy that were used to develop the approach, which will be subsequently applied to measure relaxation times for samples irradiated with lower doses. Our measurements show relaxation times in the range of hundreds of nanosecond up to one microsecond

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The influence of the blood storage temperature and anticoagulant for cytogenetic biodosimetry

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Introduction
In a radiation accident, dicentric chromosome assay (DCA) can be used for dose estimation. More than 1000 metaphases are generally analyzed in DCA [1]. In order to obtain sufficient metaphases for the analysis, it is necessary to establish a suitable culture condition of lymphocytes. In this study, we examined the effect of temperature, term, and the type of anticoagulant for the blood storage.

Methods
Peripheral blood was collected in two anticoagulants; lithium heparin and EDTA-2K, from 5 healthy donors. After the irradiation of whole blood with 0 or 3 Gy X-ray, half of the samples were stored at room temperature (20.3 ± 0.1°C) while the other half in the refrigerator (5.2 ± 1.0°C). At 6, 24, 48, 72, and 168-h storage, the lymphocytes were cultured by a standard technique [1]. After harvesting, mitotic index (MI) was determined. A fully automated hematology analyzer was used for blood count. Then, blood coagulation was identified with May-Grünwald Giemsa-stained blood smears.

Results
In heparinized bloods stored in the cold condition, white blood cell (WBC), lymphocyte, and neutrophil counts were decreased with increasing storage time irrespective of irradiation. A significant decrease of platelet count was observed in heparin blood stored at 4°C. However, EDTA blood did not show obvious blood count changes. In the case of 6-h storage, MI was ranged between 20-30% in heparinized blood samples irradiated at 0 Gy and 3 Gy respectively. This phenomenon was similar in the EDTA-washing blood until 72-h storage time. After 168-h storage at room temperature, metaphase could not be obtained from some donors" heparinized blood cultures. Interestingly, metaphase can be seen in all donors in 4°C-stored EDTA-washing blood in all donors whether irradiated or not.

Conclusion
In this study, we confirmed heparinized blood samples for chromosome analysis should be stored or transported at room temperature before the cell culture. On the other hand, 4°C-stored EDTA-washing blood showed higher MI than some cases of 4°C-stored heparinized blood due to suppression of blood coagulation in EDTA blood. This result indicates that 4°C-stored EDTA blood after washing can be used for chromosome analysis in biodosimetry when blood samples are stored or shipped for a long time.

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The effect of sunlight and cosmetic UV lamp on EPR signal in nails

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Introduction
EPR signals in nails can originate from native paramagnetic centers present in the nails" matter and from free radicals induced by physical factors: mechanical stress (e.g. caused by cutting the clippings) and by ionizing radiation [1-3]. All those signals measured in X-band after their stabilization at room temperature overlap. In this work we show that also light generates similar EPR signals.

Methods
Nail clippings were illuminated by direct sunlight (about 90 000 lx) and by 36 W regular UV lamp commonly used nowadays in nail salons for hybrid nail polishing. Some of the samples were illuminated through glass plate, thus reducing short-wave spectral components of the light. EPR signals in these samples were measured in 30 days following the illumination.

Results
A few minutes of exposure of the clippings to sunlight generated strong EPR signal similar to the other signals observable in nails. This effect was similar in clippings not exposed to ionizing radiation as well as in those exposed to 20 Gy of X-rays prior to the sunlight illumination. The amplitude of this light-induced (LI) signal saturated with time of illumination after about 20 minutes. Similar effect was observed in nails illuminated by the UV lamp. The amplitude of the LI signal was the same in clippings illuminated by the UV lamp directly as through 1 mm glass. The signal induced by sunlight was stable within one week after illumination and decayed after 10 minutes of water treatment.

Conclusion
The similar magnitude of LI signal induced by direct UV lamp radiation as through the applied glass plate suggests, that the effect can be attributed rather to long-wave UV and/or to visible light. It is concluded, that the LI signals can affect measurements of the dosimetric signal, thus contributing to overall uncertainty of EPR dosimetry, particularly, if the nails were measured within couple of days after their illumination.

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PP - 39

The project of another low-cost metaphase finder (Second Report)

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Introduction
Biological dosimetry is used to estimate one's dose by biological phenomena. The most popular and "gold standard" phenomenon is the appearance of dicentric chromosomes in metaphase. The metaphase finder is a tool for biological dosimetry that finds metaphase cells on slide glasses. The author and a software company have made new system, and are now preparing for producing the system commercially.

Methods
The metaphase finder consists of an automated microscope, auto-focus system, X-Y stage, camera, and computer. We used a Nikon Eclipse Ni-E microscope with motorized X-Y stage, 4x objective lens and 1920x1024 pixels color camera for hardware. The software uses mathematical morphology filters, and the new function to compare the color of the image. The new system was compact and low-priced. And the remarkable point is, this system can applicable for not only human blood, but also non-human samples. We also tested 10x objective lens and 3328x2496 pixels camera for speed-up.

Results
We have tested the speed and False-Positives of scanning 5 x 20 mm area of each of 10 slides. The speed was 208 to 236 seconds per slide, and False-Positive rate were 2.7 to 50.0 %. Some slides showed higher False-Positive rate, but they had problems in the slide making method. The 3328x2496 pixels camera has shown almost same image size and quality of 1920x1024 pixels camera, but for wider area.

Conclusion
The metaphase finder system"s speed and accuracy were completed. The 3328x2496 pixels camera enabled to speed-up. This accomplished the aim of the project. The next goals are to implement a new automated dicentric counter and then obtain a dose-response relationship by the new dicentric counter.

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Machine learning approach to assessment of the native background EPR signal amplitude in tooth enamel

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Introduction
The measurement of teeth in the mouth, without extraction with EPR spectroscopy in the L-band is a promising method that potentially would allow screening large groups of population in an event of an acute radiation exposure and in routine epidemiological studies. The radiation-induced signal amplitude is determined after subtraction of solar light induced and native signal amplitude (NSA).

Methods
For L-band measurements NSA is overlapped with the solar and radiation signals, but it can be assessed for the spectra recorded in X-band [1]. In our work, we conducted a search for the optimal machine learning approach for prediction of NSA. Overall, nine most popular predictive models were developed and trained using standard Python frameworks for machine learning and data processing. These approaches were applied to the dataset composed of 1200 of the EPR spectra that were recorded in the X-band at a large-scale examination of the population of the Central Russia and North Kazakhstan.

Results
To tune the performance of each model a 3-fold cross-validation on the train set was used. Finally, root mean squared error and coefficient of determination on a test dataset were calculated and averaged over 10 different train-test splits with various random numbers. For the coefficient of determination the mean performance of all employed models assessed on the test set varied in the 6.1-11.1% range. The averaged root mean squared error values were between 180.8 and 183.4 mGy which are up to 11 mGy better comparing to the values given by a baseline regressor that always predicts the mean of the training targets.

For the best models, the three most significant factors regarding the prediction were: tooth position, age of tooth and district of residence of a donor.

Conclusion
It is shown that the application of machine learning methods could noticeably improve the accuracy of NSA prediction. Two ensemble models, namely Random Forest and Gradient Boosting outperformed the others and can be considered the best candidates for NSA prediction.

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Cytogenetic biodosimetry of plutonium radiation-exposed workers

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Introduction
On June 6, 2017, five workers were accidentally exposed to Pu-239 when they were inspecting a storage container of nuclear fuel materials at the Plutonium Fuel Research Facility of Japan Atomic Energy Agency (JAEA) (Oarai, Ibaraki, Japan). Their initial internal contamination measured with a lung monitor at JAEA indicated 22,000 Bq of Pu-239 and 220 Bq of Am-241 at maximum.

Methods
The first injection of chelating agent was carried out at JAEA. The National Institute of Radiological Sciences (NIRS) (Chiba, Japan) received all five workers to conduct dose assessments and continuous treatment about 24 hours after the accident. At the NIRS hospital, the workers" skin was thoroughly decontaminated. Then, biological dosimetry by dicentric chromosome assay (DCA) [1)] and fluorescence in situ hybridization analysis using three differentially colored chromosome painting probes (3-color FISH) [2)] were conducted in the course of health examinations.

Results
Two days after the blood collection, the first report of DCA results by triage-mode scoring (0 dicentric/100 cells for all the workers) was successfully provided to the doctors-in-charge. The chromosome aberration yields observed by DCA in the full-scoring mode and 3-color FISH were at a background level, suggesting that there was little possibility of severe whole-body overexposure to acute radiation. The results corroborate the fact that Pu-239 was not detected with a lung monitor by NIRS measurement and no acute radiation syndrome was observed among the workers.

Conclusion
Cytogenetic biodosimetry was confirmed to be a powerful tool for providing helpful information for medical diagnosis in radiation emergency medicine.

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Baboon radiation quality (mixed field neutron and gamma, gamma alone) dose-response model systems: Assessment of H-ARS severity using hematologic biomarkers

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Introduction
Early-phase blood cell counts have been reported to predict hematology - acute radiation syndrome (H-ARS) severity using human data (Port et al. 2017). The need exists to develop biodosimetry tools for exposure to mixed radiation fields (i.e., neutron and gamma). We report the use of the baboon model as a relevant animal model system for validating biodosimetry tools for mixed radiation fields.

Methods
Data from archived files of experiments performed between 1986 and 1996 were acquired to establish a baboon radiation quality dose-response database with hematology and blood chemistry biomarkers time course data following exposure to mixed fields (i.e., neutron to gamma ratio: 5.5; dose: 0, 2, 4, 5, 6, and 8 Gy: n = 35). Results from studies involving gamma ray exposure included doses of 2, 4, 6, and 8 Gy (n = 12). Baseline data for relevant hematology blood counts were determined from 164 animals from previous studies.

Results
Time course hematology changes for relevant blood cell types will be shown following exposure to both mixed field (neutron to gamma ratio 5.5) and gamma rays alone. These data form the basis for scoring of H-ARS, similar to that earlier report by Port et al (2016). Planned next steps are to split the animal cohort into calibration and validation groups and to use the calibration group to develop multivariate algorithms to predict in the early-phase (<7d) H-ARS severity, and the independent validation group to test the algorithm, similar to that previously reported by Bolduc et al. 2017. In addition, efforts will be taken to also develop multivariate algorithms to predict radiation dose in the early-phase (<7d).

Conclusion
Validation of the use of early-phase hematology biomarkers to assess radiation injury and dose following exposure to mixed field (i.e., neutron and gamma) radiation using the baboon model system can provide critical scientific confirmation of use of this approach in current medical response plans. The views expressed in this abstract are those of the authors and do not necessarily reflect the official policy or position of the AFRRI, USUHS, DOD nor the U.S. Government. Funding support provided by AFRRI RBB43523 and RBB44313.

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Evaluation of the influence from difference of tooth shape and relevant calibration method in X-band EPR in vivo Tooth dosimetry

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Introduction
In the application of in vivo tooth dosimetry by X-band EPR, the shape difference of tooth from different subjects has remarkable impact on the accuracy and reliability of the measured dose. We propose an evaluation and calibration method dealing with this problem by taking the section profile of interested incisor in order to make correction for the dose estimation.

Methods
firstly, measure the incisor"s dimensions and relative position inside the aperture of EPR cavity based on a tooth modeling process and digital photography technique therefore to figure out relatively accurate model of the shape and volume of tooth from different subjects; then, calculate the detection sensitivity distribution over the area of cavity aperture. In this way, a weighted calibration method of volume and shape corresponding to relevant sensitive position could be got by combining the results of the above two steps thus a more reasonable dose evaluation result could be obtained.

Results
Experiments on a group of incisors with different shapes were carried out on an X-band in vivo EPR apparatus developed in our lab to verify the feasibility of the method. Comparing the dose response features between before and after calibration process,the correlation coefficient of dose response curve was improved by about 40% after the correction.

Conclusion
The result suggests that reasonable and efficient improvement to the accuracy of estimated dose could be obtained by this method.

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References

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The Dose-Response Calibration Curve for Cytogenetic Biodosimetry in Saudi Arabia and its Application in Cases of Radiological Emergency

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Introduction
The dicentric chromosomal aberrations (DCA) assay is a proven, IAEA and ISO standardized cytogenetic biodosimetry technique for assessing medically relevant radiation doses received. We aimed at establishing a reference biological dosimetry laboratory to help the National Radiation Emergency Preparedness Plan to respond to sporadic and mass radiation casualty incidents.

Methods
Peripheral blood lymphocytes were collected from healthy volunteers and irradiated with different doses ranging from 0 to 5 Gy of 320 KeV X-Rays. Giemsa stained cytogenetic slides were prepared from phytohemagglutinin stimulated lymphocytes according to the IAEA protocol. The Metafer4 system (MetaSystem, Germany) was used for automatic metaphase finding and assisted scoring of dicentric chromosomes. Data points were fit to the linear-quadratic dose-effect model ($Y = C + \alpha D + \beta D^2$) and have been used to estimate doses received in suspected radiation exposures.

Results
The manually assisted dose–response calibration curve ($Y = - 0.0017 + 0.026 \times D + 0.081 \times D^2$) was in range of those described in other populations. The Metafer4 automated scoring over-and-under estimates DCA at low (< 1 Gy) and high (> 2 Gy) doses, respectively. However, it showed potential for use in triage mode to segregate between victims with potential risk (> 1 Gy) to develop acute radiotoxicity syndromes who would require immediate medical attention. The applications of curve"s coefficients allowed the estimation of radiation doses received in accidental radiation exposures in non-radiation workers. The various activities of the biodosimetry laboratory offer a platform for advanced education, research and development.

Conclusion
The established laboratory is the first in the Middle-East and became member of IAEA and WHO international biodosimetry networks. It provided invaluable information in cases of suspected radiological exposure for decision-makers and health officials. Currently, we are expanding techniques to micronuclei and gamma-H2AX. Further development will include irradiation using gamma rays, protons and neutrons. Supported by Operational Transformation Initiatives #31, titled "Integrated Biomedical Physics Center: Delivery of Precision Radiation Medicine", (RAC# 2170 005).

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Reconstruction of low dose electron spin resonance (ESR) response in soda-lime glasses

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Introduction

ESR response of g irradiated soda-lime glass in low dose range were studied for retrospective dosimetry goals [1]. In this range overlapping of background signal (BKS) with radiation induced signal (RIS) inhibit dose reconstruction. Use of combination of the intensities and areas below the ESR curve and *g* shifts of RIS and BKS, was found useful for improving detection limit.

Methods

The commercially available transparent soda lime float glass samples were acquired on retail market. The samples were irradiated at a dose rate of 0.6 Gy/min. Electron spin resonance (ESR) measurements were performed on all samples using Varian E-9 spectrometer equipped with Bruker ER 041 XG microwave bridge working at X-band (ν_{mw}=9.5 GHz). A standard Bruker ER 4111 VT temperature controller with a nitrogen gas flow was used to control the temperature within 1 °C. A manganese standard reference, Mn^{2+} in MgO was used. Measurements were performed at least 2 hours after irradiation.

Results

Dose reconstruction in low dose regime where RIS and BKS signals are overlapped were studied [2,3]. Correlation of the increment of area below the ESR response curve with the increments of *g* shifts and RIS intensities as function of dose, were examined. The results showed very low increment of the RIS intensity with the dose, while increments of the areas below the ESR curve and *g* shifts show comparable behaviour in the dose range from 0 - 10 Gy. RIS intensity and *g* shifts dependences on dose indicate much lower dispersion than the area below the ESR response curve. The obtained data indicate that BKS contributions is significantly higher in RIS intensities than in ESR area dose dependence curve.

Conclusion

Combination of information on shifted *g*-values of the RIS and BKS intensities, RIS intensities and areas below the ESR curve dependences, as a function of dose, improves accuracy of the low dose detection. The greatest advantage of the information on the *g* shift is that it is least influenced by the BKS. Results indicate that RIS intensity is mostly influenced by the BKS in the low dose regime whilst areas give information on the low dose with significantly lower influence on the BKS. But on the other hand, the area data are quite dispersed.

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Optimization of Image Selection in Automated Dicentric Chromosome Analysis

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Introduction
The dicentric chromosome (DC) assay is a standard approach to estimate radiation exposure, however manual identification of DCs remains a bottleneck. We developed software to automate DC detection and dose estimation.[1] Dose accuracy relies on metaphase image selection, which depends on thresholding and sorting images.[2] Finding optimal image processing models for image selection is challenging.

Methods
We introduce and validate a framework to find the best image selection models. After each model is applied, an evaluation method determines its quality based on DC detection. Evaluation methods include the Poisson goodness-of-fit for each sample, residuals after calibration curve fitting, and leave-one-out dose estimation errors. Optimal models exhibit the minimum evaluation scores. The process iteratively searches a pool of image selection model candidates, ranking the best candidates according their scores. The candidate pool parameters can be extended until satisfactory models are found.

Results
This method provides an efficient and practical approach to obtain optimal images for dose estimation. The search process requires less than a few hours, depending on the configuration and hardware. The evaluation score of the optimal model, for example when curve fit residual is used, is minimized to 0.0475 Gy^2, compared to 1.1975 Gy^2 without image selection, indicating a highly precise curve.

Conclusion
Although over-fitting to evaluation samples and limitations of the current evaluation methods may sometimes produce less than optimal models, automated optimization provides relief from manual, heuristic image selection, thereby significantly improving the overall accuracy of the dose estimation software.

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Approach on combining imaging flow cytometry with high-throughput automated robotic systems for measuring radiation biomarkers

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Introduction
Cytokinesis-block micronucleus (CBMN) and γ-H2AX are validated radiation biomarkers in peripheral blood lymphocytes[1,2]. At the Center for High Throughput Minimally Invasive Radiation Biodosimetry at Columbia University, we have made progress on integrating an imaging flow cytometry system ImageStream$^{®X}$ (ISX) into the Rapid Automated Biodosimetry Tool (RABiT-II) for the CBMN and γ-H2AX assays.

Methods
Human peripheral whole blood samples were irradiated *ex vivo* with γ-rays up to 5 Gy. For the CBMN assay, cells were cultured and harvested after 68h using the RABiT-II Perkin Elmer cell::explorer sample preparation work station. For the γ-H2AX assay, whole blood cells were cultured for 0.5h, labeled following manual lysing and fixing in the 96-well plate format which is compatible with the RABiT-II system. Fixed samples were automatically imaged on the ISX. Micronuclei (MNi), binucleate cells (BNCs) and γ-H2AX yields were identified and quantified using IDEAS® software[3,4,5].

Results
CBMN and γ-H2AX assay protocols for imaging flow cytometry were optimized in a 96-well format (using 20-100µL of whole blood) for use on the RABiT-II system. MNi frequency acquired by imaging flow cytometry demonstrated a linear-quadratic function of dose after exposures up to 5 Gy. A dose response curve was generated for the number of γ-H2AX foci and the total fluorescence in the peripheral blood lymphocytes population following exposure up to 5 Gy. We have recently achieved end to end automation of CBMN assay from sample preparation on the RABiT-II to imaging and analysis by the ISX system.

Conclusion
Approaches for evaluation of MNi yields and γ-H2AX expression combining the imaging flow cytometry system and biotech robotic systems increased the throughput of the measurement and allowed for a reduction in the volume of blood required compared with traditional protocols. These results indicate that a novel, imaging flow cytometry system can be integrated into our RABiT-II automated system and provide high-throughput biodosimetric screening for use in large-scale radiological incidents.

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Developement of an image-processing based sample quality index for non-fluorescent micronucleus assay which offers extended robustness feature for automated scoring

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Introduction
Following carefully the IAEA protocols on the sample preparation process of cytokinesis-blocked micronucleus assay (CBMN) can be harmonized to a high extent. Despite of all the applied precision there are uncontrollable factors (e.g. varying levels of biological stress) that influence the visual features of the cells from slide to slide by the point of view of automatic image processing.

Methods
In our study we created a program which evaluates a set of sample features from images collected during the automatic scanning and scoring of CBMN slides. These parameters describes the following characteristics: size of cells, contrast and intensity of staining, number of MN-like artefacts, purity and cytoplasm texture.

The automatic slide scanning and scoring was conducted by Radosys MN-series© system which consists of the slide auto-feeder, dedicated automated microscope and image processing software. The add-in interactive control was used for the evaluation of detection efficiency.

Results
In order to define the acceptable limits of the designed indices, firstly, a preliminary automatic analysis of the samples were conducted and its detection efficiency was determined. Then a slightly modified re-dripping of the same sample was performed. The alteration was either an extra cleaning step or the changing of the conditions of the sample storage or the surface treatment of the slide. Finally we calculated the sample quality and scorer efficiency indices again and compared them with the original ones.
We found that with a proper re-dripping technique the subsequent changes in the geometrical and staining characteristics of the cells can be beneficially adjusted to obtain more accurate automatic scoring results. The improvement of MN detection rate can reach 25% at 2Gy.

Conclusion
The proposed technique contributes to the achievement of robust (e.g. laboratory and cell vulnerability independent) evaluation procedure by assuring the comparability of results obtained from blood samples whose behaviour for the same assay protocol differs. It has great importance handling low doses and fragile cells (e.g. RT patients) due to their poor signal to noise ratio.

The majority of the proposed parameters are not specific to the CBMN or the applied image processing algorithm so it offers the potential to extend this concept to other non-fluorescent cytogenetic imaging assays.

References

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A comparison of different spectra deconvolution methods used in EPR dosimetry with Gorilla® glasses

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Introduction
Interpretation of EPR spectra observed in samples of Gorilla® glass (GG) is not trivial due to large variability in both spectra shape and intensity. Several overlapped EPR signals may contribute to the cumulative signal of GG samples making questionable accurate dose reconstruction with this material. Two existing spectra deconvolution methods were compared in the present work on samples of GG.

Methods
GG samples were collected from smartphones of different brands and models as well as purchased from on-line vendors. Some aliquots of each sample were exposed to different doses with a 90***Sr***/Y beta source; these aliquots were used to construct dose response curves. Other aliquots of samples were exposed to 10 Gy dose, which simulates the emergency exposure. EPR spectra were recorded on a Bruker EMX spectrometer. Two different methods (Sholom and McKeever, 2017; Wieser et al., 2016) were used to deconvolve EPR spectra and reconstruct the simulation doses.

Results
The different sets of the reference spectra were developed for two above methods. The matrix method (Sholom and McKeever, 2017) used a combination of 5 reference spectra while the method proposed in Wieser et al., 2016 exploited a set of 7 reference EPR signals. Both sets included some numbers of reference signals for electron centers (which have g-factor <2.0023) as well as some number of such signals for hole centers (with g-factor >2.0023). It was observed that both methods of spectra deconvolution demonstrated more accurate results for samples with more pronounced EPR response in the region corresponding to hole centers. Accuracy of dose reconstruction was low for samples with a strong zero-dose electron-based EPR signal.

Conclusion
More research is required to identify and isolate different EPR centers that can be found in different samples of GG. Special attention should be paid to the samples with strong zero-dose signals, which at the present time cannot be used for dose reconstruction with an EPR technique.

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Non-Resonant ESR for Fast and Reliable Retrospective Personal Dosimetry

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Introduction
Rapid retrospective personal dosimetry is the only viable option to effectively sort through large populations to identify individuals in immediate need of medical countermeasures in the case of a nuclear exposure mass casualty event. Mass casualty retrospective dosimetry efforts have thus far had limited success due to inherent material or environmental variabilities, cost and logistical issues.

Methods
A non-resonant ESR-based sensor detects the gamma response of alanine embedded in an identification card (dosimeter) using a microstrip transmission-line interface, a highly sensitive microwave bridge circuit [1], and a compact permanent magnet apparatus. The sensor interface accepts an identification card between the signal line and ground plane of the microwave transmission line. Upon insertion, the X-band microwave bridge is rapidly tuned and the magnetic field is swept to detect the central peak in the alanine ESR spectrum. Dose is derived via comparison with a calibrated card.

Results
We detail a deployable sensor which rapidly derives a retrospective dose from an identification card dosimeter. Sensitivities of 2 ± 0.5 Gy in less than 2 minutes are demonstrated. The cumulative nature of alanine dosimeters also allows for additional periodic dose assessments following the event. The system utilizes permanent magnets and sweep coils to allow for a compact point of care system with low power consumption. Interaction with the ESR-based sensor is akin to an automated teller machine and is suitable for interactions with the general public without intervention from trained medical staff. Collectively, this approach enables a timely and efficient emergency medical response and supports the additional clinical and laboratory screening and triage for those most in need.

Conclusion
Rapid and reliable sorting of individuals in the aftermath of a nuclear event can be accomplished by using alanine-based identification card dosimeters and a highly sensitive compact non-resonant ESR sensor. This system allows for rapid, accurate, and reliable detection of 2 ± 0.5 Gy within 2 min. This approach is an extremely effective and rapid method to separate those most in need of medical countermeasures from the considerably larger population.

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Design and realization of an open EPR resonator at X-Band frequencies

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Introduction
In X-band EPR spectrometry, the resonator dimensions need the sample to be reduced in small pieces. Starting from the experience gained in the scientific literature, this work aims at designing a pinhole cavity for measurements of intact samples. The original aspect is that the cavity is designed to be easily adaptable to commercial spectrometers.

Methods
A TE111 cavity was designed and manufactured. The cavity was designed so as to achieve, at the sample position outside the cavity, the maximum magnetic field and the minimum electric field. *Ad-hoc* modulation coils were realized. In order to use the spectrometer modulation field source, an adaptive tuning circuit and a power amplifier were designed to adapt the coils. The cavity was specially designed not to alter the homogeneity of the modulation field distribution. Samples of DPPH, mineral glass, tooth enamel and alanine at different doses were measured.

Results
Measurements performed in brass and silver-coated brass customized cavities and in a conventional cavity will be reported. The dependence of the EPR signal on microwave power and modulation amplitude will be reported so as to compare the characteristics of the three cavities between them and with the calculated values. The curves of the signal intensity as a function of the modulation amplitude were similar, demonstrating that the modulation field intensity and homogeneity was reproduced with the *ad hoc* modulation coils. The dependence of the signal intensity on microwave power reflected the calculated Q-factors (brass cavity Q=5822, silver-plated cavity Q=10781).

Conclusion
A customized cavity, based on the pinhole principle, was desi*g*ned and manufactured with the aim to perform X-band EPR non destructive measurements of the sample. The cavity comes with an *ad hoc* modulation coils system (adaptive tuning circuit and power amplifier), so that it can be easily used on commercial spectrometers.

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Rapid Gene Expression Based Dose Estimation for Radiological Emergencies

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Introduction
Efforts are made to develop new methods which can provide rapid individual dose estimates with high sample throughput in case of a large-scale acute radiation exposure. Gene expression based assays have shown great potential. The purpose of this study was to optimize a protocol developed in our laboratory (1, 2, 3, 4, 5) in case of radiological emergency to provide quick estimates.

Methods
Blood from 4 donors was collected and divided into 2 groups, themselves separated into 4 sub-groups according to the dose, respectively 0, 0.5, 1, and 2 Gy. After X-Rays irradiation, tubes were placed at 37°C for 24 hours, and then samples were frozen at -80 °C with RNA later/phenol depending on the protocol. Protocol 1 (P1, validated) and Protocol 2 (P2, new), includes different RNA isolation and purification, reverse transcription, and qPCR steps. 5 genes (FDXR, P21, PHPT1, CCNG1, SESN1) previously identified as radiation-responsive in blood at the transcriptional levels were examined.

Results
The two gene expression protocols contained substantial differences with each other. P1 required 7 hours to be completed while the newly developed P2 provided a significant reduction in time with dose estimations obtained in less than 4 hours for one sample. RNA quality was comparable between P1 and P2 (p value=0.133). RNA extraction and purification was performed in 3h 12 min (P1) and 2h 30 min (P2). The reverse transcription was shortening from 2h (P1) to 20 min (P2). Lastly, qPCR step required 1h 51 min (P1) and 1h 17 min (P2). For FDXR, the fold of changes were respectively 9.4 and 9.2 at 0.5 Gy, 13.9 and 13.4 at 1 Gy, 24.9 and 19.3 at 2 Gy for P1 and P2.

Conclusion
Overall, the new protocol provided blood doses estimates with a substantial reduction in time (3 hours) without statistical significant differences in RNA quality or qPCR results. Thus, our new protocol would allow more samples to be analyzed per day and should be recommended for rapid expression based dose estimation in case of radiological emergences.

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The Automation of γ-H2AX Assay for the Rapid Triage of Biological Dose Estimates in Large Scale Radiological/Nuclear Events

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Introduction
Biological Dosimetry plays a key role in the medical management of patients for treatment following accidental radiation exposure. In the case of a mass casualty radiological or nuclear incident where hundreds to thousands of people would require biological dose assessment, rapid triage of these patients will be of utmost importance to produce dose estimations as quickly as possible.

Methods
In the hours to days post-event, dose assessment can be made quickly by using the H2AX phosphorylation assay (γH2AX). In this study, we developed an automated method for processing and analysis of the γH2AX assay for rapid triage. Samples were prepared by lyse/fix method, as described by Moquet et al (1), then processed using an ImageStream®X Mark II Imaging Flow Cytometer (IFC) and analysed with IDEAS® software. A dose response curve was developed using whole blood from 6 donors, at dose points between 0 and 5 Gy, then tested to produce triage dose estimations at unknown blinded doses.

Results
The H2AX histone becomes phosphorylated at the site of DNA double strand breaks which can then be quantified with a fluorochrome-labelled antibody. The kinetics of the γH2AX response to radiation damage is well documented, visible from minutes to three days post exposure, reaching a maximum signal at one to two hours. There are currently two well-established methods for γH2AX analysis; foci counting by microscopy and whole cell fluorescence intensity as measured by traditional flow cytometry. The benefit of the IFC is that it combines spot counting, for the sensitivity and specificity of microscopy, while adding the greater throughput and statistical power of flow cytometry. Here, we are testing whether the γH2AX assay can be used to achieve triage dose estimations up to 24 hours past exposure.

Conclusion
This method can be used to quickly and easily identify patients who have received radiation exposure doses that require immediate medical attention during a large scale event. This is useful in a large scale emergency where logistics and numbers of casualties will cause significant challenges to acquiring blood to begin analysis. It can greatly reduce the efforts of a biological dosimetry laboratory by providing early triage information in order to replace other standard biodosimetry methods for no or low dose samples during initial days post-accident.

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EPR dosimetry on human fingernails: study of the endogenous signal variability

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Introduction
Human fingernails have been studied for years by means of Electron Paramagnetic Resonance (EPR) to develop a new dosimetric technique for radiological accidents. Practical and robust dosimetric protocol has not been yet developed. One of the major obstacles for this is a presence of so-called endogenous signal with the same spectral characteristics than the radio-induced signal.

Methods
EPR measurements were carried out in Q-band. Fingernails samples were collected from 30 different donors of various origins. At first, a study on endogenous signal variability for different donors and fingers was done. Then, effect of additional factors such as effect of the water treatment, temperature, UV light exposure was also studied. Nature of the radicals responsible for the observed (endogenous) signal was examined by using chemical reactions (acid-base and redox) and numerical simulations (Easyspin).

Results
Endogenous signal intensity varied for different donors up to 300 % with dispersion of 60 %. For the same donor, it varies for different fingers up to 11 %. Harvesting period also has some effect on the signal intensity, i.e. up to 20%. Sunlight exposure and especially UVA induces a signal with the similar spectral characteristics as the endogenous signal. Water also impacts EPR signal intensity and it may help facilitate a reduction reaction with an endogenous reductant in the nail. Hypothesis that endogenous signal is originated from an o-semiquinone anion radicals is strongly supported by chemical experiments and numerical simulations.

Conclusion
Endogenous signal is a real problem to the use of a universal EPR radio-induced signal intensity standards curve for calibrating the radio-induced signal and absorbed dose in the nail for any victim since it overlaps with radio-induced signal of interest. More investigations are needed in order to discriminate these signals, such as the recent results that make use of a combination of numerical and chemical treatments to discriminate between the two signals.

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A new way of processing spectra with an application to EPR fingernails bio-dosimetry

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Introduction
Human fingernails and toenails have been studied with Electron Paramagnetic Resonance (EPR) spectroscopy to provide a novel estimate of ionizing radiation doses. Laboratories commonly process EPR spectra manually using the manufacturer's software. We present a novel approach to EPR spectra data processing that both reduces uncertainties and operator dependence, opening the way to standardization.

Methods
Chebfun polynomial data interpolation paradigm was successfully applied to EPR imaging (cf. literature); we adapted the approach to dosimetry, especially denoising. We simulated radio-induced EPR signal on fingernails using Easyspin Matlab toolbox, adding experimentally faithful noise. By comparing the residual polynomial's distribution with that of experimental noise, optimal spectrum denoising by low pass filtering was achieved. We also demonstrate how Chebfun facilitates spectra manipulation and extraction of the usual EPR parameters. The theoretical approach is presented in another talk.

Results
First, noise generated by spectrometer has been fully characterized. It follows a specific Gaussian distribution N (μ, √μ); this noise model was then used in simulated spectra. The latter were denoised by low pass filtering with different frequency thresholds. The best one was determined by comparing denoised spectra with the original ones, thanks to a preliminary representation of data as a chebfun, a polynomial interpolant made practical with the Chebfun Matlab Toolbox. The Chebfun paradigm also made it possible to represent data sets as simple functions simple to operate upon compared to bulky vectors. Extracting the EPR parameters of interest such as peak to peak amplitude, intensity or obtaining absorption spectrum or second harmonic is much easier and also instantaneous.

Conclusion
We have shown that using Chebfun together with the denoising process brings major benefits for extracting quantities of interest in EPR. For dosimetry purposes, it is urgent to generalize the use of this procedure to improve dose estimation. Indeed, most protocols are based on determining the peak to peak amplitude of the radio-induced signal. Furthermore, contrary to the usual error prone manual processing, this chebfun augmented approach is less time consuming and operator independent.

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D.RE.A.M.: A software for uncertainties analysis in retrospective dosimetry

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Introduction
Accidental exposures to ionising radiations are nowadays managed with assistance from biological and physical retrospective dosimetry which are able to provide individual estimates of dose absorbed by victims. The aim of this work is to describe the development of biodosimetry analysis software within the "EURADOS Working Group 10—Retrospective dosimetry" Task group 10.6.

Methods
The software has been developed in Python code language that is easy to learn, read, use and extensible (it is possible to add new modules). It can implement C/C++/Fortran, Java functions. It is embeddable in applications and is open source. It is extremely portable to Unix/Linux, Windows, Mac operating systems. The memory management is automatic.
The software uses many free scientific python packages (such as numpy, scipy and sympy) and has a user-friendly graphical user interface.

Results
The software developed was named "Dose REconstruction by Analytical and Monte carlo methods" (D.RE.A.M.) and enables performance of uncertainties analyses though various mathematical methods. In particular, it facilitates:

Analytical calculation of combined standard uncertainties Monte Carlo estimation of combined uncertainties

Dose reconstruction from least square calibration curves by
1) analytical inversion of the calibration curve function
2) Monte Carlo calculation

Dose reconstruction with using Bayesian Method (Markov Chain Monte Carlo Method). This last analysis is still under validation process. After complete validation process this software will be freely available for everybody and will guide the user to the requested results.

Conclusion
The above-mentioned features of the D.RE.A.M. software provide a useful and promising toolkit for uncertainty analysis, helping biodosimetry practitioners carry out effective and accurate uncertainty assessment. Further methods can be added according to the developing needs of the community. In future such software could facilitate easier communication between scientists with different backgrounds (such as biologists and physicists).

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French armed forces biodosimetry lab

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Introduction
Armed Forces Biomedical Research Institute The Radiation Biological Dosimetry Laboratory (?LDBI? in French) was created in 2008 by the French Military Medical Service to complete their physical dosimetry capabilities and to increase the national biodosimetry resources in the event of a nuclear or radiological incident.

Methods
Inside the French Armed Forces Biomedical Research Institute (?IRBA? in French) this lab has a continuous evolution of its expertise with the participation in different research projects and scientific collaborations. Here, a summary of the different research activities of this lab will be presented.

For dose estimation, the LDBI uses the standard cytogenetic techniques recommended by the International Atomic Energy Agency and is involved in inter-comparisons of several dosimetry networks.

Results
For exposures supposedly months (or even years) old, the Fluorescence in situ Hybridization assay (FISH) with whole chromosome painting is used to score translocations. These aberrations are relatively stable in time but their frequency may vary with lifestyle. To make sure we have reference background values adapted to our specific population of interest we are currently analyzing samples from 120 individuals from the French MOD to determine if different activities (?office? or ?field? work) influence translocation frequency. At the LDBI we are interested in improving triage and diagnosis of ionizing radiation exposure victims.

Conclusion
The ability to discriminate total-body and heterogenous exposures is extremely important as they will lead to different clinical outcomes and therefore require different treatments. An important past study of ours involved the search of biomarkers that can give relevant information for clinical prognostics after an ionizing radiation exposure. A project involving a Non-Human Primate irradiation model (n=18) allowed for the identification of several biomarkers useful for the distinction of partial from total exposures.

References
To validate these results a clinical study with 20 radiotherapy patients has started.

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The second harmonic detection for *in vivo* tooth dosimetry using electron paramagnetic resonance spectrometer developed at SNU

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Introduction
In situations of massive radiation emergencies, triage for screening victims by the level of exposed dose is critical to mitigate the impact [1]. We developed a novel EPR spectrometer operating at 1.15 GHz for this purpose. The second harmonic method known for advantages in dosimetric purpose was applied for detecting radiation-induced-signals from the whole tooth [2].

Methods
Spectra were recorded with a newly developed novel EPR spectrometer. The surface coil resonator was used to measure spectra from the enamel of whole human tooth. Tooth samples irradiated by x-ray beam of 320 kVp were investigated. The second harmonic of the field modulated EPR signal out-of-phase was recorded from the whole tooth. A 15N-PDT sample was measured with the tooth as a reference. The amount of exposed radiation dose was estimated and dose response curve was acquired. The results of measured spectra was compared with those of first harmonic signal.

Results
The second harmonic EPR spectra, as well as the first harmonic signal, could be recorded from the whole tooth. The amplitude of second harmonic signal was small compared to that of first harmonic. Microwave power saturation curves were investigated for the first and second harmonic spectra. The relationship of signal saturation of the field modulation amplitude including the range of over-modulation was acquired for each method. Then, a dose response curve was generated from estimated results.

Conclusion
We could successfully produce tooth dosimetry from the newly developed novel EPR spectrometer. The performance of dose estimation was evaluated using the first and second harmonic spectra. In the future, further biomedical studies will be performed with the enhanced SNR using second harmonic spectra.

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Biological and EPR dosimetry for epidemiology

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Radiation dose estimation by ESR dosimetry with tooth enamel for residents of Nagasaki city in Japan

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Introduction
Tooth enamel has not become widely used for determining radiation exposure of atomic bomb survivors, because any medical or dental diagnostic x rays of the teeth will confuse the measurement of their radiation exposure for atomic bomb. We present that the diagnostic x rays dose can be determined separately from radiation exposure of Nagasaki atomic bomb survivors.

Methods
We began to request donations of extracted teeth from Adult Health Study participants of the Nagasaki ESR project in 1986. At present, 343 teeth have been collected, but only about 30% was found to be suitable for enamel separation and subsequent ESR measurement. To assess dental x rays dose, the enamel of each tooth was removed as two sides, buccal and lingual sides, and crushed to grain sizes 0.50-1.0 mm without any chemical treatment.

Results
We turned our attention to the problem of separating the contribution due to dental diagnostic x rays. Several tooth showed considerably larger ESR estimated doses in their buccal parts than in their lingual parts, which first seemed to indicate a considerably large contribution from any medical or dental diagnostic x rays exposure. We assessed that the dose ranging 0.04-0.7 Gy would be due to dental diagnostic x rays and natural radiation. The ESR dose of lingual parts of molars is least likely affected by factors other than atomic bomb gamma rays. Using ESR dosimetry of tooth enamel to estimate atomic bomb gamma ray dose received, we have recently examined teeth donated from Nagasaki atomic bomb survivors.

Conclusion
Several teeth exposed in no shielding showed considerably lower ESR estimated doses than DS02 doses, but the other tooth enamel doses correlated quite well with DS02 doses. We found that the diagnostic x rays dose can be determined separately from radiation exposure of Nagasaki atomic bomb survivors. It is concluded that ESR dosimetry with division into two of tooth enamel is useful measures for retrospective dose estimation. Furthermore, we are going to report the low radiation dose using tooth enamel which we obtained in fallout area, Nishiyama district in Nagasaki city, Japan.

References
This work was partially supported by the Grant-in-Aid for Scientific Research (C) (No.15K08697) and Joint Research Grant from the network-type joint Usage/Research Center for Radiation Disaster Medical Science of Hiroshima University, Nagasaki University, and Fukushima Medical University.

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The INSTRA and EU CONCERT LDLensRad projects – could the lens be used as a global biomarker of individual radiosensitivity?

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Introduction
Recent epidemiological studies have suggested that the threshold for formation of radiation induced lens opacities is lower than previously considered. The mechanisms of low dose radiation cataract induction are, however, still unclear. Some past publications have proposed that the lens could be used as a biomarker of radiosensitivity (Worgul B. et al., Radiat. Environ. Biophys. 1996;35:137-144).

Methods
The INSTRA and LDLensRad projects aim to answer a number of research questions on the effects of radiation on the lens, including the mechanisms involved in radiation cataract formation, the impact of dose and dose rate and the role of genetic background. Measurement of a wide range of potential cataractogenic endpoints is supported by neurological and pathological analysis of the brain to investigate wider systemic radiation responses. Data from lens and other tissues will be compared to test the hypothesis that radiation effects in the lens might be an indicator of global radiosensitivity.

Results
Work to date has focused on collating preliminary data on radiation responses in the lens, brain and a range of other tissues. INSTRA results following low dose rate irradiation with doses up to 0.5 Gy support a greater sensitivity of organs other than the lens. LDLensRad will build on this using additional mouse models, doses and dose rates and systems biology statistical modelling to combine the data from the two projects and from the wide range of different endpoints. Preliminary lens data on DNA damage, protein and lipid responses, with initial data on potential pathways identified through NGS, will be presented, together with plans to further investigate the lens as a potential biomarker of individual radiation response. However, this seems to be more difficult than initially thought.

Conclusion

The results of the LDLensRad and INSTRA projects will have key implications for radiation research and protection. Concrete outcomes are anticipated to include definitive information regarding the shape of the dose response and dose rate effects, thus advancing knowledge regarding the risk of radiation cataract at low doses and the influence of genetic background. In addition, lens changes following exposure to ionising radiation will be investigated in detail. The aims and objectives of the project will be presented, together with preliminary data.

References

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The LDLensRad project has received funding from the Euratom research and training programme 2014-2018 in the framework of CONCERT [grant agreement No 662287].

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Tooth enamel EPR dosimetry study of Hiroshima atomic bomb victims

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Introduction
The method of electron paramagnetic resonance (EPR) dosimetry has been applied to human tooth enamel to obtain individual absorbed doses of victims of Hiroshima atomic bombing.

Methods
Only 3 teeth samples were collected from this region. According to our information there is no any dental x-ray was applied to patients.

Results
It was found that the excess doses obtained after subtraction of natural background radiation for one person is background, second is 133 mGy and third is 243 mGy. Positions of teeth were 1, 2 and 4, therefore only lingual part was used for analysis. But for this case we cannot exclude with 100 % probability the influence of sunlight"s to these samples. Another problem is the lack of samples, because not so many victims of black rain area are alive.

Conclusion
Possibly, high dose of 243 mGy in tooth enamel of radiation is due to exposure from atomic bomb.

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Dose Response of Zebra Mussels ((Dreissena polymorpha) and Pond Mussels (Ligumia subrostrata) from the Great Lakes

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Introduction
The EPR spectra and dose response of one endemic and one invasive species of bivalve mollusks, Pond mussel (Ligumia subrostrata) and Zebra mussel (Dreissena polymorpha) were studied to determine their usefulness as indicators of radioactive material contamination in the environment, since the uptake of pollutants and radioactive material especially in zebra mussels has been well documented [1].

Methods
For this purpose, the shells were cleaned, ground and separated into groups with different grain sizes. They were subsequently irradiated with a 15 MeV LINAC using gamma absorbed doses from 1 to 40 Gy in a plastic phantom and EPR spectra were measured. Reference measurements and dosimetry were done with alanine powder. The signal fading was recorded over the time span of up to 3 months.

Results
Pond mussels showed a composite spectrum with overlapping signals, and while it it may be used for identifying the specimens, it is inaccurate for dose estimation. Zebra mussels have a strong EPR signal, even when unirradiated, that could be measured and used for determining the dose response. For zebra mussels the smaller grain sizes showed additional signal which was not evident in pond musselsand is believed to have been introduced through additional grinding. This however, did not influence the signal intensity.

Conclusion
Pond mussels were shown to have no significant radiation induced EPR signal. The optimal grain size for measurements of zebra mussels was determined to be between 0.5 mm and 1 mm. At doses of 20 Gy the signal height was an order of magnitude higher compared to the background signal with a relative error of 14%, which indicates potential use of zebra mussels as passive dosimeters. The dose response in the range considered could be best described by a nonlinear function.

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Researches in EPR-dosimetry and the main applications at INP RK

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Introduction
Electron paramagnetic resonance (EPR) method at the Institute of Nuclear Physics (INP) in the Republic of Kazakhstan has been first applied for retrospective assessment of the dose loads for population and environment in the region of the Semipalatinsk test sites (STS). Advantages of EPR method are well-known, it is a nondestructive universal method with high sensitivity.

Methods
EPR- dosimetry at INP is based on equipment granted by Japan for ecological investigations at the STS including the research X-band EPR-spectrometer ESP300E, measurements are performed at room temperature. For additional irradiation the Co-60 γ-source was used with dose rate 0.72 Gy/min. Methodical base of measurements includes International and local standard guides.

Results
EPR study of radiogenic paramagnetic centers (PMC), revealed in mineral objects of STS, showed the correlation of PMC quantity with α- and γ-isotope content. The defects in silica oxide fraction of soils can be used probably as detectors at retrospective dosimetry. EPR signals of analogous PMC were found in hot particles taken from the test points. Similar approach was applied in regions of uranium ore mining with increased content of natural nuclides, for example, in storage of nuclear wastes Koshkar Ata, and in the test point Azgir. EPR study of dose loads on TE has been conducted for the population of the same regions. Investigations of imported food products by EPR was performed at INP to work out the control of preliminary radiation processing.

Conclusion
EPR study showed that presence of radiogenic centers of E"1 type and peroxide centers in mineral objects can be useful for dosimetry. Estimates of doses on EPR in TE have been analyzed to study dependence on age, time of residence and other factors. It was shown that additional irradiation of fruits in presence of excessive content of vitamins or sugars can influence on the radiolysis direction.

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Networking in biological and EPR dosimetry, QA & QM

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Improving the capacity of biodosimetry in Vietnam through RENEB intercomparision exercises

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Introduction
The samples of human peripheral lymphocytes were exposed at different doses, coded and transported to the regional laboratories for culturing and slides preparation. There were 2 blind exposed samples (RE_5 and RE_6) for RENEB exercise in 2014, Vietnam received slides from NIRS (National Institute of Radiological Science, Japan), scoring for triage mode. There were 3 blind exposed samples (A, B and C) for RENEB exercise in 2017, Vietnam received metaphase images from KIRAMS (Korea Institute of Radiological & Medical Science, Korea), scoring for full mode

Methods
The calibration curve exposed by 60Co (at dose rate 0.47 Gy/min) was used for dose estimation in the 2014 RENEB exercise. Scoring 50 cells/sample, the estimated dose for RE_5 and RE_6 were questionable compared to actual doses, while the number of dicentrics were agree with the mean of all laboratories. We determined that these unprecise estimated doses dute to the data of calibration curve. In the 2017 RENEB exercise, a new calibration curve exposed by 60Co (at dose rate 0.275Gy/min) was used. Scoring 500 cells/sample, the estimated dose for A, B and C sample were agree with the actual doses. The data of calibration curves, the estimated doses will be assessed to indicate the preparedness of the laboratory for radiation emergency events.

Results
The capacity of biodosimetry laboratory in Vietnam has been improved after participating each intercomparision exercise. It is necessary to organize the intercomparision exercises annually for quality control and quality assurance in each biodosimetry laboratory and promoting the regional/international networks

Conclusion
International Atomic Energy Agency (IAEA). 2011. Cytogenetic dosimetry: applications in preparedness for and response to radiation emergencies. EPR-biodosimetry. Vienna, Austria: IAEA

References
Dicentric of human peripheral blood lymphocytes is considered as "the gold standard" for biodosimetry. In order to improve laboratories capacity, optimize dicentrics chromosome assay (DCA), verify dose estimation by biological analysis technique, the biodosimetry laboratory of Vietnam participated 2 intercomparision exercises organized by RENEB in 2014 and 2017

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Establishment of a reference biological dosimetry laboratory in Oran (Algeria)

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Introduction
In a near future Algeria will produce electricity from nuclear power plants. This will require competences in this field, however in radioprotection and especially those needed for dose-assessment in cases of radiological accidents. Our Department aimed to establish a biodosimetry laboratory in Algeria, elaborating firstly a dose-effect curve to be used in cases of overexposures.

Methods
Peripheral blood samples from of a healthy Algerian person, with no history of an exposure to ionizing radiations were exposed to 0, 0.25, 0.5, 1, 1.5, 2, 3, 4, and 5 Gy. Lymphocytes were then cultured for 48h, arresting cell division using Colcemid. Chromosome extensions were obtained after hypotonic and fixative treatments. As biomarker of dose the analysis of radio-induced chromosomal modifications, in particular the presences of dicentric chromosomes were considered. All the processes were done following IAEA (2011) recommendations.

Results
The frequency of dicentric chromosomes increases as the dose increases.

For each dose the dicentric cell distribution agreed with the Poisson distribution proving that blood samples were irradiated homogenously.

Curve fitting was dose using the he observed frequencies of dicentric and adjusting to a linear quadratic model. The obtained curve is: $Y= 1.4 \pm 0.7\ (10)^{-10} + 1.80 \pm 0.91\ (10^{-2})\ D + 1.23 \pm 0.07\ (10^{-1})\ D^2$.

Conclusion
The dose- effect curve obtained from the analysis of dicentric chromosomes obeys the linear quadratic model and allows its use in cases possible overexposures by our laboratory

This laboratory is intended to be a reference dosimetry and will be included in an international network of biological dosimetry laboratories.

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A VIRTUAL LABORATORY CONCEPT AS USEFUL TOOL FOR NETWORKING DEVELOPMENT IN THE CYTOGENETIC BIODOSIMETRY FIELD

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Introduction
For radiation accident management cytogenetic biodosimetry is an important part of countermeasures. But the accidents are quite rare events and it is often not easy for the economical reasons to keep running biodosimetry laboratories in medical hospitals, research institutions and radiation protection institutions only as a part of medical preparedness and response plans.

Methods
We applied the idea of a virtual biodosimetry laboratory that becomes possible with advanced technologies. This idea allowed combining the efforts of experts both in cytogenetics and radiation protection fields from different institutions and countries. The main technical requirement for a virtual laboratory is an image capturing system.

Results
The captured images were sent to scorers at various locations. It was recognised that for operating this system some different skills than microscopy analysis were needed.

In order to determine the narrow points in all stages of biodosimetry procedures starting from cell cultivation to dose estimation we have conducted several in vitro and in vivo studies. Inter-comparisons study design with increasing complexity for harmonization of the most importing steps has been developed, successfully tried and will be presented. Using the lessons from previous inter-comparisons we have conducted our dicentric dose-response curve with 7 dose points up to 2 Gy which can be used both for virtual and participants" laboratories. The next step will comprise data comparison for partial body exposure.

Conclusion
We conclude that virtual laboratory as a small network gave enough flexibility to radiation protection and radiation accident authorities in building up biodosimetry service including accidental overexposure in occupational and other fields. The peculiarities of QA/QC procedures, image vs. microscope analysis, data comparison for the triage and expert mode have to be considered and further studied.

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Capabilities of ARADOS-WG03 Network for Large Scale Radiological and Nuclear Emergency Situations

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Introduction
To identify and assess, among the participants in the ARADOS-WG03 (Asian Radiation Dosimetry Working Group 03; Biological Dosimetry), the emergency preparedness and response capabilities that can be evolved in the event of a large scale nuclear or radiological emergencies.

Methods
A questionnaire was prepared and sent to the participants of 2017 ARADOS-WG03 inter-comparison exercise in order to acquire information about the current infrastructure and operational techniques from 11 laboratories of 4 countries (China, Japan, South Korea and Vietnam), and to assess the capacity of response in the event of radiological or nuclear accident involving mass casualties.

Results
The survey focused on several main areas: the laboratory"s general information, the number of staff involved in biological dosimetry, the number of available assays in each laboratory, and the involved international activities for emergency preparedness. The analysis of this survey understood an existing capacity of the Asian biological dosimetry network for the cooperative response to nuclear or radiological mass casualties.

Conclusion
This regional sustainable network in biological dosimetry is very important to assure a quick and effective response against the nuclear or radiological events. The development of the scientific and technical capabilities existing within the ARADOS-WG03 members could be helpful to other neighboring countries with less or no capacity for biological dosimetry in case of a radiological or nuclear accident involving a large number of victims.

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Planning a new international comparison on EPR dosimetry with tooth enamel: a EURADOS WG10 proposal.

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Introduction
Between 1994 and 2011, several inter-laboratory comparisons (ICs) on EPR/tooth enamel dosimetry were conducted with the aim of validating the method. Since seven years have passed from the last exercise, EURADOS WG10 has planned to propose a new IC which will be shown and opened to discussion in this presentation, starting from a review of the past ICs and including new developments of the method.

Methods
A review of the past ICs was performed. Lessons learned, weakness and gaps were identified, focusing on the steps of the procedures used by the participants and the design of the exercise itself.

On this basis, a survey was sent around by email, consulting the EPR laboratories participating in the past ICs. The survey included questions on the instrumentation, protocol and expertise for EPR dosimetry with tooth enamel. The results of this survey will be shown as a state of the art of the EPR/tooth enamel dosimetry laboratories and will serve as basis to design the structure of the new IC.

Results
The idea of organizing a new IC arises from the need of a performance re-check for those laboratories that took part in the past ICs and of an involvement of new laboratories that during the last years have developed an EPR method whose performances should be tested for the first time.

In the last years, new techniques and methods have emerged that should be tested, at least in a preliminary way, for the first time, e.g., it would be desirable to carry on a validation of innovative EPR/tooth enamel methods, like those involving the use of Q-band or L-band microwaves. One of the important outcomes of the preliminary consultation about availability and capabilities of the EPR laboratories is that most of the consulted laboratories are willing to participate in a new IC.

Conclusion
A review of the past ICs and lessons learnt as well as a presentation of the planned EURADOS WG10 IC will be shown. The hypothesized structure of the new exercise will be based on the results of the preliminary consultation and of the specific needs and issues arising from innovative EPR/tooth enamel methods.

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EPR dosimetry and dating

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DETECTION OF IRRADIATION IN PLANT FOODS WITH HEALTH BENEFITS BY ESR TECHNIQUE

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Introduction
European Directives require labelling of the irradiated food and checks at the product marketing stage. EN 1787 method, based on ESR technique, is applicable to all matrices containing cellulose but its effectiveness is limited by the storage conditions and the complexity of ESR spectra of some products. This study aimed to verify the applicability of EN 1787 on plant foods with health benefits.

Methods
Plant Food Supplement (PFS) ingredients such as *Camellia sinensis* (leaves) *Ginkgo biloba* (leaves), *Glycine max* (seeds), *Silybum marianum* (fruits), *Vaccinium myrtillus* (fruits), nuts (almonds, hazelnuts, peanuts, pistachios, walnuts) and fresh blueberries were analyzed. ESR measurements were carried out at room conditions with different Bruker spectrometers: Elexsys, E-Scan Food Analyzer and ESR Bruker EMX, operating in X band with the recording parameters indicated in the EN 1787 Standard. A procedure, based on EN 1787 Standard, was elaborated and validated by five Italian laboratories.

Results
The intralaboratory results obtained by the five laboratories were in good agreement. Not irradiated samples showed symmetric signals, with intensities depending on the specific sample. In all irradiated nuts the typical triplet of irradiated cellulose, which allows the detection of irradiation, was visible up to about 2 years and all samples were correctly identified. As for PFS ingredients, the overlapping of different signals due to the presence of many radicals, even intrinsic, made generally difficult to recognize the radiation induced triplet and led to more than 10% of false negative results. Blueberries were correctly identified up to 3 weeks after treatment, but only those samples that had been irradiated at 1 kGy. A blind test performed on 180 samples confirmed these results.

Conclusion
This study provided data useful to extend the applicability of the EN 1787 method to almonds, hazelnuts, peanuts and walnuts. The study confirmed also that PFS ingredients give false negative results, due to the complexity of some ESR spectra, as reported in literature. Further investigations are necessary to guarantee the routine control on these products taking into account that considerable percentages of PFS are still found not compliant with the European Directives and often give inconclusive responses (EU reports). Blueberries detection depends on the dose of treatment.

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EPR dosimetric potential of mineral-eyeglasses: Preliminary results

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Introduction
Determination the radiation dose after possible nuclear or radiological accident is crucial to helping the authorities take the necessary precautions. For this purpose, daily used items (watch glass, smart phone screen glass), chemicals (sugar and drugs) and human tissues (bone, tooth enamel, finger nail, etc.) are reported to be used for dose determination by EPR spectroscopy[1-3].

Methods
Dosimetric features of different type of glasses are reported[1], and the phone screen glasses are reported to be the most promising material[2]. The common use of mobile phones by public makes it a perfect candidate for EPR dosimetry. However, determination alternative material could improve the usefulness of the EPR spectroscopy for radiation dosimetry. Therefore, in the present work the dosimetric features of anti-reflection coated and un-coted white and photochromic mineral eyeglasses are investigated by EPR spectroscopy at intermediate (0.5-10 kGy) and low dose (1-10 Gy) regions.

Results
While the investigated four samples were presented unresolved complex EPR spectra at intermediate radiation doses, the coated-white mineral eyeglasses were present an EPR signal that easily distinguished from the noise signals. The dependency of the EPR spectra to the microwave power (MwP), modulation amplitude, and environment condition such as temperature and storage time were also investigated. The linear increase of the measured EPR signals with MwP and modulation amplitude makes it possible to increase the EPR signal intensities. However, the EPR signals are found to be affected from the temperature and storage time.

Conclusion
The undesired decay during storage make them not good candidate to be used as retrospective dosimeter. Nevertheless, the radiation sensitivity and linear dependency to the spectrometer conditions enhance their usability as an accidental EPR dosimeter. The existence of glasses with different characteristics encourages us to investigate their dosimetric properties more detailed.

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Use of carob pods (Ceratoniasiliqua L) as retrospective or accident EPR dosimetric material

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Introduction
Carob tree is a natural plant that grows in the Mediterranean region. The high sugar contain (>50%) of carob fruit[1] lead us to consider it as additional EPR dosimetric material. As it has reported in the literature that sugar has the potential to be used as dosimetric material[2]. Therefore, the aim the present work is to determine the EPR dosimetric features of sugar rich powder of carob.

Methods
The powder form of the carob fruits are supplied from local market and used as it is without additional processing. The carob samples are irradiated to doses between 0.5 and 20 kGy. The table sugar samples were also irradiated to 10 kGy to make comparison. The EPR measurement and irradiation were carried at ambient condition to stay in the radiation accident conditions.

Results
The unirradiated carob present a singlet EPR signal located about g=2.0041, and have the linewidth of 0.33 mT, which is concluded to be originated from semiquinone-like free radicals. The observed EPR spectra were found to be perfectly match to the sugar EPR spectra. The dose-response were found to be linear and the dependency to the microwave power and modulation amplitude are the same as the sugar"s. It is found that while increasing the temperature the EPR signals were decreased except the increase in the signal intensity of the naturally occurred free radical[3].

Conclusion
The high sugar content of powder of carob fruits present promising EPR dosimetric features[3]. These features make it possible to use it as retrospective dosimetric material at the location that could not be the opportunity to collect sugar samples. This is important because many nuclear reactors are located at countryside far from the public population.

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Using fish otoliths in EPR dosimetry

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Introduction
Fish otoliths are the organs, which are used as gravity, balance, movement, and directional indicators. Otoliths are the most calcified tissues in the fish body In contrast to fish bones, the otoliths do not affected by remodeling and, therefore, they can be used as individual dosimeters accumulating the dose during all lifetime.

Methods
In current study, otoliths of three fish species (roach (*Rutilus rutilus*), pike (*Esox lucius*) and perch (*Perca Fluviatilis*) from 4 special industrial storage reservoirs of liquid radioactive waste from Mayak PA and from the upper reach of the Techa River, which have been contaminated with different levels of radionuclide activity concentration, were tested with EPR spectroscopy.

In parallel, otoliths were measured with beta counter to detect 90Sr/90Y. Samples were also tested on the presence of alpha-emitters.

Results
It was shown, that the radiation induced EPR signal of otoliths is stable and demonstrates linear dose response. However, the slope of calibration curves (the radiation sensitivity) is not the same for different species; it may be caused by difference in mineralization. No alpha-emitters were reliable detected. However, significant concentration of $^{90}Sr/^{90}Y$ were measured (from 10 to $2*10^4$ Bq g^{-1}).

Conclusion
The reconstructed doses were found to be in the range from undetectable (the upper stream of the Techa River) to 270 Gy (the roach of most contaminated waterbody). The doses measured by the EPR correlate with ^{90}Sr activity concentration in otoliths.

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Role of EPR spectroscopy in synthesis and sterilization of dental bone graft materials

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Introduction
Calcium sulphate and calcium phosphates are commonly used for various dental applications such as fillers for periodental defects. Due to their resorption in the body and direct contact with tissues, they are mostly sterilized by γ-irradiation. EPR spectroscopy was used for characterisation of the subtle structural differences within different ion substitutions and radiation induced defects.

Methods
Commercially available dental bone substitution materials were compared with synthetic calcium sulphate (hemihydrate and dihydrate) and calcium phosphate (hydroxyapatite and ß-tricalcium phosphate) obtained from Sigma Aldrich. Samples were irradiated with 60Co gamma rays at 25 kGy dose at room temperature. EPR spectra were recorded at Varian E109 X-band EPR spectrometer using a Bruker ER 041 XG microwave bridge, operating at 9.5 GHz with 100 kHz modulation, equipped with a variable temperature unit ER4111VT by Bruker Instruments. DPPH was used as external magnetic field marker.

Results
EPR spectra of these samples show that spectroscopic parameters depend on each step of synthesis procedure and therefore, on the structure of the bone graft materials and its constituents. Therefore obtained impact of sterilization by irradiation is different regarding each sample, as expected (1,2). It is shown that EPR spectroscopy is the only technique for characterization of free radicals with which it is possible to simultaneously determine not only content, but also the position and the structure of free radicals formed by γ-sterilization in the investigated materials as well as the paramagnetic substitutions incorporated in the materials during the synthesis. Additionally, data on stability of irradiation induced radicals in investigated materials were obtained.

Conclusion
The obtained results suggest that EPR spectroscopy is inevitable technique in the procedure of development new dental bone graft materials. In addition to detecting structural details due to ionic substitutions and the free radicals induced during the sterilization processes, EPR can provide data on radical stability as well as suggest processes for reducing them. Therefore, it should be considered as valuable technique in both, development and quality control of new dental bone graft materials.

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Electron spin resonance dating of *Toxodon* teeth from Baixa Grande, Bahia, Brazil

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Introduction
Although the extinct Quaternary megafauna is widely recorded in northeastern Brazil, the geochronological studies carried out in fossiliferous deposits are still scarce. In this work the ESR was used to date 12 teeth of *Toxodon platensis* (Mammalia, Notoungulata) from Baixa Grande, Bahia, Brazil.

Methods
The enamel of each tooth was separated, subjected to a 1: 5 HCl treatment. After manually crushed were divided into 10 aliquots of ~60mg for irradiation. The soil, enamel and dentine, were submitted to Neutron Activation Analysis (NAA), to determine the concentration of U, Th and K. The ESR spectra of aliquots were recorded in Jeol FA200. The peak-to-peak intensity of the dosimetric signal was used for the construction of the dose-response curve. The Equivalent Dose(De) was determined after fitting with single saturating exponential function[1]. The conversion into age by the DATA[2] program.

Results
The ages found vary from 34 ±6 to 60 ± 6 ka.

Conclusion
The results of ages obtained in this work associated to data in literature3 indicate a *time-averaging* in this fossiliferous assembly. These dates fill gaps in the occurrence of *Toxodon* in Brazil.

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LOW DOSES RADIATION-INDUCED ALANINE AND QUARTZ RADICALS' LONG-TERM ANALYSIS AND RADICAL KINETICS FACTS.

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Introduction
Low doses radiation-induced stable free radicals in polycrystalline L-alanine compare to those in quartz at room temperature (295 K) are examined by electron paramagnetic resonance (EPR). The alanine produces typical 5-peaks, while the quartz gives a characteristic simple-single-signal of g-factor = 2.0043 ± 0.00013. Both EPR signals weres found unchanged in shape and intensity in five years after irradiation.

Methods
Both alanine and glass tubes were irradiated in air and at room temperature to doses up to 20 Gy using a 130 Ci 137Cs gamma irradiation device. The dose rate of the source was determined to be 0.215 Gy/h using the standards of NIST. The EPR spectra of irradiated alanine dosimeters were recorded at room temperature using upgradeed MiniScope MS300 spectrometer, magnettech GmbH, to fast registry by Adani, Belarus, operated at 9.5 GHz. The dose-response of irradiated quartz tubes and alanine were assessed using the maximum peak-to-peak amplitude of the EPR spectrum.

Results
The quartz single signal has been obtained at 0.4 mW Microwave power while the quintet signal of alanine has been observed at 10 mW power. The structured peaks of alanine were attributed to the overlapping spectra from at least three different radical species, of which the radical CH3-ĊH-COOH was the major contributor to the central EPR resonance line. For quartz, the signal was attributed to silicon-vacancy centers as a vacancy defects. These vacancy effects involve either a missing oxygen atom or an absent silicon atom. A missing oxygen atom is known to be responsible for the formation of a number of electron-like paramagnetic defects, including the well-known E1' center.

Conclusion
The annealing of the quartz materials at ~ 450 oC "reset" the quartz's radiation-induced radical signal to zero. The "stable" radicals' signals were quantitatively investigated in the presence of an external standard reference (Mn2+/MgO) to correct for spectrometer sensitivity variation. The calibration results indicated that the quartz materials produce better sensitivity than alanine and lower detection limit compared to the recent alanine-in-glass (AiG) dosimeter [1,2]. The long-term stability of the radicals and their decay at various temperatures to optian thermodynamic parameters of activation and lifetime at 295 K.

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Electron Paramagnetic Resonance data processing standardization using the Chebyshev polynomials

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Introduction
The Electron Paramagnetic Resonance (EPR) spectroscopy processing usually requires painstaking and time consuming manual adjustments and arbitrary choices, especially in EPR imaging (EPR-I), with the added cost of many hard-to-evaluate errors. That makes the data analysis very user dependent, which is incompatible with repeatability.

Methods
To get rid of manual adjustments, we propose a unified EPR data processing approach based on the "Chebyshev Technology" made available through a Matlab toolbox developed by the Numerical Analysis Group in Oxford: it expresses any function as special polynomials called "chebfuns"[1]. We adapted chebfuns to express data: all processings become simple polynomial transformations. Traditional EPR procedures are vastly improved, as we demonstrated for EPR-I[2], allowing non-specialist users to analyze any spectrum through simple, repeatable, automatic functional expressions.

Results
After expounding the general procedure, we apply it to an EPR spectrum simulated using the Matlab toolbox Easyspin to which we added a white noise, mimicking a real spectrum. Having transformed the latter into a chebfun, all the usual EPR processings become automatic and repeatable since parameters are obtained by applying the same Matlab functions which we re-implemented inside Chebfun. The peak to peak amplitude is one of the parameters that we further improved by using the full power of chebfuns to devise a Chebfun denoising protocol. Resulting spectra are less than 1% different from the ones obtained from the noiseless simulated spectra, while usual processing techniques result in spectra more than 20% different.

Conclusion
Working within the Chebfun paradigm solved two problems: the repeatability of the processings, and both accuracy and precision. With chebfuns, the portability of the processings and different algorithms comes easily. One of our most important goals is to unify and standardize all EPR processings by relying on the power of Chebyshev polynomials that were implemented in the state of the art Chebfun toolbox: we initially used it to renew EPR Imaging processings, and we now generalize its application to all EPR processing, clearing the path to a standardization from 1D-spectra to 3D-images.

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Improvement of the electron spin resonance spectroscopy detection limit for tooth dosimetry

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Introduction
Electron spin resonance spectroscopy for tooth dosimetry is a useful method for evaluating doses of external radiation exposure. However, the current dosimetry detection limit exceeds a few tens mGy [1,2]. In this study, we attempted to improve the dosimetry detection limit and thus facilitate the measurement of low radiation exposure doses in an epidemiologic study among children in Fukushima.

Methods
Tooth enamel isolated from the dentine of Japanese human milk teeth and Japanese macaque teeth was crushed into particles with diameters of ~700 μm. These particles were irradiated with ^{60}Co gamma-ray doses ranging from 0 to 1000 mGy (0, 22.34, 50, 75, 100, 125, 150, 175, 200, 500, and 1000 mGy for milk teeth; 0, 20, 40 and 60 mGy for macaque teeth; N=7 per irradiated dose point). The observed ESR spectra were deconvoluted using an EPR-dosimetry program to determine the intensities of CO_2 radicals, which were plotted against the irradiated gamma-ray doses to construct calibration curves.

Results
Both calibration curves exhibited satisfactory linearity (R^2=0.997 for human milk teeth and 0.991 for macaque teeth, respectively). The respective estimated detection limits based on the 95 % confidence limits for human milk teeth and macaque teeth were 15 and 7 mGy, respectively.

Conclusion
The Fukushima Daiichi nuclear power plant accident, which resulted in the release of radioactive materials, exposed local residents to ionizing radiation. The ability to determine the actual extent of radiation exposure and the availability of precise dosimetry methods that can estimate prior individual exposure doses are important. Our results suggest that the currently available electron spin resonance spectroscopy-based tooth dosimetry technology might be useful for measuring external radiation exposure, even in cases where the dose is less than 100 mGy.

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Determination of Detection Limit of EPR Dosimeter using Weighted Least-squares (WLS) Approach

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Introduction
The detection limit is defined as the true concentration at which a given analytical procedure may be relied upon to lead a detection. The detection limit of potassium tartrate hemihydrate (PT) and ammonium tartrate (AT) as a radiation sensitive material for electron paramagnetic resonance (EPR) dosimetry was investigated using weighted least squares (WLS) method.

Methods
The samples were subjected to different doses, in the range of 1 – 8 Gy of Co-60 gamma rays at room temperature. The detection limit of the sample is computed based on the assumption that the variance is proportional to the concentration (dose). To compute the detection limit, the value ($\alpha = 0.01$) for upper $(1-\alpha)100$ percentage point of Student's t-distribution with n-2 degrees of freedom were used. The results from WLS method were compared with the detection limit method using mean value of the background signal in unirradiated dosimeters plus three standard deviations.

Results
From the calculation, the detection limit using WLS method for PT was about 0.7 Gy and for AT was about 2.3 Gy.

Conclusion
As a conclusion, WLS method can estimate much lower detection limit compared to method of using mean value of the background signal in unirradiated dosimeters plus three standard deviations.

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Detection of ionizing radiation treatment in glass used for health care products

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Introduction
The treatment with high doses (1 kGy) of ionizing radiation is widely used for the terminal sterilization of health care products such as medicines and medical devises. The aim of this work was to verify the efficacy of physical techniques in detecting the radiation treatment in glass tubes for blood tests, in order to highlight possible frauds and guarantee the safety of the products.

Methods
Two batches of glass tubes (A and B), provided by the same manufacturer, were used. Fragments of a few millimeter size of glass were collected from the tubes, cleaned with ethanol and weighted. The radiation treatment performed at the manufacture stage was simulated with a Gammacell 220 (Nordion, Canada) providing a rate of 1.08 Gy/min. Thermoluminescence (TL) measurements were performed with a Harshaw 3500. For Electronic Paramagnetic Resonance (EPR) measurements a continuous wave spectrometer (EleXsys Bruker) operating in X-band and equipped with a super high Q cavity (SHQ Bruker) was used.

Results
EPR and TL measurements were performed on glass fragments before and after irradiation (1 kGy). Both techniques revealed signals specifically induced by ionizing radiation and detectable for long time (years) in both A and B batches. Irradiated samples showed broad TL glow peaks, specific of irradiation, with a maximum at different temperatures (around 200 °C for A and 250 °C for B batch) and different intensities (integrated glow curve), depending on the batch. As for EPR, both samples A and B presented a radiation induced feature with g-values in the 2.015-2.0025 range, probably due to an oxygen based radical [Engin et al., 2006]. Irradiated sample A also showed a feature at g=1.9676 which could be an impurity-associated defect.

Conclusion
This work has demonstrated that EPR and TL techniques can be adequate for revealing illegal omission of irradiation at the manufacturer stage in forensic analysis. Both techniques, in fact, could detect the treatment of the glass through the identification of TL and EPR signals specifically induced by ionizing radiation and stable for long time (years). The results, slightly different for A and B samples, suggested also that the tubes of the two batches are made of glass with different chemical composition.

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ESR Dating at Golema Pešt: The Effect of U Uptake on Ages for a Middle Paleolithic Site

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Introduction
In a cave 3.5 km from Zdunje, and 65 km SW of Skopje, Golema Pešt is the only Middle Paleolithic archaeological site known in Macedonia. The cave sits 480 m amsl overlooking the Treska River valley. A reservoir now rises to within a few metres from the cave entrance. The cave fill reaches to > 6 m deep with > 20 distinct, flat-lying, geological layers.

Methods
Middle-early Upper Pleistocene fossils indicate that mixed paleoenvironments ranging from predominantly forests to grasslands in drier times occurred near the cave. In Layers 5 and 6, the Mousterian assemblage includes denticulates, notched tools, discoid cores, Levallois cores and flakes. Layer 6 exceeds the 14C limit. Since ESR can date tooth enamel from ~ 5 ka to > 2 Ma, with ~ 2-5% precision, six herbivore teeth from Layers 3-5 were dated by standard and isochron ESR.

Results
Accumulated doses were calculated using the additive dose method using precisely characterized doses. To measure the volumetrically averaged sedimentary dose rates, > 20 sediment samples from seven layers were analyzed by NAA. Cosmic dose rates were calculated by ramped box averaging using geological data regarding sedimentary cover. Teeth collected from the testpit near the cave mouth had dentine with 5-10 times more U than those from the testpit in the cave centre about 6 m away. Recent inundations of the front testpit may explain their high U concentration.

Conclusion
In the central testpit, the LU ages ranged from 71.4 ± 6.5 to 73.4 ± 2.5 ka, which correlates with the Marine Isotope Stage (MIS) 5a boundary or the earliest MIS 4. The teeth from the front were much younger using LU (p = 0). These age differences derived totally from their very high U concentrations. Assuming p = 2, ESR ages for teeth from the front testpit dated at ~ 76.8 ± 6.3 ka, and agrees best with the geologically expected ages from the faunal analyses. Nonetheless, p values must be confirmed with coupled ESR-230Th/234U analyses.

References
More teeth from each layer must be dated to confirm these results and check for reworked teeth.

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ESR response of alanine films exposed to low-energy (1-40 keV) X-rays

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Introduction
L-a-alanine has aroused considerable interest for use in radiation ESR dosimetry. In this work, we examined the energy response of alanine ESR films in the low energy X-photon energy range between 1 keV and 40 keV. Dose measurements through a reference ionization chamber and a semiconductor detection system were also performed to complement ESR measurements.

Methods
Commercial alanine ESR films were used. All ESR signal measurements were also done using an X-Band (9.7 GHz) Bruker spectrometer.

The dosimeters were irradiated at the "Livio Scarsi" Laboratory (LAX) of the University of Palermo, where X-ray beams in the 1–40 keV energy range are produced using a Seifert SN60 tube. Reference dosimetry measurements were made using a plane parallel chamber with thin polyethylene membranes. X-ray fluxes and energy spectra were measured with an innovative system based on semiconductor detectors (CdTe, Si) and digital pulse processing (DPP) electronics.

Results
The response of alanine to low-energy X-rays was characterized experimentally. The response as function of dose, the dependence of the ESR signal on the photon energy as well as the stability of the signal with time were investigated. Comparison of the ESR response to high energy photons was also carried out. The relative effectiveness is lower if compared to high-energy photons.

Conclusion
Alanine dosimeters show very interesting dosimetric features also for these low-energy X-ray beams. To our knowledge, these data have not been previously reported and they may be extremely relevant, e.g., when mapping the high-gradient treatment fields used in microbeam radiation therapy (MRT) with synchrotron radiation.

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