



EPR BioDose Paris 2022

June 7th-10th 2022

Institute of Radiological
Protection and Nuclear
Safety (IRSN)
Fontenay-aux-Roses
France

Book of abstracts



Tuesday, June 7th		Wednesday, June 8th	
		08:30	Invited lecture A. Romanyukha (45 min)
		09:30	Invited lectures Eberlein (30 min) A. Flood (30 min)
		10:30	Break + poster (45 min)
		11:15	Port (15 min) + Marrale (15min) +Wilkins (15 min)
		12:00	Lunch
13:00	Introduction (S. Swarts) + Invited lecture JF Barquinero (45 min)	14:00	Lima (15 min)+Bucher (15 min)+Popp(15 min)
14:00	Badie (15min)+Andersen (15min)+ Balajee (15min)	14:45	Round table bio-indicators (45 min)
14:45	Round table ILC (45 min)	15:30	Break + poster (45 min)
15:30	Break (45 min)/poster session	16:15	Alsbeih(15 min)+Stremcki (15 min)+Arizaca (15 min)+ Hayes (15 min)
16:15	Fast poster presentation (oral 5 min, 1h15)	17:15	End of session
17:30	End of session		

Thursday, June 9th		Friday, June 10th	
08:30	Invited lecture G. Gruel (45 min)	08:30	Invited lectures M. Lopez-Riego (SU) (30min) + V. GOH (NUS) (30 min)
09:15	Invited lectures N. Ollier (CEA) (45min) +Swarts (30 min)	09:40	Grunewald (15 min) +Oestreicher (15 min)
10:30	Break + poster (45 min)	10:15	Break + poster (45 min)
11:15	Michalec (15 min)+Semra (15 min) +Romanyukha(15min) +Martinez (15 min)	11:00	Barnard (15 min)+Seredavina (15min) +Trompier (15 min)
12:00	Lunch	11:45	Closing session+announcements (next meeting)
13:45	Round table Ukraine crisis (45 min)	12:15	End of conference
14:30	Poster award ceremony + IABERD report (30 min)		
15:00	Gonzales Lorenzo (15 min)+ Dos Santos (15 min)+Seredavina (15 min)	13:00-16:30	WHO Biodose net meeting
15:45	Break + poster (45 min)	16:30-17:30	IRSN lab visit
16:30	M'kacher (15 min)+Kortmis (15 min)+Amiot (15 min)+Ancel(15min)		
17:30	End of session		

Invited lectures

Tuesday

The odd couple DNA damage and ionizing radiation by **J.F. Barquineiro (UAB) (Abstract ID 73816)**

Wednesday

Last Decade Achievements of EPR Dosimetry by **A. Romanyukha (Naval dosimetry Center) (Abstract ID 72859)**

Biodosimetry and internal dosimetry in Nuclear Medicine by **Eberlein U. (University of Würzburg) (Abstract ID XXX)**

How in vivo EPR nail dosimetry could be utilized to significantly improve the response to a large radiation event by **A.B. Flood (Geisel School of Medicine at Dartmouth College) (Abstract ID 74044)**

Thursday

Overview of 20 years of dose reconstructions at IRSN by **G. Gruel (IRSN)**

Points defects in mineral glass: an overview by **N. Ollier (CEA) (Abstract YYY)**

Implications of “FLASH” for Biodosimetry by **S.Swarts (Abstract ID 74039)**

Friday

Inter- and intraindividual response to alphas, X-rays and mixed beams analysed at exon-level gene expression and chromosomal aberrations by **M. Lopez-Riego (SU) (Abstract Id 73862)**
– **Best Poster awarded at EPRBiodose Japan 2022**

Shortened 48 h cytokinesis-block micronucleus assay for triage dose assessment by **V. Goh (NUS) - Best Poster awarded at EPRBiodose Japan 2022**

List of participants and abstracts

- YYY Nadège Ollier, Laboratoire des Solides Irradiés (LSI) – IRAMIS, CEA, Points defects in mineral glass: an overview (invited)
- XXX Uta Eberlein, University of Würzburg, Biodosimetry and internal dosimetry in Nuclear Medicine (invited)
- 72854 Petya Todorova, Military Medical Academy-Sofia, Dosimetric monitoring of the person exposed to chronic, occupational, low-dose radiation during the Pandemic COVID-19 /2019 to 2021/ (Poster)
- 72858 Alexander Romanyukha, Naval Dosimetry Center, EPR dosimetry in tooth enamel of former United States nuclear workers (Oral)
- 72864 Iara Lima, University of São Paulo, Platinum Nanoparticle's Dose Enhancement in Alanine-EPR Dosimeter (Oral)
- 72867 Tanja Popp, Bundeswehr Institute of Radiobiology, affiliated to the University of Ulm, Munich High throughput method for dose estimation after ionizing radiation (Oral)
- 72868 Martin Bucher, Federal Office for Radiation Protection (BfS), Dose variations using an X-ray cabinet to establish in vitro dose-response curves for biological dosimetry assays (Oral)
- 72869 Hasan Tuner, Balikesir University, Use of Double integral for tooth enamel EPR dosimetry (Poster)
- 72872 Anthony Bonfrate, Institut Curie - Proton Therapy Centre of Orsay, Alanine dosimetry for Very High Dose Rate proton therapy (Poster)
- 72917 Stephen Barnard, United Kingdom Health Security Agency, Inter- and intra-individual variability of gamma-H2AX in healthy volunteers and clinical radiotherapy patients (Oral)
- 72919 Shu Xian Teo, National University of Singapore, Estimation of Dose received during Radiotherapy and its effects on miRNA expression (Poster)
- 73043 Matthias Port, Bundeswehr Institute of Radiobiology, RENE B INTER-LABORATORY COMPARISON (2021) FOR BIODOSIMETRY AND RETROSPECTIVE PHYSICAL DOSIMETRY (Oral)
- 73056 Ruth Wilkins, Health Canada, Analysis of inter-laboratory comparison data from the Canadian Biodosimetry Network (Oral)
- 73057 Maja Vojnić Kortmiš, IBA Dosimetry GmbH, Energy dependence of g-values for the purpose of dose reconstruction of soda-lime samples irradiated in a dose range 0.1 – 10.0 Gy (Oral)
- 73058 Claus E. Andersen, Technical University of Denmark, Alanine dosimetry for radiotherapy auditing and preclinical research: Assessment of a robust procedure for handling of EPR spectra at doses below 3 Gy (Oral)
- 73153 Barbara Michalec, Institute of Nuclear Physics Polish Academy of Sciences (IFJ PAN), Alanine doses measured in the mailed dosimetry intercomparison at CCB IFJ PAN ocular proton therapy facility (Oral)
- 73173 Ursula Oestreicher, Federal Office for Radiation Protection (BfS), RENE B Inter-laboratory comparison (ILC) 2021 applying dicentric chromosome assay for biological dosimetry (Oral)

- 73337 Semra Tepe Cam, Nuclear and Mineral Research Agency, Is sulfanilic acid used as ESR dosimeter for medical applications? (Oral)
- 73394 Maurizio Marrale, Università Degli Studi di Palermo, Could alanine/EPR dosimetry be useful for ultra-high dose rate beams used for FLASH radiotherapy? (Oral)
- 73825 Jakob Grünewald Hjørringgaard, Technical University of Denmark, Beam Quality Effect on Relative Response of Alanine Pellet Dosimeters in Kilovoltage X-rays (Oral)
- 73828 Christophe Badie, UK Health Security Agency, Dynamics of gene expression in circulating leukocytes during radiotherapy (Oral)
- 73830 Juan Martinez, Institut de Radioprotection et de Sûreté Nucléaire (IRSN), Twenty-two years later: Consistent dose estimation of an accidental overexposure by retrospective biological dosimetry (Oral)
- 73835 François TROMPIER, IRSN, On the importance of dosimetry in radiobiology studies: an overview of critical problems in dose assessment and dosimetry protocol description (Oral)
- 73839 Miray Razanajatovo, DSIN, EPR retrospective dosimetry with sugars: results of the 2019 EURADOS Field exercise (Poster)
- 73843 Nadica Maltar-StrmeckiRBI Recent Outcomes of NATO SPS Project: Novel biological and physical methods for triage in (R/N) radiological and nuclear emergencies “BioPhyMeTRE”
- 73846 Edy Cuevas Arizaca, University of Sao Paulo, Dating sediments from Paranagua barrier by EPR (Oral)
- 73848 Carlos D. Gonzales Lorenzo, Universidad Nacional de San Agustin (UNSA), EPR and TL studies of synthetic CaSiO₃ and Li₂SiO₃ polycrystals for gamma dosimetry (Oral)
- 73849 Morgane Dos Santos, IRSN, End-To-End test with alanine dosimetry for verification of TPS dose calculation for small animal irradiation with small diameter X-rays beam (Oral)
- 73850 Shyue Wei Pang, DSO National Laboratories, Developing A Mass Casualty Triage Test For RN Incidents (Poster)
- 73851 Yoan Ristic, IRSN, Alanine reference dosimetry for radiobiology experiments with small rodents irradiated with MV X-rays (Poster)
- 73855 Mahinour Mobasher, IRSN, EPR dosimetry on touch screen of smartphones: dosimetric investigations of the latest generation of glass (Poster)
- 73858 Veronique Menard, CEA, Dosimetry of a self-shielded gamma irradiator small animal whole body irradiations with alanine pellets (Poster)
- 73867 Morgane Dos Santos, IRSN, Evaluation of absorbed bone dose by EPR spectroscopy of a preclinical model mimic interventional radiology expositions: dose and time effect (Poster)
- 74043 Radhia M'kacher, Cell Environment, A novel and sensitive method using telomere and centromere in situ hybridization improves detection of chromosomal and telomeric aberrations induced by low doses gamma-irradiation in vitro (Oral)
- 74044 Ann Barry Flood, Geisel School of Medicine at Dartmouth College, How in vivo EPR nail dosimetry could be utilized to significantly improve the response to a large radiation event (invited)

74045 Tatyana Seredavina, Institute of Nuclear Physics (INP), Ministry of Energy (ME), Study of soils by EPR method in the region of testing sites RK (Oral)

74084 Marina Mirijanyan, Research Center of Radiation Medicine und Burns, A Comparative study of the thyroid gland pathologies among the Armenian liquidators of the Chernobyl Nuclear Power Plant accident and general Armenian population (Poster)

74316 Marie-Noelle Amiot, CEA, End-to-end tests with alanine pellets read by EPR in a heterogeneous phantom for radiotherapy treatments (Oral)

74331 Adayabalam Balajee, REACTS, Long-term cytogenetic follow up studies on humans with internal and external exposure to ionizing radiation (Oral)

Abstract ID YYY

Points defects in mineral glass: an overview

N. Ollier

Laboratoire des Solides Irradiés (LSI) – IRAMIS, CEA

This talk will be dedicated to point defects in glasses. We will speak about their formation, their nature in silica and other glasses, the methods to identify them. Then in the last part of the presentation, the impact of several parameters (temperature, glass composition...) on point defects will be addressed.

Abstract ID XXX

Biodosimetry and internal dosimetry in Nuclear Medicine

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External and internal exposures to ionizing radiation leads to molecular damages in cells, of which DNA double strand breaks (DSBs) pose a severe threat to genome integrity. For diagnostic procedures in nuclear medicine, mostly γ - and β^+ -emitters are administered, whereas for radionuclide therapies, β^- or α -labelled radiopharmaceuticals are applied. The radionuclides irradiate the body internally with time-dependent dose-rates, which cause DNA DSBs in hit cell's nuclei. The aim of our research is to analyse the time- and dose-dependent induction and repair of the radiation-induced DSBs with the biomarkers γ -H2AX+53BP1 in peripheral blood mononuclear cells (PBMCs) in vivo and ex vivo after internal irradiation with β^- - and α -emitters.

For the ex-vivo study, blood samples were taken from volunteers and activity of different concentrations of radionuclides (^{131}I , ^{177}Lu , ^{223}Ra , ^{224}Ra) were added. The radioactive blood aliquots were then incubated for 1 h to reach absorbed doses to the blood up to 150 mGy. For ^{131}I and ^{223}Ra the time course of DNA repair was studied at 4h and 24h.

For the in vivo studies, radiation-induced DSBs were quantified in blood samples of patients receiving a therapy with either [^{131}I]NaI, [^{177}Lu]Lu-DOTA-TATE/TOC, [^{177}Lu]Lu-PSMA or [^{223}Ra]RaCl₂ taken before, and up to 168h after radionuclide administration. For all studies, the time-dependent absorbed dose to the blood was calculated.

In all blood samples, PBMCs were isolated, ethanol-fixed and stored until analysis. All samples were immuno-stained with γ -H2AX+ 53BP1 antibodies and co-localizing foci and α -tracks were counted manually.

The ex vivo experiments revealed a linearity between the number of radiation-induced foci (RIF) / α -tracks and the absorbed dose to the blood below 150 mGy absorbed dose after internal irradiation. Furthermore, a decrease in the RIF numbers and α -track frequencies was seen 4 h and 24 h after irradiation. Efficient repair was seen for both β^- or α -irradiation. The repair rates are comparable to that of external irradiation with γ - or X-rays.

For the β^- -labelled radiopharmaceuticals and the average number of RIF in-vivo showed a linear dose-response relationship within the first hours after administration. For the α -irradiation for absorbed doses below 3 mGy and up to 3 h a linear correlation could be seen. At later time points (> 4 h) a diminishing number of RIF/ α -tracks was observed in accordance with the progression of DNA repair and concomitant declining dose rates. The observed RIF/ α -track numbers were higher as expected from the extrapolation of the ex-vivo studies.

Overall, we provide evidence that the biomarkers γ -H2AX+53BP1 in PBMC nuclei in conjunction with internal dosimetry quantify the induction and repair of DSBs by radiopharmaceuticals ex vivo and in vivo, even at very low absorbed doses to the blood.

Abstract ID 72854

Dosimetric monitoring of the person exposed to chronic, occupational, low-dose radiation during the Pandemic COVID-19 /2019 to 2021/

Todorova, P.A., Racheva G.P., Galev, A.R., Petrunon, P.S.*

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The biological effects of very low doses (up to 20 mSv) of ionizing radiation on occupationally exposed individuals have been the focus of radiobiology in recent decades and a major topic of research for radiobiologists. The long-term impact of low doses of ionizing radiation in occupational conditions is a problem related to the real assessment of the consequences of these effects. It is assumed that the radiation exposure in professional conditions is low doses and low dose rates. It is also characterized as chronic and protracted. It is known that the main risk and the main health consequences of this type of occupational exposure is the risk of malignancies after varying lengths of latency. Risk assessment under conditions of protracted or fractionated occupational exposure with low doses of ionizing radiation is difficult, often disputed and very debatable in the scientific literature. At present, it is based mainly on extrapolation of data from high doses of ionizing radiation. Therefore, every human population and professional activity exposed to low-dose radiation and with good physical dosimetry is an object of well-deserved interest on the part of radiobiology to clarify the problem. The present study aims to review, systematize and analyze the accumulated data in the field of monitoring the occupational, low-dose radiation exposure of personnel working in the environment during the period of the COVID-19 Pandemic (2019 - 2021).

Individual passive thermoluminescent dosimeters (TLDs) were used for periodic reading of the personal dose from external radiation caused by exposure to IDUs of professionally engaged persons in the clinics of the Military Medical Academy - Sofia.

The results show a significant increase in the average individual effective dose of staff involved in the treatment of COVID-19. The correlation analysis performed reported a strong relationship between the individual effective dose received by medical staff during the COVID-19 Pandemic period.

Ionizing radiation; thermoluminescent dosimeters; dosimetry

Abstract ID 74329

Assessing the kinetics of formation of dicentric chromosome aberrations and the effects of fractionated irradiation exposure

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Biological dosimetry using dicentric chromosome (DC) aberration is an important assay to estimate radiation doses received in radiation accidents. The yield (Y) of DCs following acute exposures is a linear-quadratic function of dose (D), $Y = C + \alpha D + \beta D^2$. In fractionated (or low dose-rate) irradiation, the yield of DCs is decreased by reducing the quadratic component (β) by affecting a time dependent function (G). However, the kinetics of DCs formation in function of time after irradiation has not been sufficiently studied experimentally.

We have examined the kinetics of formation of DCs as a function of time after irradiation and the effects of dose fractionation on the yield of DCs. Blood samples were collected from healthy volunteers after signing an informed consent. Whole blood was transferred to 10 × 25 ml cell culture flasks (each containing 2ml) and exposed to X-rays 320 keV for studying the kinetics of dicentric appearance following 2 and 4 Gy, split dose of 2Gy, fractionated doses (total 2 and 4 Gy) or single doses of (0.1, 0.25, 0.50, 0.75, 1, 2, 3, 4) for dose-response curve. The samples were processed as per EPR-Biodosimetry 2011 report.

Results of studying the kinetics of DCs yield as a function of time after irradiation, showed so far that the initial yield of DCs increased with increasing time to reach a maximum at about 4 hours after 2 Gy and 1-2 hours after 4 Gy of incubation after irradiation. This phase of sharp increase is followed by a quick decrease after 4-8 hours and remained almost constant to 24 hours of lymphocytes incubation before PHA stimulation. The DCs yields was also studied in split-dose and multi-fractions (which are at least 6 hours apart) experiments and compared to single doses. Both methods showed decrease in DCs yield that was proportional to the number of fractions (DCs/metaphase' were 0.337 compared to 0.275 in 2 Gy split dose and 1.318 compared to 0.981, 0.809 and 0.568 in fractionated 2 x 2, 4 x 1 and 8 x 0.5 Gy, respectively).

In conclusions, DCs yield increases quickly to reach a maximum at about 1-4 hours, possibly depending on the dose, then decreases to 4-8 hours and remains almost constant to 24 hours' post-irradiation. Exposure to fractionated irradiation that are separated by 6 hours or more decreases the DCs yield proportionally to the number of fractions. Further studies are needed for the evaluation of the effect of dose fractionation on the (G) function. Ultimately, a method could be derived to estimate doses after fractionated irradiation from calibration curves with conventional acute single doses.

Abstract ID 72858

EPR dosimetry in tooth enamel of former United States nuclear workers

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Electron Paramagnetic Resonance (EPR) dosimetry in tooth enamel was applied to estimate doses of external irradiation received by early nuclear workers, victims of various radiological accidents [1]. EPR has been proven to be a reliable method of retrospective dosimetry.

The United States Transuranium and Uranium Registries (USTUR) is a research program that studies actinide biokinetics in occupationally exposed individuals with known intakes of these elements. The Registries is operated by the College of Pharmacy and Pharmaceutical Sciences at Washington State University [2]. Samples of tissues and organs are acquired post-mortem from volunteer donors (Registrants). A majority of USTUR Registrants also had significant doses of documented external radiation exposure.

Eighteen molars and premolars were collected from ten USTUR Registrants. For seven individuals who worked with plutonium, life-time effective equivalent dose from penetrating external exposure ranged from 24 mSv to 375 mSv (GM = 110 mSv) with the exposure period ranging from 8.0 y to 41.4 years (GM = 27 y). Of the remaining three individuals, two worked with uranium and one was medically exposed to thorium with no records of external exposure. Powderized samples of tooth enamel were prepared using a standard technique and measured by EPR. In order to obtain radiation dose peak-to-peak amplitude of radiation-induced signal was related to calibration curve. This gives an opportunity to re-analyse samples independently using different EPR methodologies.

Radiation doses in enamel obtained by EPR were compared with officially recorded doses and the results can be used for further epidemiological studies.

Keywords Tooth enamel; EPR; radiation epidemiology; plutonium workers; USTUR.

References

[1] International Commission on Radiological Units and Measurements. Retrospective assessment of exposure to ionising radiation (Report 68). J. ICRU 2 (2002)

[2] Kathren R.L., Tolmachev S.Y. The United States Transuranium and Uranium Registries (USTUR): A five-decade follow-up of plutonium and uranium workers. Health Physics 117(2): 118-132; 2019.

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Abstract ID 72859

Last Decade Achievements of EPR Dosimetry

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This presentation discusses the main achievements of EPR dosimetry since 2010. It is personal and subjective. The achievements in several directions are considered, e.g. technical developments, applications to the radiation accidents, new dosimetric materials, validation including intercomparisons, publication of reviews and consensus documents.

Currently only calcified and keratinized tissues are used as radiation biomarkers for humans measured by EPR. Most technical developments in the EPR dosimetry with biomarkers were done for in vivo and biopsy techniques. Uses of rapid scan and pulse EPR were also tested.

EPR dosimetry was applied for dose measurements (dose reconstruction) after several radiation accidents occurred recently and long time ago. There were also several radiation background studies. These include radiation background studies in Japan, Russia, Malaysia, dose reconstruction for A-bombing survivors, inhabitants of the Techa river valley, residents of Kazakhstan exposed because of the radioactive fallouts from A-bomb testing, Fukushima accident, and several small-scale accidents. Most of these studies use tooth enamel as dosimeter. There were a few studies, which use fingernails as accident dosimeters.

Several new dosimetric materials were proposed as new EPR dosimeters, these include walnuts, tartaric acid, talc, zircon, cotton, Kevlar, different plastics, barium dithionate, various types of saccharides, taurine, aminoglycoside antibiotics, xylitol, sorbitol and some other materials.

Several EPR intercomparisons using tooth enamel and glass were conducted. Generally, they demonstrated a good performance of EPR dosimetry. ICRU report, two ISO standards, and several significant reviews on the EPR in tooth enamel, glass and fingernails were published in the last decade too.

Keywords EPR dosimetry; tooth enamel; radiation accidents;

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Alanine-EPR and Gel Dosimetry Combined for Intensity-Modulated Radiotherapy Treatment Quality Assurance Containing Bilateral Metallic Prostheses

Lima J.S¹, Tomazi B², Silveira M. A1., Pavoni J^{1,2}. F., Bruno A. C², Guidelli E. J¹. and Baffa O¹.

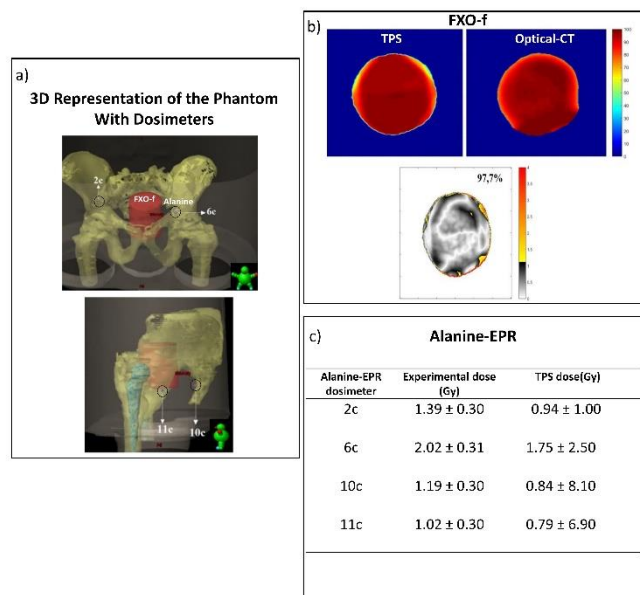
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The presence of metallic prostheses in patients undergoing radiotherapy can generate scattered doses, making the treatment planning irreproducible. This work aims to check the dose in the PTV and its vicinity, using a water phantom containing pelvic bones and bilateral metallic prosthesis. Intensity Modulated Radiotherapy (IMRT) was used with optimization tools that avoid input dose to the prosthesis. Experimental checking was done using the FXO-f gel dosimeter (for dose checking in the PTV) and alanine dosimeters (for dose checking in the vicinity). The gamma evaluation performed with the FXO-f dosimeter resulted in gamma indices <1 in 97.7% of the data when compared to the TPS, indicating good agreement with that reproduced by the linear accelerator. The alanine dosimeter results had larger relative differences compared to the TPS average doses, what is being investigated. Overall, the work obtained good results regarding the technique used, which enters fields towards the prosthesis, exploiting the optimization tools to block only the region of interest, without harming the dose distributions and the compliance index of the plan.

Keywords: Alanine-EPR dosimeter, Fricke Xylenol Orange modified dosimeter (FXO-f), Metallic Prostheses, radiotherapy treatment, IMRT technique.

Figure 1: Summary scheme of the work a) experimental 3D representation of the locations of the dosimeters b) results obtained for the FXO-f dosimeter c) results obtained for alanine-EPR dosimeter.



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Platinum Nanoparticle's Dose Enhancement in Alanine-EPR Dosimeter

Lima I.S., Guidelli E.J. and Baffa O.

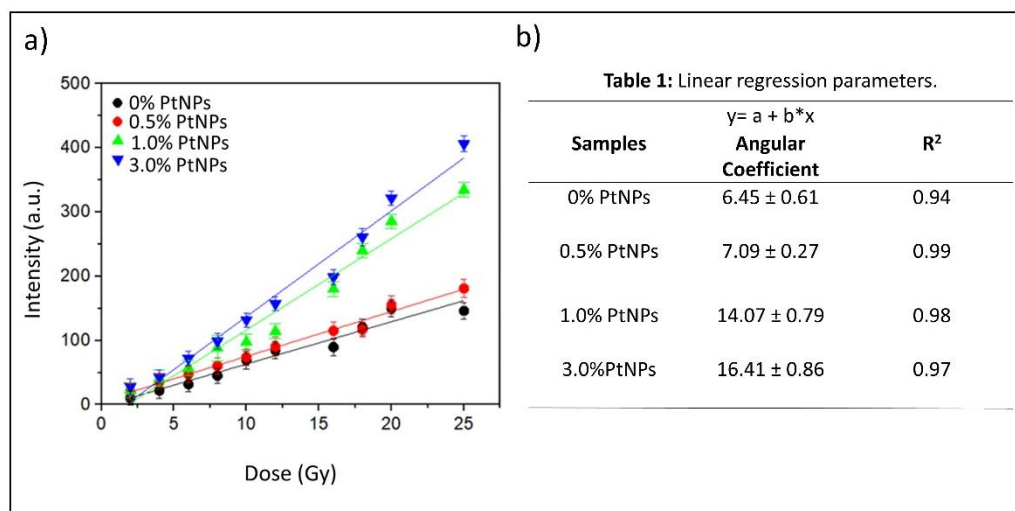
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Noble metals (Au and Ag) have been successfully employed to increase the sensitivity of alanine-EPR dosimeters. The increase in sensitivity is due to the high atomic number of the nanoparticles, which results a cross-section for x-ray interaction greater than that of alanine, causing the probability of interaction events with ionizing radiation to increase, providing a gain in dosimetric sensitivity. In this context, platinum nanoparticles (PtNPs) could be viable for dosimetric application, due to their high atomic number as well. Therefore, alanine dosimeters with different mass percentages of platinum nanoparticles were produced, followed by the physicochemical characterization of these nanocomposites (alanine/PtNPs), aiming applications in radiation dosimetry. The physicochemical characterization shows that the increase in the mass percentage of platinum nanoparticles led to an increase in the average size of PtNPs, however, without destabilizing the system. Platinum nanoparticles also influence the alanine crystallization process, and possibly the interaction pathway between the platinum nanoparticles surface is with the NH group of the alanine molecules. The dose enhancement factor (DEF) obtained for the different mass percentages of platinum, are 1.1 ± 0.3 , 2.2 ± 0.8 and 2.5 ± 0.9 for samples of 0.5%, 1.0%, and 3.0% of PtNPs, respectively. Samples containing 1.0% and 3.0% of PtNPs presented a sensitivity around 2.5-fold compared to pure alanine. Therefore, the insertion of PtNPs to increase the dosimetric sensitivity of alanine is also feasible, as is Au and Ag in alanine.

Keywords: Alanine-EPR dosimeter, nanocomposites, platinum nanoparticles, dose enhancement factor (DEF).

Figure 1:

Results obtained by the insertion of platinum nanoparticles into alanine-EPR dosimeter a) Dose-response for different mass percentage of PtNPs, showing the amplification of the sensitivity of the alanine-EPR dosimeter by the PtNPs b) table of the linear regression parameters calculated by the linear fitting and the correlation coefficient R^2 .



Acknowledgements

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Abstract ID 72867

High throughput method for dose estimation after ionizing radiation

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¹ Bundeswehr Institute of Radiobiology affiliated to the University of Ulm, Neuherbergstr. 11, 80937 Munich, Germany

Due to re-emerging radiobiological and nuclear (RN) threats, it is indispensable to drive research to the next level. The field of radiation biodosimetry has the task of identifying new methods to improve and especially to accelerate dose estimations that are critically needed in mass casualties in terms of rapid triage.

Ionizing radiation induces DNA damage, particularly double-strand breaks, leading to cellular dysfunction and cell death. Double-strand breaks provoke the phosphorylation of histone H2AX, which as a consequence recruits additional factors needed for DNA repair. Its staining and manual counting are suitable and well-established procedures to determine the absorbed dose.

However, our goal is to speed up the determination of γ -H2AX foci numbers per cell by automated imaging flow cytometry (IFC).

Therefore, venous EDTA-stabilized whole blood from healthy donors was irradiated with 240 kV X-ray resulting in 0.25, 0.5, 1, 2, or 5 Gy absorbed dose or sham (0 Gy). After 24h incubation in RPMI medium at 37°C, cells were stained with antibodies against γ -H2AX and cell markers like CD15, whereas the nuclei were labeled with DRAQ5. Subsequently, cells were measured with the Amnis Image StreamX MkII (Luminex) at 60x magnification, and spot count was performed by choosing adequate classifiers within the associated software INSPIRE™. We were able to measure about 5.000 cells per minute and analyzed reproducible γ -H2AX foci in lymphocytes. We could show a linear increase of γ -H2AX foci up to 2 Gy for the investigated dose range with comparable slopes for each volunteer.

In conclusion, IFC can offer significant benefits in determining DNA damage foci by counting γ -H2AX spots in thousands of cells within some minutes. However, additional dose-response calibration curves are needed to evaluate the influence of many confounders present within a heterogeneous population, which will be the potential patient cohort after an RN event.

Keywords: γ -H2AX; image flow cytometry; whole blood; triage;

Dose variations using an X-ray cabinet to establish in vitro dose-response curves for biological dosimetry assays

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In biological dosimetry, dose-response curves are essential for reliable retrospective dose estimation of exposure in case of a radiation accident. Therefore, blood samples are irradiated in vitro and evaluated based on the applied assay. Accurate physical dosimetry is a critical part of the experimental procedure and is influenced by the setup, especially when X-ray cabinets are used. The aim of this study was to investigate variations and pitfalls associated with the setups used to establish calibration curves in biological dosimetry with X-ray cabinets.

In this study, irradiation was performed with an X-ray source (195 kV, 10 mA, 0.5 mm Cu filter, dose rate 0.52 Gy/min, 1st and 2nd half-value layer = 1.01 and 1.76 mm Cu, respectively, average energy 86.9 keV). Blood collection tubes were irradiated with a dose of 1 Gy in vertical or horizontal orientation in the center of the beam area with or without usage of an additional fan heater. To evaluate the influence of the setups, physical dose measurements using thermoluminescence dosimeters, electron paramagnetic resonance dosimetry and ionization chamber as well as biological effects, quantified by dicentric chromosomes and micronuclei, were compared.

The results of this study revealed that the orientation of the sample tubes (vertical vs. horizontal) had a significant effect on the radiation dose with a variation of -41% up to +49% and contributed to a dose gradient of up to 870 mGy inside the vertical tubes due to the substantial difference between the distance of the sample to the tube focus and the distance of the reference surface to the tube focus. The number of dicentric chromosomes and micronuclei differed by approximately 30% between both orientations. An additional fan heater had no consistent impact.

Therefore, dosimetric monitoring of irradiation setups is mandatory prior to the establishment of calibration curves in biological dosimetry. Careful consideration of the experimental setup in collaboration with physicists is required to ensure traceability and reproducibility of irradiation conditions, to correlate the radiation dose and the number of aberrations correctly and to avoid systematical bias influencing the dose estimation in the frame of biological dosimetry.

Keywords biological dosimetry; thermoluminescence dosimeter (TLD); EPR alanine dosimetry; dicentric chromosome (DC); micronuclei (MN);

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Use of Double integral for tooth enamel EPR dosimetry

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The presence of a background signal in tooth enamel EPR dosimetry is the most difficult situations to overcome [1]. This becomes even more important because it shields/obscured the radiation induced signal, especially at radiation doses below 1 Gy. In order to overcome this problem, subtraction of the unirradiated sample signal from the irradiated one and simulation methods are the most widely used methods in the literature [1-3].

Obtaining the double integral of the experimental EPR spectra (1st derivative) of tooth enamel and its advantages for retrospective dose determination are discussed. Data obtained from 5th international comparison of tooth enamel EPR dosimetry study were used in the present work [4-5]. This method offers the opportunity to handle the whole experimental spectrum, both background and radiation induced signals, without performing any subtraction or simulations operations. A comparison was also made with the results obtained from the spectrum subtraction method. It is concluded that, double integration have the potential to increase the sensitivity of the minimum detectable radiation doses in tooth enamel EPR dosimetry.

Keywords: EPR, tooth enamel, double integral, retrospective dosimetry

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Abstract ID 72872

Alanine dosimetry for Very High Dose Rate proton therapy

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Purpose: The dosimetry for very high dose rate (VHDR) irradiation is a critical research topic since this delivery modality became popular due to the benefits of the FLASH effect [1] together with the technological growth making those VHDR easily accessible in research and clinical facilities. While a previous work has characterized ionisation chambers under a VHDR proton beam [2], alanine pellets were considered in this study as they appear to be a suitable candidate due to their dose rate independence and their linear response with dose [3].

Methods: The local clinical beamline using the pencil beam scanning technique was adjusted to enable VHDR irradiation with instantaneous dose rate up to 1000 Gy/s. Alanine pellets were positioned behind 2.1 cm thick solid water slabs (PTW RW3) and irradiated at the entrance plateau of a 226 MeV pristine Bragg peak for different mean dose rates ranging from 4 Gy/s and up to 388 Gy/s. Dose results were compared to the Advanced Markus ionisation chamber measurements which is used as a reference dosimeter in our facility. Finally, the readout of the pellets was performed at room temperature with an X-band electron paramagnetic resonance (EPR) spectrometer (Bruker E500) equipped with a high Q resonant cavity. Ahead of the measurements, preliminary alanine pellet irradiations at known doses (from 5 Gy to 130 Gy) were carried out with 10 MV photons in order to determine the response curve between the absorbed dose in water and the EPR signal intensity.

Results: Discrepancies between the alanine pellets and reference dose measurements were within experimental uncertainties and always smaller than 1% for doses above 20 Gy. Furthermore, the alanine response was found to be linear with the dose, which is identical to the response for conventional dose rates and therefore emphasizes the dose rate independence.

Conclusion: Alanine seems to be a suitable and reliable dosimeter for VHDR proton irradiation with promising results for all the tested conditions. However, the readout is time-consuming and requires knowledge of EPR spectroscopy as well as an access to a specific equipment.

Keywords Alanine pellets; Dosimetry; Proton therapy; Very High Dose Rate; EPR.

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Inter- and intra-individual variability of gamma-H2AX in healthy volunteers and clinical radiotherapy patients

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The γ H2AX assay has the potential to be a useful triage tool during large scale radiation accidents/incidents to identify critically exposed individuals and reassure the worried-well. It is important to understand inter- and intra-individual variability and how these impact dose estimations. Knowing background frequencies of γ H2AX foci within healthy, non-exposed control populations is important to determine minimum detectable doses and uncertainties. Similarly, inter- and intra-individual variation in the yields and kinetics of radiation-induced γ H2AX foci must be considered important modifiers for uncertainties associated with dose estimations. 339 samples from 32 healthy donors were analysed to determine spontaneous and ex vivo-induced foci yields following exposure to 0 – 1 Gy, 1- and 24-hour post-exposure. Under the US CMCR funded RTGene project[1], blood samples were taken from 20 radiotherapy patients with γ H2AX foci analysed prior to first fraction, 24 hours post-first fraction, prior to 5th or 6th fraction, and prior to penultimate fraction. Doses were estimated using a previously published bi-exponential model of γ H2AX foci repair kinetics, to test this model in vivo, and the data were compared to previously published dose estimated using the dicentric chromosome aberration assay and through modelling the exposed fraction of blood. For healthy normal controls, smoking status, gender and age had no significant effect on spontaneous or radiation-induced γ H2AX foci in this small cohort. Residual γ H2AX foci following ex vivo radiation exposure was a function of dose and time (both $p < 0.001$), but not of donor, with similar levels of intra- and interindividual variability observed among the healthy donors. For patients, while the doses estimated from the baseline γ H2AX foci yields did not vary on an interpatient basis, significant variation in foci yields and doses estimated using the bi-exponential model was identified. Time of sampling was critical for dose estimation. However, the previously published bi-exponential model assumes a continued low level of repair in time at a level which was not seen with the radiotherapy patients. As such, this method of dose estimation was not validated in vivo. To conclude, genetic or environmental factors do not appear to significantly modify baseline and radiation-induced γ H2AX foci yields in healthy adult donors. The identified range of variation will refine uncertainties associated with γ H2AX-based dose estimations for accidental exposures. For radiotherapy patients, given the level of interindividual variation in response between irradiated patients, the assay is not currently recommended for further research in clinical scenarios.

Keywords: H2AX, radiotherapy, biomarker, dose estimation, DNA damage

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Abstract ID 72919

Estimation of Dose received during Radiotherapy and its effects on miRNA expression

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Radiotherapy using X-ray irradiation is a commonly deployed method of targeting tumours in cancer patients. It is currently unclear if samples obtained from these patients serve as a suitable model for identification of biomarkers of radiation exposure. The goal of this study is to determine if Dicentric Chromosome Assay (DCA) and gene expression markers would be appropriate for analysing radiotherapy patient samples in the aspects of dose estimation (to verify the dose delivered during radiotherapy) and the effects of the delivered dose on miRNA gene expression.

This study used blood samples drawn from radiotherapy patients with prior ethical consent. Two sets of blood samples were collected from each patient: the first draw before their first radiotherapy (Baseline) and the second draw was performed between 8 - 48 hours after their first radiotherapy session (Irradiated). Peripheral blood mononuclear cells (PBMCs) were isolated and used in DCA and miRNA gene analysis according to standard protocols. Metaphase images were captured by MetaSystems Metafer Slide Scanning Platform and scored. Dose estimation was performed using our laboratory's modified open source software (DotDotGoose) with the scored metaphases in reference to our in-house 320-kVp, 1Gy/min, 12.5mA X-ray dose response curve. Isolated miRNA from each patient was analysed with NanoString nCounter SPRINT and Partek® Genomics Suite® software, v7.0 [1] to identify differentially expressed miRNA.

Based on the 19 samples analysed, no distinct trends were observed in samples with different tumour types, treatment modality, or existing chronic illnesses etc. It is likely that these factors vary in the extent to which differential miRNA gene expression and dicentric chromosome formation could be affected. Hence, subsequent analysis was performed on a fixed set of 10 breast cancer radiotherapy patients. Ellipsoid clustering of the baseline and irradiated samples in a principal component analysis (PCA) suggested that there is a difference in variation between the two groups, albeit with some overlap. Interestingly, it was also observed that CT simulation prior to collection of the baseline sample affected the analysis of differential gene expression. Subsequent analysis will focus on determining if dose estimation of whole and partial body exposure can be accurately determined using DCA. These preliminary results suggest that the radiotherapy patient samples can provide insights into differential gene expression and dose estimation. Analysis of more samples stratified based on tumour types and other factors will serve to enhance this study.

Keywords

Dicentric Chromosome Assay (DCA); Radiotherapy; Dose Estimation; miRNA expression

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End-to-end tests with alanine pellets read by EPR in a heterogeneous phantom for radiotherapy treatments

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Context: To calculate the dose delivered to patients treated by radiotherapy, Treatment Planning Systems (TPS) rely on dose calculation algorithms with known limitations including the management of heterogeneities and small fields. This work aims at evaluating the TPS performance in such critical conditions by performing end-to-end tests in a heterogeneous phantom with the Alanine/Electronic Paramagnetic Resonance (EPR) dosimetry system.

Materials and methods: Inserts suitable for alanine dosimeters were designed to perform end-to-end tests using alanine pellets positioned in different regions: normal tissue, lung or bone region of the CIRS 002 LFC thorax phantom (Figure 1). Irradiations were undertaken using a Varian medical accelerator for eleven different configurations. Measurements were also conducted with a CC04 ionization chamber (IBA). Dose to water calculations were performed with the Eclipse TPS (Varian) using the two Anisotropic Analytical Algorithm (AAA) and the AcurosXB (AXB) algorithms. Comparison between measured and calculated doses were performed for a reference field and for clinical treatment plans performed with either Dynamic Conformational Arctherapy (DCA) or volumetric Modulated ArcTherapy (VMAT).

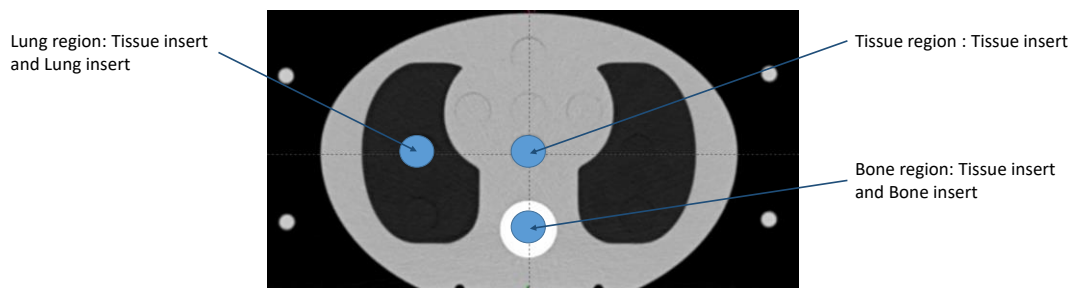


Figure 1: Description of the configurations studied on a Computed Tomography slice of the CIRS Thorax phantom

Results: In all irradiation configurations, the Eclipse AXB algorithm calculations agree with the alanine dosimeter measurements within the uncertainties, with a coverage factor $k = 2$. For the Eclipse AAA algorithm, calculations agree with the alanine dosimeter measurements within the uncertainties, with a coverage factor $k = 2$, for all irradiation configurations except for the DCA clinical planes which had the smallest field aperture (2.5 cm x 1 cm) and for which the dose difference is larger than 5 % in the lung region. Ionization chamber measurements overestimate the delivered dose compared to the alanine dosimeter measurements with a discrepancy larger than 6 % in the bone region.

Conclusion: In this work, alanine dosimeters were used to control the dose delivered during end-to-end tests in clinical configurations. Comparison with the ionization chamber highlighted the effectiveness of alanine dosimeters for the phantom bone region. Alanine/EPR dosimetry results revealed the difficulties of the Eclipse TPS AAA algorithm to deal with heterogeneous lung region of the phantom and a small field aperture.

Keywords Radiotherapy; alanine; End-to-end test; Dosimetry; EPR

Abstract ID 73043

RENEB INTER-LABORATORY COMPARISON (2021) FOR BIODOSIMETRY AND RETROSPECTIVE PHYSICAL DOSIMETRY

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Keywords:

RENEB, Inter-laboratory comparison, biological dosimetry, retrospective physical dosimetry, radiation preparedness

Abstract:

Biological and retrospective physical dosimetry are important tools for radiation exposure reconstruction to support medical management of radiation victims in radiological or nuclear incidents. Quality-controlled inter-laboratory comparisons (ILCs) are one possibility to test the performance of laboratories and the international networks to meet basic diagnostic demands in radiation preparedness.

In 2021 the European legal association RENEB e.V. (Running the European Network of Biological and Physical retrospective Dosimetry) performed a worldwide exercise to improve, validate and test various cytogenetic methods (dicentric chromosome assay [DCA], cytokinesis-block micronucleus assay [CBMN], stable chromosomal translocation assay [TRANS] and premature chromosome condensation assay [PCC]), molecular biological assays (gene expression (GE) and gH2AX-foci (gH2AX)), and also physical methods (electron paramagnetic resonance spectroscopy (EPR) and luminescence assays (LUM)) in parallel.

Three blinded coded human blood samples were exposed in vitro to 0, 1.2, and 3.5 Gy X-ray reference doses (240 kVp, 0.63 mm HVL(Cu), 1 Gy/min). These doses were chosen to focus on the clinically relevant groups of unexposed, moderately exposed (no acute health effects expected), and highly exposed (intensive medical care necessary) patients. The samples were sent to 86 specialized teams in 46 organizations from 27 nations to identify the three clinically relevant groups and for dose estimation.

First dose estimates/categorizations were reported within 5-10 h of receipt for GE, gH2AX, LUM, EPR, 2-3 days for DCA, CBMN, and estimated to be available within 6-7 days for the TRANS assay. All assays achieved successful categorization into clinically relevant groups for 86 to 100%. The percentage of reported precise dose estimates within the uncertainty interval for the 0 Gy reference samples was about 90-100 % for all assays. For most assays, 50-80 % and 40-100 % for the 1.2 Gy and 3.5 Gy reference samples, respectively. There was a trend of overestimating the physical reference dose for many assays.

The RENEB-ILC 2021 proved the clinical usefulness of the biological and physical dosimetric techniques offered within the RENEB network for radiation preparedness. Limitations, needs and hints for optimization will be discussed.

Abstract ID 73056

Analysis of inter-laboratory comparison data from the Canadian Biodosimetry Network

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For emergency biodosimetry, the development of inter-laboratory networks is paramount to being able to provide rapid dose estimates in order to inform the medical community, and manage health impacts of exposures. In order to participate in a network, it is essential that all laboratories' results be validated to ensure comparable dose estimates for similarly exposed samples. This can be accomplished through inter-laboratory comparison (ILCs), where irradiated and blinded samples are shared amongst the participating laboratories and the dose estimates are submitted and tested for acceptance. This has commonly been accomplished using a Z-score with a robust standard deviation (s^*) [1,2]. However, with doses close to 0 Gy, the distribution of the dose estimates from the laboratories loses its normal distribution, which is required for this approach.

Health Canada is the lead laboratory in the Canadian Biodosimetry Network and has the responsibility of conducting annual ILCs. Since 2007, 12 of these ILCs have been completed. These comprised of 10 irradiated and blinded blood samples or slides being sent to 4-10 laboratories for dose estimation by the dicentric assay or other assays available in the laboratory. The ILCs have included up to 4 Canadian laboratories but have also expanded to include the United States, Taiwan, the Republic of Korea, Singapore and Argentina [3]. These ILCs have resulted in a vast amount of data that can be used to determine the best way to test the success of each laboratory in correctly identifying a dose in the range of 0-4 Gy with triage level scoring of 50 cells or fewer.

In order to address the issue of low doses, we have been investigating options for performing acceptance testing including predefining standard deviation values for dose ranges instead of calculating s^* . Drawing from our large data set, we are able to compute the s^* as a function of dose to help determine reasonable values for the standard deviation that could be used as a priori values. These predefined s -values could then be applied to Z-score models to determine which best suits our data. The results from this analysis will be used to validate the accuracy of the participating laboratories for rapid dose estimation.

Keywords: Biodosimetry, Inter-laboratory Comparison, Acceptance testing

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Abstract ID 73057

Energy dependence of g-values for the purpose of dose reconstruction of soda-lime samples irradiated in a dose range 0.1 – 10.0 Gy

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In the field of Electron spin resonance (ESR) dosimetry variety of materials are being investigated for the purpose of dose reconstruction of the victims of radiological and nuclear accidents. One of the desirable properties of ESR dosimeter is energy independence since the radiation accidents are mostly caused by the mixed radiation sources.

Soda-lime glass has been proven to be a good ESR dosimeter in the dose range above 2 Gy by using the ESR signal amplitudes, but below 2 Gy the radiation induced signal is overlapping with the intrinsic ESR signal. It was shown [1,2] that in the range below 2 Gy is possible to reconstruct the dose from the soda-lime glass samples by using the g-value dose dependence of ESR signals.

All irradiated soda-lime samples exhibit ESR spectra that can be decomposed to inhomogeneous background signal (BKS) with associated gBKS value, and homogeneous radiation induced signal (RIS) with associate gRIS value. The effective g-value of the irradiated sample is combination of these two.

In this study, the dependence of g-effective value on the radiation energy of the ESR signal was investigated. The g-effective value has exponential dependence on the dose as shown before [1,2]. The samples were irradiated with gamma sources of different energies, X-ray source of energy 39.40 keV and Co-60 source of the mean energy 1.25 MeV in the dose range from 0.1 – 10.0 Gy.

All irradiations were performed in IBA Dosimetry Laboratory and the ESR readout was performed on the Bruker Magnetech ESR5000 spectrometer in the Laboratory for Electron Spins Spectroscopy at the Ruđer Bošković Institute.

As a conclusion, the preliminary study shown that the g-values of the samples are independent on the energy of radiation source for the energies used in this research.

Keywords

ESR Dosimetry; Soda-lime glass; ESR signal; g-values; energy dependence.

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Abstract ID 73058

Alanine dosimetry for radiotherapy auditing and preclinical research: Assessment of a robust procedure for handling of EPR spectra at doses below 3 Gy.

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Alanine pellet dosimetry is normally carried out using peak-to-peak analysis of electron paramagnetic resonance (EPR) spectra. This procedure is challenged at low doses, where it becomes apparent that the EPR spectra contain contributions not only from the alanine in the sample dosimeter, but also contributions from other sources. Therefore, EPR spectra at low doses (e.g. below 3 Gy) are not simply scaled down versions of the spectra recorded at large doses, and simple peak fitting-procedures are unable to accurately estimate the background signal. In the past [1], we implemented an iterative procedure that first resolved all spectra into an alanine part and a residual part following research carried out at NPL [2]. However, this is a relatively complex process, and we have therefore now developed a simplified, robust procedure, that does not rely on peak fitting, but instead sums over fixed regions of the EPR spectra.

Extensive measurements have been carried out over a 2 year period using uncoated alanine pellets (4.81 mm diameter and 2.7 mm height) from Harwell Dosimeters Ltd. and a Bruker EMXmicro spectrometer. New software for the spectrum analysis and data management have been developed and validated.

The method is now the basis for an ISO-17025 accredited measurement service for the 0 Gy to 200 Gy dose range, mainly intended for applications related to radiotherapy auditing and preclinical research [3] with beams of high-energy photons, electrons and protons. The standard uncertainty ($k=1$) for measurements close to 0 Gy is about 0.25 Gy for one single pellet. At 50 Gy, the relative standard uncertainty ($k=1$) is about 1% for one single pellet and 0.53% for a group of five pellets.

This work discusses the features of the new method and we compare results with the conventional peak-to-peak method. For example, it is demonstrated that the main part of the background signal within each read-out session is additive to all dose levels and that the uncertainty estimates associated with the read-out process are realistic.

Keywords alanine; EPR; dosimetry; radiotherapy; spectrum analysis

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Abstract ID 73153

Alanine doses measured in the mailed dosimetry intercomparison at CCB IFJ PAN ocular proton therapy facility

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Introduction. Quality control of therapeutic photon beams in the form of postal dose audits is widely used in photon radiotherapy centres. On the other hand, no commonly used, standardized dosimetry auditing program has been established for proton centres so far. This situation motivated EURADOS Working Group 9 (WG9) to investigate selected passive detectors in therapeutic proton beams in terms of their application for routine dose audits. The studies have shown that EPR/alanine dosimetry should be strongly considered as one of the methods which could be potentially applied for dosimetry audits in proton radiotherapy [1].

The next step undertaken by IFJ PAN in the frames of WG9 was organizing the dosimetry intercomparison among ocular proton therapy facilities. Alanine was one of the detectors used in this activity. In the paper we present a part of the intercomparison results i.e. alanine doses measured at the IFJ PAN proton eye radiotherapy facility.

Material and methods. In the reported part of intercomparison alanine detectors from three laboratories were used; Synergy Health detectors from Istituto Superiore di Sanità (ISS), the same type of detectors from Institute of Nuclear Physics Polish Academy of Sciences (IFJ PAN) and Harwell Dosimeters detectors from Research Group NuTeC, University Hasselt (UH). All detectors were irradiated in the dedicated PMMA phantoms at CCB IFJ PAN facility in 70 MeV passively scattered proton beam, in fully modulated Spread-out Bragg Peak (26 mm range), with nominally dose of 15 Gy. Then they were read out according to the individual procedures applied in each of laboratories.

Results and conclusion. The obtained results show a very good agreement between measured and planned dose. This result confirms the earlier studies [1] pointing to alanine as a promising candidate for detector used for routinely dosimetry audits of therapeutic proton beams.

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RENEB Inter-laboratory comparison (ILC) 2021 applying dicentric chromosome assay for biological dosimetry

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Abstract

Regular quality-controlled inter-laboratory comparisons (ILCs) are important to allow the comparison of laboratories and to identify needs to optimize international networking in the field of biological dosimetry. ILCs are regularly performed in the frame of the European legal association RENEb (Running the European Network of Biological and Physical retrospective Dosimetry) to validate and improve the procedures for various assays. The dicentric chromosome assay (DCA) is considered as the “gold standard” for radiation biodosimetry and is an important tool for dose assessment in small and large-scale radiation accidents. For a large-scale accident, where many individuals are potentially exposed to ionizing radiation, the scoring procedure has to be adjusted to handle the large amount of samples in a reasonable amount of time and it is crucial to test the performance of the laboratories under conditions simulating a real accident situation. 33 laboratories from 22 countries participated in the current RENEb ILC (2021) for the DCA. The study design included the irradiation of blood samples, blood shipment, sample processing, analysis of chromosome aberrations and dose assessment. Blood was irradiated in vitro with X-rays and three blind coded blood samples were sent to each participant. The task was to culture samples, to prepare slides and to assess radiation doses based on the observed dicentric yields. The main aims were to test the response time of the participants, to determine whether the estimated radiation doses of the participating laboratories were in good agreement with the reference doses and to identify potential needs for further training and harmonisation. The participation of laboratories from countries around the world gave the opportunity to compare the results on an international level. The results of the ILC for the DCA will be presented the potential and limits of the DCA in the case of a large-scale accident will be discussed.

Keywords:

RENEb, Inter-laboratory comparison, biological dosimetry, dicentric chromosomes

Abstract ID 74331

Long-term cytogenetic follow up studies on humans with internal and external exposure to ionizing radiation

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Human exposure to ionizing radiation inflicts a wide spectrum of DNA lesions and among them DNA double strand break is the most deleterious lesion as its persistence leads to either cell death or genomic instability depending on the severity of radiation exposure. Mis-rejoining of DNA double strand breaks results in the formation of stable and unstable chromosomal aberrations. Chromosomal aberrations are surrogates for estimating a person's absorbed radiation dose since their formation is reflective of radiation quality, dose and dose rate. Besides estimating absorbed radiation dose, cytogenetic analysis can be useful for long-term monitoring of any stochastic health effects in radiation exposed victims because chromosomal aberrations are indicators of genomic instability. At the REAC/TS CBL, we have been performing cytogenetic follow-up studies spanning from 5-50 years on some of the radiation victims with various modes of exposure: (I) internal radioiodine exposure, (II) diagnostic over exposure with X-rays during fluoroscopy procedure, (III) uranium blast exposure during the Y12 criticality accident in Oak Ridge and (IV) accidental external γ -rays exposure to workers in an industrial sterilizing unit in Bulgaria. To perform the cytogenetic follow up of these victims, REAC/TS CBL utilizes a wide variety of techniques including multicolor fluorescence in situ hybridization (mFISH) and chromosome specific multicolor BAND (mBAND) for analyzing stable and unstable chromosome aberrations as a function of post-exposure time. Our studies suggest that the nature and persistence of chromosomal aberrations observed in these cases depend on radiation quality and mode of exposure. Molecular mechanisms for the persistence of simple and complex chromosome translocations and their potential impact on chromosome instability of hematopoietic system in the exposed victims will be discussed.

Key words: Ionizing radiation; internal exposure, external exposure, retrospective cytogenetic biodosimetry; stochastic effects; chromosome instability

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Is sulfanilic acid used as ESR dosimeter for medical applications?

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The development of new dosimeters with good dosimetric properties is important for quality control in radiation applications. Sulfanilic acid has tested as a radiation therapy dosimeter by recently studies (Maghraby, A. and Tarek, E. 2006, Alzimami et al.,2014). In this study, the potential of gamma-irradiated sulfanilic acid (C₆H₇NO₃S) powder form as a dosimeter for quantitative analysis of the effects of low-dose ionizing radiation was analyzed by Electron Spin Resonance spectroscopy. Irradiations were performed at room temperature (290 K) using a ⁶⁰Co gamma cell, supplying a dose rate of 32 Gy/h as an ionizing radiation source at the TENMAK Nuclear Energy Research Institute in Ankara. ESR measurements were carried out using a Bruker EMX-131 X-band ESR spectrometer operating at 9.5 GHz provided with a TE102 rectangular resonance cavity and 100 kHz modulation field. Although unirradiated (control) sulfanilic acid exhibited no ESR signal, irradiated one showed single line ESR spectrum spread over a magnetic field range of 100 G as shown in Figure 1. Variation of the peak heights with the sample mass irradiated at 2 Gy were studied in the range of 130-300 mg. The ESR signal intensity observed at g-factor =2.0053 of this compound has been observed dependent to sample mass, so ~250 mg was chosen at each step of study. The paramagnetic center formed in the gamma-irradiated sulfanilic acid was followed during 50 days, the variation in signal intensity during this period did not exceed ±13.8%. The dose response curves in the dose range of 0.05 Gy-1 Gy and 2-10 Gy were reported. The fitting values of function that best describes dose response curves are calculated. The minimum detection dose limit was detected as 50 mGy by measuring ESR signal intensity. With all these investigations, sulfanilic acid can be used to estimate gamma radiation dose with reasonably well accuracy in the radiation therapy (medical applications).

Keywords ESR, Sulfanilic acid, dosimeter, gamma irradiations

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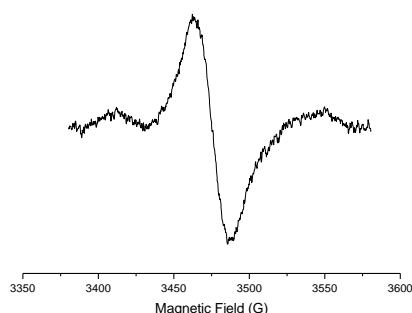


Figure 1. Room-temperature ESR spectrum of sulfanilic acid sample irradiated at a dose of 30 Gy.

Could alanine/EPR dosimetry be useful for ultra-high dose rate beams used for FLASH radiotherapy?

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In the last years a large interest has aroused towards radiation therapy treatments with dose rates much larger with respect to the conventional ones since experiments support the evidence of a considerable normal tissue sparing effect [1]. Indeed, in-vivo experiments showed an increasing of the therapeutic window for dose rates over 50 Gy/s [2]. If confirmed, the 'FLASH effect' has the potential to re-shape the future of radiation treatments, with a significant impact on many oncology patients [3]. Significant dosimetric challenges should be dealt with for Ultra-high dose rate (UHDR) beams for FLASH radiotherapy [4]. In particular, ionization chambers are affected by ion recombination effects, although novel approaches for decreasing or correcting for this effect are being proposed [5]. Passive dosimeters, as radiochromic films and alanine [6], could be used for UHDR measurements, although dose determination is typically time consuming. Detectors for real-time measurements are under investigations such as solid state detectors (mainly diamond or Silicon Carbide (SiC) detectors).

This work aims at investigating the response of alanine pellets exposed to UHDR electron beams. The electron beams used with energies of 7 and 9 MeV, accelerated by a SIT-Sordina ElectronFlash Linac, at conventional and UHDR regimes were used. High average dose rates (up to several hundreds of Gy/s) were adopted for the experimental campaign, characterized by instantaneous dose rate even more than two orders of magnitudes larger. Pulse structure of the used accelerator is characterized by a pulse duration between 1-4 μ s and a frequency up to hundreds of Hz. In order to investigate a possible dependence of alanine response on the dose rate for these UHDR beams, the depth dose profile accomplished by stacking alanine pellets along the electron beam direction was analysed. Monte Carlo simulations were performed and compared with experimental results. The results will be presented and discussed in details.

Keywords Alanine, FLASH radiotherapy, ultra-high dose rates, EPR dosimetry

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Abstract ID 73816

The odd couple DNA damage and ionizing radiation

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Biological dosimetry began about 60 years ago, and it was thanks to a high number of previous research. The proposed conference will give a brief history of how the idea of measuring absorbed dose arose from biological parameters, and will present certain aspects related to the establishment of effect dose curves that we consider valid but which may not be so valid.

Keywords: DNA damage; ionizing radiation, biological dosimetry

Beam Quality Effect on Relative Response of Alanine Pellet Dosimeters in Kilovoltage X-rays

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With the introduction of small self-shielded kilovoltage (kV) x-ray emitters as a possible replacement for the widely used gamma emitters for purposes such as blood irradiation, an enhanced interest in characterizing the energy dependence of the alanine/EPR dosimetry system has been sparked. The induced EPR-response per dose to the alanine pellets is decreased for irradiations in a kV x-ray field (Q) relative to a reference Cobalt-60 field (Q₀). Several studies (e.g. [2]) have argued that the energy dependence, quantified by the relative response $F(Q, Q_0)$, consists of contributions from the relative ratio of dose-to-alanine to dose-to-water $H(Q, Q_0)$ and the relative ratio of intrinsic efficiency in signal production, the relative detector efficiency, $G(Q, Q_0)$.

The alanine/EPR dosimetry system is typically calibrated in a Cobalt-60 reference field. For use of the alanine/EPR dosimetry system in kV x-ray fields it is therefore essential to establish a beam quality correction factor $k_Q = F(Q, Q_0)^{-1}$ for correcting a Cobalt-60 calibrated dose measurement. This correction factor can be assessed based on literature values for the relative response, however it is not clear whether this value can be unambiguously determined based on reported beam qualifiers (the same accelerating potential of an x-ray emitter can lead to different beam qualities depending on the filtration of the beam).

In the present study microdosimetric model calculations of the relative detector efficiency $G(Q, Q_0)$ of the alanine pellet dosimeter [1] are combined with Monte Carlo calculations of relative dose ratios $H(Q, Q_0)$, for a wide range of low and medium energy x-ray spectra, to examine the variation in relative response $F(Q, Q_0)$. The aim of the study is to both determine the optimal beam qualifier for assessing the relative response of the alanine pellet dosimeter in kV x-ray field based on literature values, as well as to quantify the uncertainty of this value based on the applied beam qualifier.

Results show that the average energy of the x-ray spectral distribution serves as the optimal beam qualifier for unambiguously determining the relative response $F(Q, Q_0)$ of the alanine pellet dosimeter. The variation in predicted relative response was estimated by fitting a third order polynomial to the model calculations and calculate the residuals. Using HVL/effective energy results in standard deviation of residuals $\approx 2.5\%$ for the low energy part of the spectra, while using the average energy as beam qualifier reduces the standard deviation of residuals to $\approx 0.6\%$.

Keywords Kilovoltage x-rays; Alanine; Dosimetry; Relative response; Monte Carlo.

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Abstract ID 73828

Dynamics of gene expression in circulating leukocytes during radiotherapy

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Introduction

External beam radiation therapy leads to cellular activation of the DNA damage response (DDR). DNA Double-Strand Breaks (DSBs) activate the ATM/CHEK2/p53 pathway inducing the transcription of stress genes. The dynamic nature of this transcriptional response has not been directly observed in vivo in humans.

Methods

We monitored the messenger RNA transcript abundances of several p53 downstream target genes in circulating blood leukocytes at different time-points (2, 6-8, 16-18 and 24 hours) in cancer patients undergoing radiotherapy with different volumes exposed (lung, neck, brain, and pelvis)

Results

We found that the calculated mean physical dose to the blood was very low (0.038-0.169 Gy) and Ferredoxin reductase (FDXR) was the only gene sensitive enough (1) so that a transcriptional up-regulation was detectable 2 hours after exposure and was dose dependent from the lowest irradiated percentage of the body (3.5 % whole brain) to the highest, (up to 19.4%, pelvic zone) reaching a peak at 6-8 hours. Following multiple fractions, the expression level increased further and was still significantly up regulated by the end of the treatment. Moreover, we compared FDXR transcriptional responses to IR in vivo with healthy donors' blood cells exposed ex vivo and found a good correlation in the kinetics of expression from the 8 hours' time point onwards suggesting that a molecular transcriptional regulation mechanism yet to be identified is involved.

Conclusions

To conclude, we provided the first in vivo human report of IR-induced gene transcription temporal response. An extended study would provide individual biological dosimetry information and may reveal inter-individual variability to predict radiotherapy-associated adverse health outcomes.

Keywords

Biological dosimetry, radiotherapy, gene expression, blood, FDXR

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Abstract ID 73830

Twenty-two years later: Consistent dose estimation of an accidental overexposure by retrospective biological dosimetry

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As the chromosomal translocation rate increases with age in the non-exposed population, the translocation-based dose estimation of an external radiation exposure victim needs to take into consideration such background. We sought to retrospectively estimate the dose of exposure of a victim from the Lilo radiological accident in Georgia twenty-two years afterwards and compare it to the original biological dosimetry-based dose calculation performed in our laboratory. Similar types of studies have retrospectively estimated a radiation dose, notably involving victims of the Chernobyl, Goiânia and Tammiku accidents¹⁻³. Nevertheless, their estimations were done after shorter periods of time post-exposure and in some cases, the exposure might not have been exclusively of an external nature^{1,2}.

In this study, we used Fluorescence In Situ Hybridization (FISH) to detect and score chromosomal translocations in lymphocytes from a recent blood sample of the victim. We performed the analysis using our laboratory's updated FISH dose-effect curve and taking into account translocation data from a large panel of unexposed individuals. We found the mean exposure dose to be similar to the original assessment obtained by the dicentric chromosome assay (DCA) more than 22 years ago. Furthermore, the confidence interval from the DCA analysis was contained within our FISH confidence interval, which as expected, was slightly larger. Altogether these observations confirm a comparable dose estimation.

In conclusion, retrospective biological dosimetry by FISH allowed us to estimate a dose that is consistent with the original assessment 22 years prior. This suggests that our current dose-effect curve could be used for relative dose estimations long time after external exposure.

Keywords Retrospective biological dosimetry; FISH; Chromosomal translocations; Accidental overexposure.

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Abstract ID 73835

On the importance of dosimetry in radiobiology studies: an overview of critical problems in dose assessment and dosimetry protocol description

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As outlined in several papers [1-7] over the last 35 years, the importance of reliable and repeatable dosimetry in radiobiology studies is very frequently underestimated nor ignored in radiobiology publications. Very few publications correctly report the dosimetry methodology with all information and parameters allowing to reproduce the experiments. This problematic will be discussed by providing an example for the current literature and by proposing a list of parameters to be reported depending on the type of the irradiator. In addition, the methodology is also not always appropriated to be able to determine the absorbed dose in the biological sample under investigation. Some examples of errors classically made will be provided and discussed. Part of the discrepancy highlighted for example in inter-laboratory comparison programs can be explained by wrong set-up or difference in dose quantities reported or inappropriate protocols of dosimetry [5]. The role of physicists in radiobiological studies will be discussed as well as the necessity to reach a minimum of quality assurance concerning the irradiation and the dosimetry aspect.

Keywords Radiobiology studies, dosimetry, quality assurance, protocol,

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Abstract ID 73839

EPR retrospective dosimetry with sugars: results of the 2019 EURADOS Field exercise

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During the EURADOS-RENEB field exercise organized in 2019 in Sweden [1], beside biological dosimetry and OSL/TL techniques, different types of sugars (sucrose, mannose,) and ascorbic acid were also exposed and analysed by EPR spectroscopy for dose estimation. Those types of materials are likely to be found in food or medicine pills possibly carried by victims of irradiation. Samples were exposed at different locations on the surface of 3 anthropomorphic phantoms irradiated with and Ir-192 source mimicking a radiological accident with a gamma radiography device. Phantoms were placed at different distances and orientation to investigate various configuration of irradiation with different level of dose heterogeneity [1]. We present in this paper, the methodology use to assess the dose by EPR spectroscopy and the comparison of the results with reference dosimetry perform by Radiophotoluminescent dosimeters. A good agreement was found (<10%) on the different locations between EPR and references doses for doses above 1 Gy. For doses between 0.5 and 1 Gy the maximal error is about 25 %.

Keywords EPR retrospective dosimetry; sugars; field exercise dosimetry

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Recent Outcomes of NATO SPS Project: Novel biological and physical methods for triage in (R/N) radiological and nuclear emergencies “BioPhyMeTRE”

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The “BioPhyMeTRE” project (2020-2023) focuses on the validation of innovative biological and physical methods for a rapid screening/triage of potential victims involved in radiological and nuclear (R/N) accidents by using inexpensive and user-friendly analytical procedures and devices [1]. In this regard, the validation of a novel biological dosimetry method combining the dicentric chromosome assay (DCA) and the micronucleus test (MN) in a single protocol is ongoing. The method was optimized modifying key steps (i.e. colcemid treatment and fixation) in order to obtain an adequate number of good quality metaphases and binucleated cells for triage procedure, both in control and in irradiated samples. The combined biological protocol was compared to the standard methods for DCA and MN in terms of numbers of dicentrics and micronuclei induced by ⁶⁰Co gamma rays at the following doses: 0.5, 1, 2, 3 Gy. Moreover, the automation of the scoring for the combined protocol has been performed by the METAFER 4 scanning platform: for the analysis a single classifier is used, which combines three different search/analysis algorithms by executing them in an ordered sequence. Simultaneously, physical dosimetry study on the everyday personal objects of low cost, that people give up easily in the event of an accident emergency with optically stimulated luminescence (OSL) technique was conducted. Encouraging results obtained applying this technique to personal objects have already been reported in literature, but the novelty of this study is the instrument proposed for the analysis: a low-cost, portable system applicable in situ for rapid tests (about 60 s) on samples as received. Among different kind of examined samples, salty crackers and supplements containing vitamins and minerals appeared very promising given the high radiation sensitivity of some of their components (mainly salts). Radiation sensitivity and dose response in the range of interest for R/N emergency dosimetry (0.1-5 Gy) were investigated by using different stimulations, infrared (890 nm) or blue light (470 nm).

Acknowledgements: “BioPhyMeTRE” Project is fully funded by Science for Peace and Security NATO Programme (Grant G5684).

Keywords Retrospective dosimetry; radiation triage; dicentric chromosome assay; micronucleus assay; photo-stimulated luminescence

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Dating sediments from Paranagua barrier by EPR

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Quartz is one of the minerals useful for EPR dating, as calcite, aragonite. [1] The method is based on the principle, being same as luminescence dating, that unpaired electrons are created by natural radiation and accumulated in the mineral in the geological time scale, where the number of unpaired electrons are measured as the intensity of the EPR signal. Al, Ge and Ti centers are observed in natural quartz and have been used for EPR dating [1]. The EPR signal due to aluminum center, an aluminon impurity replacing a silicon trapping an electronic hole, is $[AlO_4]^\bullet$, an aluminum impurity replacing a silicon trapping an electronic hole, is one of the useful signals for this method [2].

Barrier Paranagua is located in state of Parana, Brazil. This barrier extends for about 25 km from the sea coast and its height varies from 3 to 10 meters. Dating of sediments by EPR is part the purpose of the present work.

Samples for dating have been collection from 10 km from sea coast in four levels from the top called 10K1X, 10K2X, 10K3X and 10K4X. As usual the sediments were washed in solution of 10% H₂O₂, 10 % HCl and 20% HF to eliminate organic particles and iron compounds, and iron compounds [3]. Sieving was carried out to retain quartz particles with diameter between 75 – 180 μ m [2].

Quartz sample was separated into 10 aliquots of 100 mg. Nine of them were irradiated with a panoramic Co-60 gamma ray source with a dose between of 5 and 250 Gy. Measurements of all the samples were carried out with an EPR spectrometer in MiniScope mini 5000 Bruker, at Sao Paulo, University. at 98 K using a nitrogen gas flow system. The microwave power was 60 mW, the modulation amplitude was 0.12 mT scanned in 82 s, with frequency of 100 kHz, with 100 mg of sample. The Al center intensity was measured from the top of the first peak to the bottom of the 16th peak [4].

Equivalent dose was determined by the additive method with dose-response curves, results are: 78 ± 24 Gy (10K1X), 87 ± 21 Gy (10K2X), 93 ± 5 Gy (10K3X) and 112 ± 16 Gy (10K4X).

Keywords Quartz; dating by EPR, dose recovery.

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EPR and TL studies of synthetic CaSiO₃ and Li₂SiO₃ polycrystals for gamma dosimetry

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In this project, synthetic polycrystals of CaSiO₃ doped with Eu (1000 ppm) were synthesized by the devitrification method. That is, appropriate quantities of CaO, SiO₂, and Eu₂O₃ were mixed and placed on the furnace up to 1500 °C for 2 h and cooled slowly for about 24 h. The polycrystal obtained exhibits three thermoluminescence (TL) peaks at 119, 236, and 365 °C when used and heating rate of 4°C/s. For this sample, EPR signals shown center at about 2.0086, 2.0052 and 2.0006 centers. On the other hand, undoped and doped with 0.5 % mol of Ce, Eu, Tb, Cu, Sm, Ti of lithium silicate Li₂SiO₃ were produced by the solid-state method. That is, appropriate quantities of Li₂CO₃, SiO₂, and the dopant were mixed and placed on the furnace up to 900 °C by 24 hours and cooled up to reach room temperature. All samples, in this case, showed TL peaks at about 150 °C and 280 °C. EPR measurements for samples, except for the one doped with Cu, shown center at about 1.9840, 1.9684, and at about 1.9218. In this work, electron paramagnetic resonance (EPR) spectroscopy was used to study the defect centers induced in the polycrystal by gamma irradiation and to identify the centers responsible for the TL process. These results will be shown in the meeting.

Keywords: CaSiO₃, Li₂SiO₃, EPR, Devitrification, Solid-state method.

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End-To-End test with alanine dosimetry for verification of TPS dose calculation for small animal irradiation with small diameter X-rays beam

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The small animal radiation research platform (SARRP, Xstrahl Inc.) is an advanced small animal image guided radiation platform enabling state-of-the-art image guided therapy (IGRT) research to be performed by combining high-resolution cone beam computed tomography (CBCT) imaging with an isocentric irradiation system and a dedicated treatment planning system (TPS, muriplan). Such platforms are capable of replicating modern clinical systems similar to those that integrate a linear accelerator with on-board CBCT image guidance. The commissioning of the treatment planning system is performed by a procedure developed by Xstrahl Inc. using EBT3 radiochromic films [1]. The aim of this work was to develop and implement an end-to-end dosimetry test to validate the dose calculated by the TPS. The proposed method is based on EPR alanine dosimeters. Alanine dosimeters were wrapped in a thin waterproof film and introduced in the abdomen of mice sacrificed beforehand. The mice with the inserted alanine dosimeters were imaged to define the irradiation sequence focused on the alanine dosimeter and to calculate the dose to the alanine dosimeter with the TPS (Figure 1). Alanine dosimeters were then irradiated with 5x5 mm and 10x10 mm beam size with single beam or arc therapy treatment at 220 kV. For the 10x10 mm field, ten different beam configurations were tested (various single angle and arc), and 3 configurations for the 5x5 mm for a calculated dose of 90 Gy. Alanine dosimeters were read out with X-band E500 EPR spectrometer. The average dose estimated with alanine dosimeters were respectively 95.1 Gy with a relative standard deviation (RSD) of 5.5% for the 10*10 mm field and 100.9 Gy with a RSD of 6.6 % for the 5x5 mm field. The maximal relative error was found to be of 18 % for the 5x5 mm field. Regarding the overall uncertainty with alanine, a fairly good agreement was found, but configuration with the largest error have to be investigated more in details to identify the causes of such deviation (cf. bone attenuation).

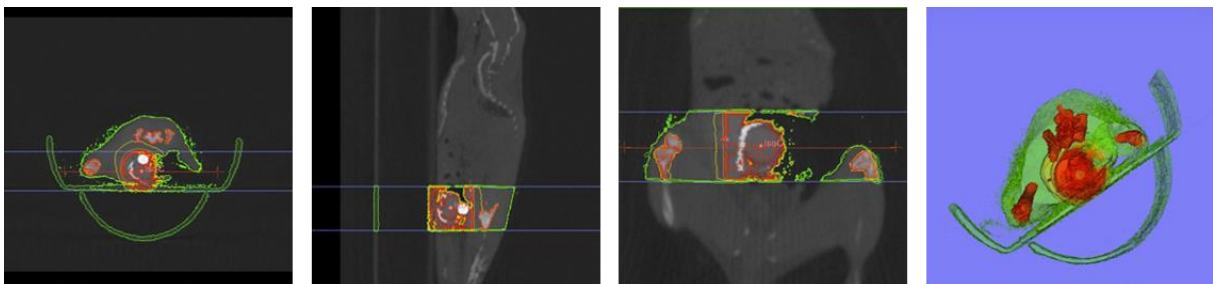


Figure 1: treatment plan for 10x10 mm field with arc (-90°;+90°)

Keywords Radiobiology studies, dosimetry, end to end verification, TPS

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Abstract ID 73850

Developing A Mass Casualty Triage Test For RN Incidents

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Background. Developed as means of rapid triage of mass casualties in the event of a radiological/nuclear (RN) incident to differentiate the “worried well” from casualties requiring prompt medical attention, this qualitative triage test utilises radiation-responsive genes to provide “stay in hospital” or “safe to return home” advice based on blood samples exposed to ≥ 2 Gy whole-body equivalent ionising radiation, within 48 hours of radiation exposure.

Approach. Potential protein and genetic radiation biomarkers were identified via literature review, and evaluated on ex vivo irradiated (0 – 3 Gy X-ray) blood samples (215 healthy donors, and 200 donors with common potentially confounding chronic ailments such as asthma, diabetes mellitus, hypercholesterolaemia, and hypertension, of different ethnicities, representative of Singapore’s multi-ethnic population). Three genes were shortlisted and validation work with blood samples collected from patients undergoing radiation therapy is on-going.

Method. Reverse transcription – quantitative PCR (RT-qPCR) is conducted on ribonucleic acids (RNA) isolated from blood samples. The difference between the Cq values of the target and reference genes (Δ Cq) is calculated, and analysed with a decision matrix to triage the samples. The decision matrix is based on threshold Δ Cq values, which were arbitrarily established from the dataset, aimed at correctly identifying all ≥ 2 Gy and 0 Gy (un-exposed) samples as far as possible.

Advantages. The RT-qPCR test utilises generic RNA isolation and qPCR reagents/ equipment. Being similar to the RT-qPCR method used in CoVID-19 testing, sufficient equipment and trained personnel should be available to conduct large-scale testing.

Testing throughput. With minimal automation, it is estimated to take 5 h per 90 samples, from sample sorting (1 h) to sample processing (2 h) to RT-qPCR (1 h) to data analysis/ reporting (1 h). A five-person team can complete triaging 1,000 samples within 12 hours.

Results. The test exhibited 94% sensitivity (113/1801 samples were mistakenly identified as “safe to go home” – false negatives), and 70% specificity (334/1101 specimens were mistakenly identified as “medical treatment required” – false positives).

Considerations.

(1) As the consequences of false positives were less dire than false negatives, the arbitrary threshold values were adjusted to keep the false negatives to a minimum, while maintaining the false positives at a manageable level.

(2) To simplify the triage process, a single set of threshold values were applied to varied samples of different timepoints (8 – 48 h post irradiation), ethnicities (Chinese, Malay, Indian, and Others), with or without pre-existing chronic health conditions.

Keywords: radiation biomarker; triage; gene expression; worried well; mass casualty

Abstract ID 73851

Alanine reference dosimetry for radiobiology experiments with small rodents irradiated with MV X-rays

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In this work, we will present the methodology used for the dosimetry of partial body irradiation of rodents (mice and rats) in the MV X-rays range and the results obtained with different techniques.

Irradiations were performed at 4 and 10 MV for rats and 4 MV for mice with a conventional LINAC (Elekta) located at IRSN dedicated to radiobiology experiments. Localized irradiations concern the colorectal area. The beam sizes were 2x3 cm for rats and 1x1 cm for mice. When dosimetry with classical ionization chamber is difficult or impossible, such as in the case of small size field of irradiation, alanine dosimetry is used to assess reference doses. Anatomic phantoms of mouse and rat were moulded with a tissue equivalent material (Mix-D) in a moulding cavity made with animal cadaver plug in alginate moulding powder mixed with water. The two phantoms were then cut in two along the longitudinal axis and a cavity in the colorectal area was done to place an alanine pellet. Another set of identical phantoms was drilled for the insertion of the ionisation chamber. Alanine pellets were read with an X-band Bruker E500 EPR spectrometer supplied with high Q cavity. Doses were reported in terms of absorbed dose in water with overall uncertainty of 5.5% ($k=2$).

In the rat configuration (2x3 cm), the doses estimated with alanine data agree with the ionization chamber doses (1.5%) but in the mice configuration (1x1 cm) the ionisation chamber estimation exhibits an underestimation of 7% due to the effect of small field sizes.

As it is difficult to define correction factor for the ionisation chamber, alanine dosimetry is a reliable, robust and affordable means of dosimetry in this small size field.

Keywords Alanine dosimetry, small rodents, radiobiology, rodents' phantom

EPR dosimetry on touch screen of smartphones: dosimetric investigations of the latest generation of glass

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In the context of malevolent or accidental use of radioactive materials, there is an identified need for a fast and reliable method to sort out the individuals actually exposed to ionizing radiation and needed immediate medical cares. A proposed method uses the smartphone touchscreens analysed by EPR as a radiation dosimeter in order to determine the dose of exposure to a person [1]. EPR has been used to estimate dose of exposure to radiation with a wide variety of materials collected on exposed individuals [2]. However, the huge advantage of tempered glass of touchscreen is that everyone has currently a smartphone and therefore a fortuitous dosimeter in their pocket. The work here is focused on the study of the latest generations of Corning® Gorilla® Glass. Gorilla® glasses are known to be alumino-silicate glasses but the specific compositions are not published. By being able to identify in the glass of the touch screen, the stable induced defects caused by irradiation along with the detection of the type of glass generation, the exposure dose can be quantified. The EPR spectra are complex in their analysis as radio induced defects could overlap with defects present already in the glass (Figure 1) or generated during their manufacturing process or even due to exposure to UV irradiation.

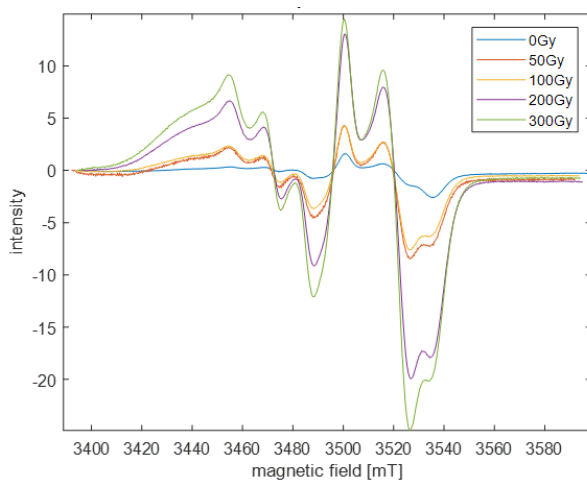


Figure 1. EPR spectra of Gorilla® Glass 4th generation according the irradiation dose

Keywords EPR spectroscopy, accident dosimetry, touchscreen glass, radio-induced defects.

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Abstract ID 74332

microRNAs as new biomarkers of localized radiation injury

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IRSN/PSE-SANTE/SERAMED

A radiological accident, whether from industrial, medical, or malicious origin, may result in localized external exposure to high doses of ionizing radiations. Such exposure leads to the development of a local radiation injury (LRI) whose kinetics and severity depend on the absorbed dose, the duration of exposure and the volume of irradiated tissue. After an asymptomatic phase of variable latency, the LRI manifests as an erythema that may evolve from dry desquamation to deep ulceration and necrosis through unpredictable inflammatory waves. Early diagnosis and prognosis of victims of LRI is therefore crucial for the effectiveness of medical management and the reduction of deleterious effects.

To respond to the constraints of a radiological emergency, a fast and non-invasive diagnostic method is needed to facilitate identification and care of victims. This study aims to identify in biofluids new biomarkers associated with LRI in a preclinical C57BL/6J mouse model of hind limb irradiation. We used a LINAC to locally deliver different 10 MV X-ray doses (20, 40 and 80 Gy), with a dose rate of 3 Gy/min, that lead to injuries of different severity grades. Two weeks after irradiation, we collected and processed plasma and urine to perform broad-spectrum profiling of microRNAs (miRNA) using quantitative real-time polymerase chain reaction (qPCR).

Localized X-ray irradiation resulted in the development of LRI within 2 weeks with various degrees of severity, from mild erythema at 20 Gy to moist desquamation and ulceration at 80 Gy, as compared to sham-irradiated animals. Using a multivariate sparse partial least square discriminant analysis (PLS-DA), we identified panels of miRNA in both biofluids, that can differentiate groups of mice according to the radiation dose and the severity of the injury. Furthermore, an integrative analysis was conducted to establish multi-scale correlations between specific miRNA levels and various biological parameters, i.e. blood cell counts and circulating C-reactive protein levels (inflammation markers), as well as physiological/functional parameters including observational injury score and cutaneous blood perfusion (laser Doppler). The identified miRNA signatures were further confirmed in an independent validation mice cohort.

Our study identifies relevant plasma and urine miRNA signatures correlated with radiation dose and LRI clinical signs in mice and suggests the use of miRNA in biofluids as suitable molecular biomarkers for the diagnosis and medical follow-up of LRI.

Keywords : non-invasive biomarkers ; localized radiation injury ; microRNA ; biofluids

Abstract ID 74335

Mechanisms of post-traditional destabilization of the erythron system and their consequence on the blood rheology in the post-radiation period.

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Understanding the mechanisms of long-term stochastic and tissue effects of radiation exposure is a serious problem in modern life sciences and medicine. Even in early radiobiological studies, it was experimentally established that in the post-radiation period post-radiation stabilization of leukocytes and hemostasis does not occur without stabilization of the erythron system, which can be continued for years. From these positions, the dynamics of the functional state of the erythroid system of the body in the post radiation period can have a significant information load from a prognostic point of view.

The mechanisms of post-radiation decrease in the life cycle of circulating erythrocytes are quite clear and are associated with the intensification of free radical chain reactions of lipid peroxidation in the early postoperative period, it is also known that this leads to long-term destabilization of erythrocyte system.

From these positions, the subject of the study was to elucidate the leading mechanisms of post-traditional destabilization of the erythron system and their consequence on the blood rheology in the post-radiation period.

Mice whole-body irradiation with ¹³⁷Cs was performed at a dose rate of 1,1Gy/min for the total dose of 5 Gy with a "Gamma-capsule-2". The rheological properties of the erythrocytes, their EPR spectra, and membranes' protein were studied after 48 hours, 7, and 14 days after radiation

Results show that absorption for proteins of erythrocytes' membrane at 280 nm wavelength time-dependent decreased after irradiation, which may be related to Tyr-phosphorylation of membrane's Band 3 protein (B3p) in radiation-induced oxidative stress conditions, leading markedly reduces its affinity to ankyrin, and release of band 3 from the spectrin/actin membrane skeleton, enhancement of the lateral mobility of band 3 protein in the bilayer, its progressive vesiculation, and loss from the plasma membrane of radiated cells, triggering a cascade of events inducing alteration of deformability, the resistance of erythrocytes membrane, its destabilization. EPR signals of hemichromes were detected.

Abstract ID 73858

Dosimetry of a self-shielded gamma irradiator small animal whole body irradiations with alanine pellets

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In this work, we will present the methodology used to estimate the whole body dose of mice irradiated in a self-shielded irradiator with Cs-137 gamma-rays sources. The self-shielded irradiator employed is a GSRD 1 from Gamma-Service Medical GmbH Company containing 4 Cs-137 sources. For irradiation, up to five mice were placed in a sterile and sealed plastic box. As it was not possible to use in that case an ionization chamber, the dosimetry was performed with alanine pellets. In order to take into account the effect of the box and the scattered radiation from side animals, reference doses were estimated by alanine pellets placed in tissue equivalent murine phantoms. Phantoms were moulded with a tissue equivalent material (mix-D). Five irradiations were performed with respectively 1 to 5 mice. For each configuration, measurements were performed in all phantom to estimate the dose variability. The secondary objectives of this experiment was to demonstrate the effect of number of mice on the mean dose rate and that a specific dosimetry is needed depending on number of mice. EPR measurements were performed with a Bruker E500 X-band spectrometer supplied with a high Q cavity. Doses were reported in terms of absorbed dose in water with a relative uncertainty of 5.5% (k=2).

Keywords EPR dosimetry, alanine, mice, whole-body irradiation

Abstract ID 73862

Inter- and intraindividual response to alphas, X-rays and mixed beams analysed at exon-level gene expression and chromosomal aberrations

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Introduction: In preparedness for a radiological emergency, further validation of transcriptional ionizing radiation biomarkers, including isoform expression, require a better understanding of inter- and intraindividual variability to exposures of different single and mixed radiation qualities. Mixed beams of alphas and X-rays lead to inter- and intraindividual variable responses at the gene expression level [1]. Here, we investigated the interindividual and seasonal stability of the response after the same single and mixed beam exposure conditions at the exon-level. In parallel, frequencies of chromosomal aberrations were evaluated.

Methods: Blood from two donors was drawn in triplicate during three different seasons and exposed to 0-2 Gy of X-rays, alphas or 1:1 dose of X-rays and alphas. Differential variant expression of FDXR, CDKN1A and MDM2 was analysed by qRT-PCR at 24 h after exposure. For chromosomal aberration analysis, blood cultures were set up and harvested 48 hours post-exposure by standard cytogenetic procedure.

Results: The magnitude of the dose-dependent upregulation of FDXR, CDKN1A and MDM2 alternative transcripts varied inter- and intraindividually, with the exception of a stable response after alpha particles for the most strongly upregulated FDXR variants. Despite the seasonal variability, the response of each set of targeted alternative transcripts seemed very consistent between donors. FDXR variants 1-8 showed an overall synergistic response after mixed beams in both donors. On the contrary, when FDXR variants 4 and 7 were excluded by primer design, the overall interseason response was subadditive in both donors. All tested MDM2 alternative transcripts showed an additive response to mixed beams, while CDKN1A variants varied between additive and subadditive depending on the level of fold change selected for the construction of the envelope of additivity.

Scoring of chromosomal fragments is currently being completed. Seasonal variability was observed after mixed beam exposure in one of the donors, and after X-rays in the other. A general synergistic interaction of alphas and X-rays was detected in both donors.

Conclusion: Inter- and intraindividual seasonal variability occur at the expression level of alternative transcripts in human lymphocytes, but overall, there is good agreement in induction of FDXR, CDKN1A and MDM2 transcripts between the two donors tested in the present study. The mixed beam effect was alternative transcript-dependent, but a synergy was generally seen after aberration analyses.

Keywords Gene expression; alternative transcripts; aberrations; mixed beams; variability

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Evaluation of absorbed bone dose by EPR spectroscopy of a preclinical model mimic interventional radiology expositions: dose and time effect

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Interventional radiology, commonly used for diagnosis and treatment, is performed under low-energy X-ray imaging guidance or control (70–120 kV). Although mostly beneficial and mastered, medical accidental overexposures can occur where high doses (>10Gy) can be delivered to soft tissue leading to deterministic effects like erythema, alopecia or tissues necrosis. The highest doses are found close to the soft tissue surface. Nevertheless, doses to bone tissue can be significantly higher. Indeed, the dose deposition is mainly due to the photoelectric process which is dominant at low energy with higher dose delivered for higher Z materials. Therefore, even if the dose to soft tissue can be lower than the dose threshold for necrosis (25Gy), in bone absorbed dose can exceed the dose threshold for bone necrosis (40Gy). As the bone composition has a strong impact on the dose estimation, EPR dosimetry on small bone fragments provide the absolute dose in bone and has been used in several accident cases. However, even if the radio-induced free radicals (RIFR) in bone are stable in extracted bones, in living bone a loss of RIFR may be expected due to the bone turnover. Therefore, when bone sampling is performed weeks or months after irradiation, the measured doses may have to be corrected. No published data exist on the impact of the bone turnover on the quantity of RIFR. In addition, the lack of knowledge about the biological consequences at low-energy, due to the heterogeneity of dose deposition, makes the prognosis very uncertain for bone tissue. The development of preclinical experimental model is therefore essential to improve the knowledge about the biological effects of this type of expositions and characterize the radiopathological specificities.

A new C57Bl6/j mice model of localized paw exposition was implemented on the SARRP at 80kV, allowing to mimic interventional radiology expositions. Animals were exposed to single exposition of 15, 30 and 45 Gy in terms of air kerma. At different time points post irradiation, tibias were collected, cleaned, dried and cut in small pieces for EPR spectroscopy analysis. The additive dose method was used to estimate absorbed dose in bones. 6 interest time points from 0 to 84 days after exposition were studied to estimate the initial bone dose (D0) and characterize the evolution of the EPR spectroscopy signal over time.

EPR measurements allow to estimate an initial absorbed bone dose of 100.2 ± 7.6 Gy, 208.6 ± 21.3 Gy and 316.6 ± 26.9 Gy respectively for 15, 30 and 45 Gy Kair expositions. An experimental conversion factor of 6.89 ± 0.60 between the bone dose and the air dose was determined. Furthermore, whatever the initial dose, the measurements at the different post-exposure time points (D14 to D84) have shown a decrease of the EPR signal over time, tending to stabilize for the latest time points (D42 and D84).

This new approach allows to perform exposition under interventional radiology conditions. The initial bone dose has been determined by EPR spectroscopy measurements and the decrease of the EPR signal over time likely suggest the establishment of the biological processes and bone turnover. MicroCT and histological analysis will allow to characterize and quantify the biological response and also the effect of the dose

Keywords Interventional radiology, dosimetry, EPR spectroscopy, preclinical model

Implications of “FLASH” for Biodosimetry

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Recent interest in extremely high dose rate radiation delivery (FLASH) has arisen because of the empirical observation that there could be significant improvement in radiobiological effectiveness of radiation using FLASH. This delivery approach has shown lower damage to normal tissues such as brain, colon, lung, and skin, with indications that this reduction is equivalent to a 1.3-2.0 times lower dose, while tumor tissue has the same radiotoxic effect. The ongoing research into the mechanisms for the FLASH effect have some very pertinent implications for the field of Biodosimetry. First, it could be argued that delivery of radiation at very high dose rates is a good model for simulating the delivery of radiation from the initial part of the detonation of a nuclear weapon or some types of radiation accidents. Second, studies of the underlying mechanisms leading to differential effects on tumors and normal tissues provide insights as to how dose rates could impact the phenomena underlying various types of biodosimetry. These in turn lead to a need to determine the effects of extreme variations of dose rate on various types of biodosimetry.

Potential changes in the radiation physics from the delivery of radiation at very high dose rates can occur because of variations in the densities of primary products, leading to variations in the amounts and types of secondary products. These in turn can have a significant effect on the subsequent radiation chemistry, including the reactions of intermediates with oxygen. Subsequently the early phase radiation chemical changes are likely to change the biological responses to the radiation. Oxygen may have a particularly important role because of the sensitivity of many biological signals to changes in key intermediates, including oxygen, that in turn can change cellular homeostasis that the cell must overcome to maintain viability.

It is important but challenging to try to apply these concepts to biodosimetry. The potential impact will be very different depending on the type of biodosimetry technique. In general it will be desirable and in many cases, essential, that empirical studies on the effects of dose rate on the response of the biodosimeter be undertaken in appropriate experimental models. While it is appealing to try to do studies in very simplified model systems (e.g. water) these are likely to be very misleading. The complex radiation chemistry that occurs after the initial physical events will be greatly impacted and modified by interventions with the environment.

For physical biodosimetry based on EPR the principal variable will be the number of unpaired electrons formed in the stabilizing matrix (e.g. enamel for teeth; glass for cell phones) where the effect of dose rate could be fairly readily determined. The situation will be more complex for biological dosimeters based principally on direct effects on the biological target (e.g. chromosomal aberrations). The effects may be somewhat accessible to direct studies, but there will be a need to determine the systems that potentially modify the initial biological damage through repair have not been affected. For most other biodosimetry techniques it may be especially complex to try to model the effects with simple variations of dose rate because of the many intervening steps between the initial absorption of radiation and downstream events that produce the parameter that is observed (e.g. gene expression or cell signaling).

Keywords EPR biodosimetry, unplanned exposure, health risks

A novel and sensitive method using telomere and centromere in situ hybridization improves detection of chromosomal and telomeric aberrations induced by low doses γ -irradiation in vitro

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Background: Exposure to low doses of ionizing radiation is an inevitable byproduct of modern life and is an ongoing health concern. Dose response curves of DNA damage after exposure to medium or high doses of ionizing radiation are already well established. However, the effects on DNA damage to low doses of radiation (<100mGy) remains unclear. In this study, we reevaluate the sensitivity of the gold standard methods for detection of DNA damage using in situ hybridization with specific probes for telomeres and for centromeres (TC staining) after low doses of gamma-irradiation of human peripheral lymphocytes. We provide a possible link between formation of telomere aberrations and exposure to low doses of gamma-irradiation.

Materials and methods: Human peripheral blood lymphocytes from 15 healthy donors were exposed to cobalt 60 γ -irradiation at four doses from 10mGy to 200 mGy at a dose rate of 10mGy/min. The blood lymphocytes were cultured for 48h after exposure and chromosomal aberrations in metaphases in the first mitosis were scored after telomere and centromere staining. Telomere length and telomere aberrations were assessed concomitantly in each metaphase. Clonality of telomere aberrations was assessed using TC staining followed by the M-FISH technique (TC+M-FISH) in three of the donors.

Results: Using TC staining, every single unstable chromosomal aberration can be scored thus enabling precise calculations of the number of double strand breaks (DSB) in a metaphase preparation. The main finding of our study was a significant difference between the frequency of calculated DSB after exposure to gamma-irradiation at all of levels of the low doses compared to those of controls. However, there was nonlinearity in the low dose effect relationship. Significant differences were observed between telomere aberrations (telomere loss and telomere doublets) after exposure of lymphocytes at all doses and those in controls. Furthermore, the altered telomere lengths after low exposure depended on the telomere length baseline. Using TC+M-FISH, we demonstrate the involvement of the same chromosomes in radiation-induced telomere aberrations.

Conclusion: Our TC staining method improves detection of unstable chromosomal aberrations thus increasing the sensitivity of the previous gold standard technique used to monitor effects of low doses of radiation. Thus, our technique will be a valuable tool in the field of research on low doses of radiation. The nonlinearity of the dose response curves at low doses of irradiation could be related to hypersensitivity phenomenon. The formation and the clonality of telomere aberrations after low doses of exposure to gamma-irradiation needs further investigations.

Keywords low doses, dicentrics, telomeres, centromeres, M-FISH.

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How in vivo EPR nail dosimetry could be utilized to significantly improve the response to a large radiation event

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After an ionizing radiation event, decision-making for medical intervention must be done effectively at the level of the individual, where it is essential to have knowledge about the heterogeneity/homogeneity of the distribution of the exposure as well as the biological impact of the dose. This will be especially important in a large-scale event, where it will be essential to make informed decisions on the allocation of resources, because the needs are likely to exceed the available resources. There currently is no established method for rapidly determining dose and its distribution with immediate readout. However, in vivo electron paramagnetic resonance (EPR) dosimetry of nails, based on the measurement of the radiation induced free radicals generated in the keratin of human nails, has the capability of making this determination. EPR dosimetry of nails can provide rapid and robust indications of homogeneity by making measurements at four widely separated sites, i.e., the two hands and two feet. It also will clearly distinguish between the worried well and subjects who have received doses of radiation that could lead to significant morbidity and mortality. It is important to note that this approach is complementary, not competitive, to the information obtained by bioassays that are based on organ specific damage.

There are two important places where in vivo EPR nail dosimetry could significantly improve the response to a large radiation event. First, we have established the feasibility to have spectrometers make such measurements in the field. By expanding the capability of these instruments to allow for making measurements simultaneously on multiple digits in each limb, dose resolution would be significantly improved. Second, instead of using this technique only for initial screening, it could be very effective to have instruments that would be located in the facilities set up for secondary evaluation of subjects already determined to be at high risk of having a significant exposure (e.g. by location, clinical symptoms or measurements with other types of biodosimetry). The added knowledge from in vivo EPR nail dosimetry would be used to determine whether the exposure was homogenous, which would greatly facilitate decisions regarding the priority for immediate interventions in subjects with a high risk of having acute radiation syndrome.

We already have demonstrated the feasibility of our approach, but there is an opportunity and a need to enhance the sensitivity and the automation of the measurements (see poster on prior technical developments). Developments can be carried out first, using volunteers with paramagnetic materials placed on the surface of their nails. Ultimately the robustness of the technique can be validated in patients undergoing therapeutic whole-body irradiation (or other therapeutic treatments involving exposure to the nails).

Study of soils by EPR method in the region of testing sites RK

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For estimation the ecologic situation at the regions around testing sites in RK the study a range of soil probes taken at the territories around of Semipalatinsk test site (STS) [1] and the Lira underground cavities [2] has been carried out by EPR (electron paramagnetic resonance) method; paramagnetic centers (PMC) have been registered, earlier study had shown radiation origin of E1' type PMC [1, 3]. Additional irradiation and other factors influenced these signals characteristics [4]. As a result of study was shown that changing EPR signal of E1'- centers under condition of annealing and irradiation can indicate on the external radiation factor influence. Supposed approach was tested on model samples, the data obtained can allow to estimate amorphous and crystal silica dioxide content in the studied natural probes.

The electron beams and gamma-rays were successfully used for modelling of technogenic radiation factors for the probes [4, 5]. Linear PMC accumulation with the dose applied using the control by alanine dosimetry is promising from point of view the EPR-dosimetry [1, 4, 5]; for obtaining the linearity of dose dependence, the preliminary irradiation was carried out.

The developed experimental techniques were tested on the samples of soils from various sampling points, as well it was shown that for correct interpretation of the results it is necessary to study and take into account the type and properties of the soils under study.

Keywords EPR, soil, PMC, annealing, dosimetry

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A Comparative study of the thyroid gland pathologies among the Armenian liquidators of the Chernobyl Nuclear Power Plant accident and general Armenian population

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Research findings of the prevalence of the thyroid gland pathologies among the Armenian liquidators of the Chernobyl Nuclear Power Plant (CNPP) disaster revealed during two years (2017-2018), thus, 30 years after the irradiation, are presented.

The number of Armenians among the liquidators is 100%. Among them (n=82), the thyroid gland function abnormalities were diagnosed in 23,2% of cases, and nodular lesions- in 8,2% of cases. In the most cases, the nodules were up to 1 cm, and were of a tissue nature. In one case the relapse of multinodular goiter after subtotal resection of the thyroid gland (due to precancerous proliferation) was revealed. Most often, the pathologies were detected in the 61-70 year old age group. When comparing the presented data with the data of general Armenian population, no definite differences were revealed.

Thus, the possible impact of the radiation on the prevalence of the thyroid gland diseases among the Armenian liquidators of the CNPP accident has not been confirmed.

Keywords : the Chernobyl Nuclear Power Plant disaster, the Armenian liquidators, general Armenian population, the thyroid gland pathologies

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[http:// www.armstat.am /file/ doc/ 99504368. pdf](http://www.armstat.am/file/doc/99504368.pdf)

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EPR dosimetry with commercial drywall material

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Rapid dose determination from building materials for emergency response (and similar retrospective dosimetry applications) include drywall (e.g., sheetrock or plasterboard). This material was found to have electron paramagnetic resonance (EPR) and Optically stimulated luminescence (OSL) signals in proportion to the radioactive dose. The initial dose can be found by OSL using a single aliquot regenerative method. We found a strong exponential decay over time for the OSL signal. EPR has also been used in determining the dose through assaying CO₃⁻ radicals using an additive dose method. The EPR radicals have been found to be stable over the lifetime of the OSL signal, resulting in differential decay modes for different signals that may be used to extract additional forensic information. This also shows that EPR analysis, (although less precise) will be more accurate than the OSL analysis although using their combination enables opportunities for additional forensic information.